# MUC4-Targeted Nanoparticles Deliver MRTX1133 and MDP5 to Overcome Pancreatic Cancer Chemoresistance

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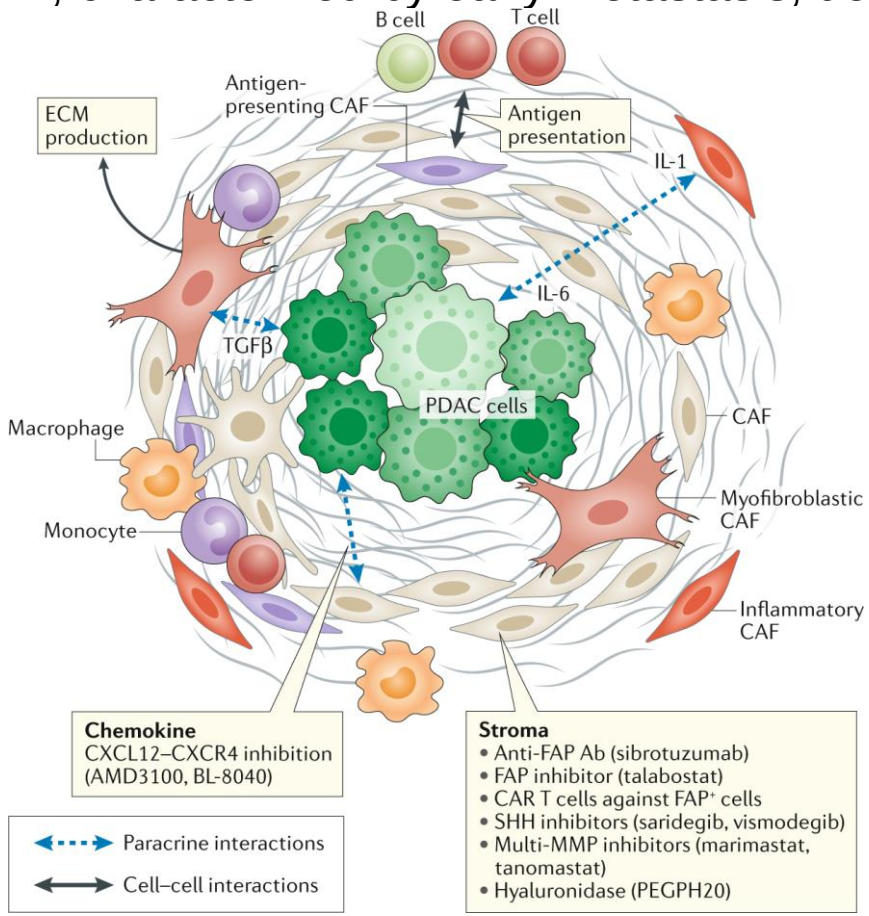
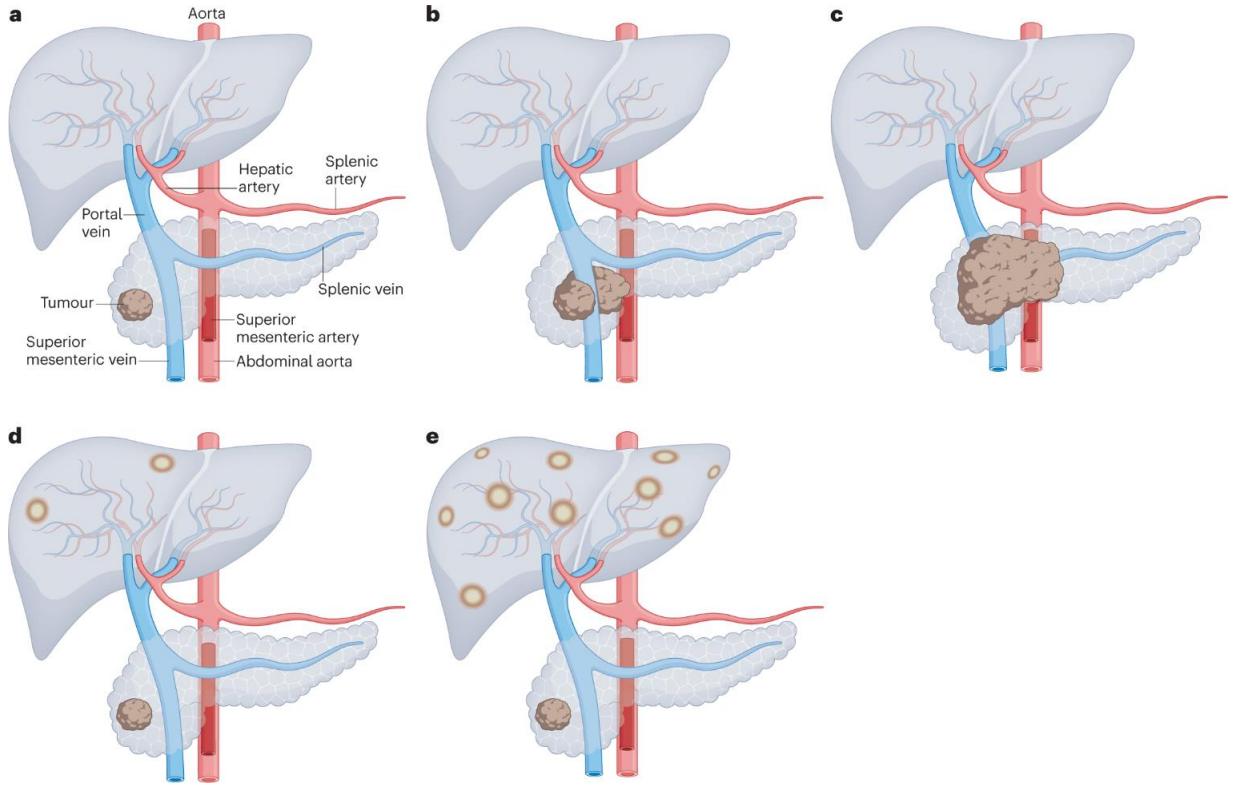
NEXT-GENERATION DELIVERY INNOVATIONS

