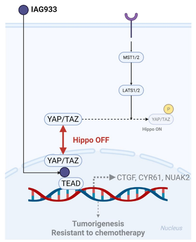
TEAD Inhibition by IAG933 as a Novel Therapeutic Strategy for Cholangiocarcinoma

Hidemi Nishi, M.D., Ph.D.[1], Erik Jessen, Ph.D.[2], Danielle M. Carlson[1], Amro M. Abdelrahman, M.B.B.S., M.S.[1], Enis H. Ozmert, M.D.[1], J. Pedro F. Safi, Brandon A. Wilbanks, Ph.D.[1], Shelby K. Yee, M.D.[1], Jack W. Sample, M.D.[1], Nathan W. Werneburg, M.S.[1], Rory L. Smoot, M.D.[1]
[1]Department of Surgery, Mayo Clinic, Rochester, MN, [2]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN

CCF 13th Annual Conference | Salt Lake City May 1-3 2026

BACKGROUND

- Cholangiocarcinoma (CCA) is an aggressive malignancy with limited treatment options and poor prognosis
- KRAS mutations and treatment resistance remain major challenges
- YAP/TAZ–TEAD signaling is frequently activated in CCA and promotes tumor progression and resistance
- IAG933 is a pan-TEAD inhibitor that targets this pathway



OBJECTIVE

- To evaluate the antitumor activity of IAG933 in CCA models
- To determine whether combined TEAD and KRAS inhibition (RMC-6236, pan-KRAS inhibitor) enhances antitumor efficacy in CCA models

METHODS

- Human CCA cell lines (HuCCT1, RBE) , murine CCA cell lines (SB1, FAC), and normal human cholangiocytes (NHC) cell line were used
- Treatment with IAG933 alone or in combination with GemCis or RMC6236
- Cell viability and TEAD activity assays
- In vivo efficacy was evaluated using PDX models

RESULT 1

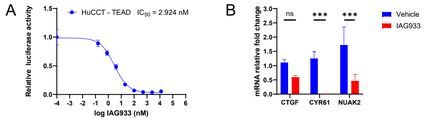


Figure 1. IAG933 inhibits TEAD signaling pathway. (A) Dose-dependent inhibition of TEAD activity. (B) Suppression of TEAD transcriptional activity following IAG933 treatment.

RESULT 2

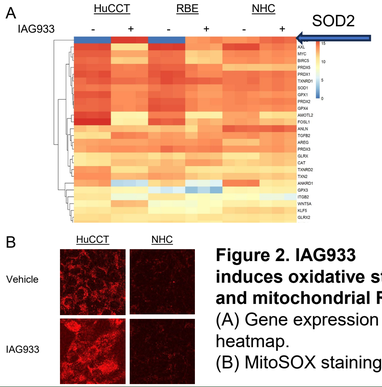
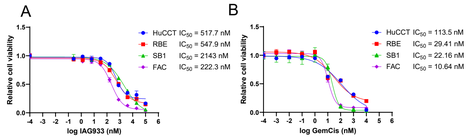


Figure 2. IAG933 induces oxidative stress and mitochondrial ROS. (A) Gene expression heatmap. (B) MitoSOX staining.

RESULT 3



C

Cell lines	CI at Fa 0.5
HuCCT	0.654
RBE	0.472
SB1	0.913
FAC	0.607

Figure 3. Combination of IAG933 and GemCis shows synergistic effects in CCA. (A–B) Dose–response curves of IAG933 and GemCis. (C) Combination of IAG933 and GemCis shows synergistic effects (CI < 1

RESULT 4

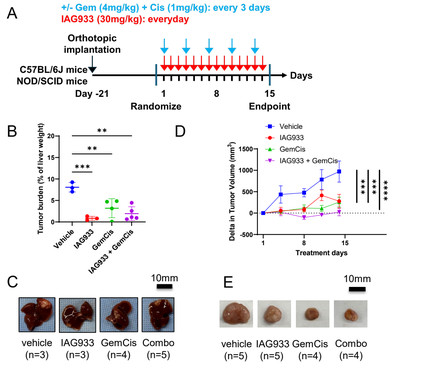
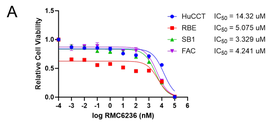


Figure 4. IAG933 shows antitumor activity comparable to GemCis in CCA. (A) Treatment schema in orthotopic and PDX models. (B) Tumor growth is reduced with IAG933 alone and in combination treatment. (C, E) Representative tumor images. (D) Tumor growth curves.

RESULT 5



B

Cell lines	CI at Fa 0.5
HuCCT	0.202
RBE	N/A
SB1	0.465
FAC	0.327

Figure 5. Combination of IAG933 and RMC6236 shows synergistic effects in CCA. (A) Dose–response curves of RMC6236. (B) Combination of IAG933 and RMC6236 shows synergistic effects (CI < 1).

RESULT 6

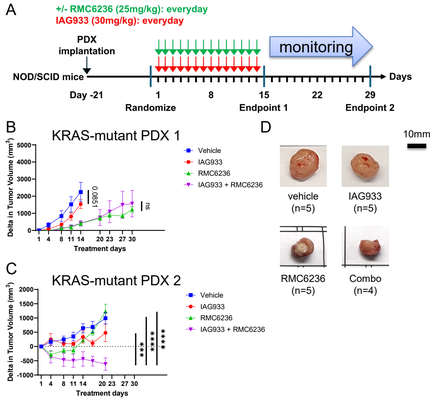


Figure 6. Dual TEAD and KRAS inhibition leads to improved tumor control in some models, with delayed regrowth after treatment cessation in CCA. (A) Treatment schema in KRAS-mutant PDX models. (B, C) Tumor growth curves show improved antitumor activity with combination treatment. Improved tumor control with delayed regrowth after treatment cessation. (D) Representative tumor images.

CONCLUSIONS

- IAG933 suppresses YAP/TAZ–TEAD signaling and inhibits CCA growth in vitro and in vivo
- In vivo, IAG933 shows single-agent activity comparable to GemCis, with limited additional benefit when combined with GemCis
- Combination with RMC6236 shows stronger synergy than GemCis
- In KRAS-mutant CCA models, dual TEAD and KRAS inhibition delays tumor regrowth after treatment cessation
- These findings support combined TEAD and KRAS targeting as a potential therapeutic strategy for KRAS-mutant in CCA

Patient-Friendly Lay Summary

Background / Objective

Bile duct cancer is hard to treat. This study tested a new drug, IAG933, which blocks signals that help cancer grow. We also checked if it works better with current treatments.

Methods

The drug was tested in cancer cells and in mice, using the drug alone or with other treatments.

Results

IAG933 slowed tumor growth. When combined with other treatments, it sometimes worked better than a single treatment alone. In some cancers, the effect lasted longer even after treatment stopped.

Conclusion

IAG933 could become a new treatment option for bile duct cancer, especially when used with other therapies. These findings may help guide future treatments.