# Pancreatic ductal Adenocarcinoma (PDAC)

- Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy arising from the pancreatic ductal epithelium, characterized by early metastasis, dense desmoplastic stroma, and resistance to therapy.

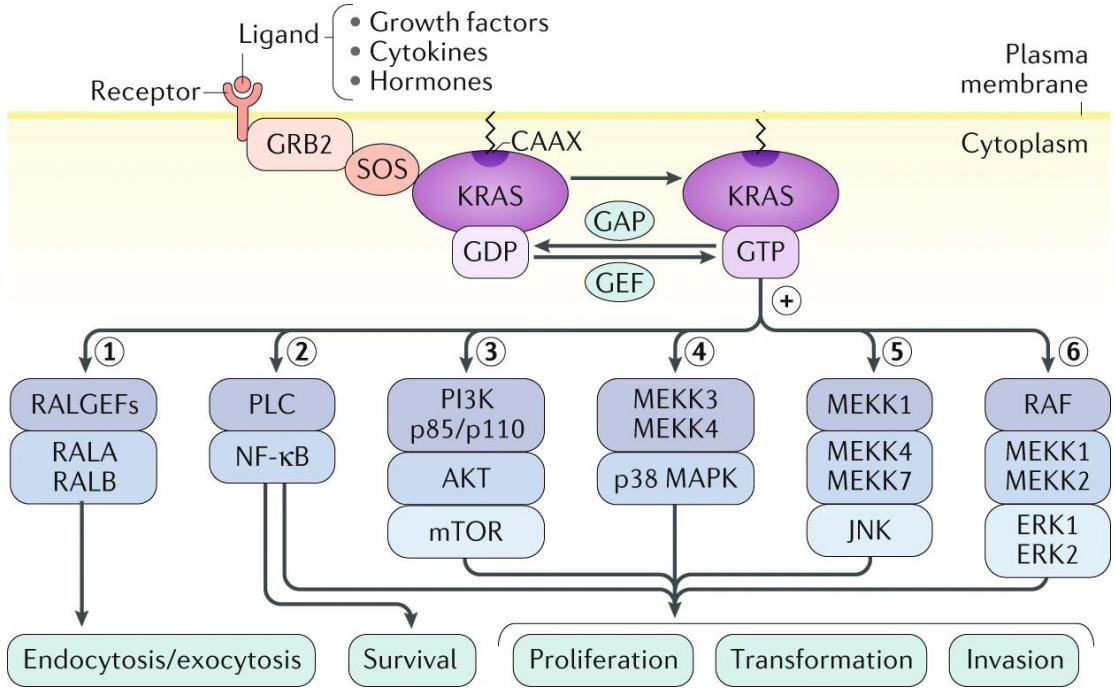



**Stages of pancreatic cancer**




*Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer—clinical challenges and opportunities. Nature reviews Clinical oncology. 2020 Sep;17(9):527-40.*

# KRAS: the critical driver and therapeutic target for pancreatic cancer



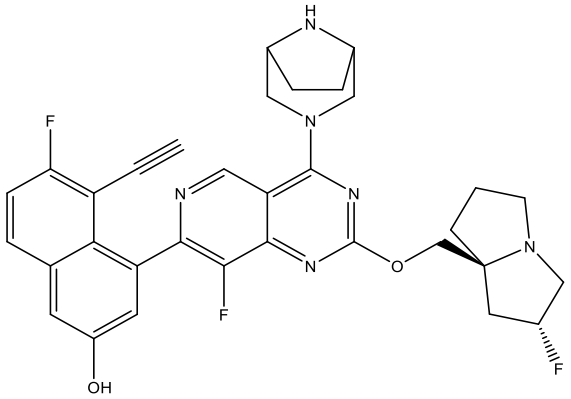

- Oncogenic KRAS mutations are single nucleotide mutations at codon 12 (exon 2), where the GGT sequence (glycine encoded) is replaced by different amino acid sequences, accounting for over 90% of PDAC cases.
- KRAS G12D mutation where GGT sequence (glycine) is replaced by GAT sequence (aspartic acid) is most common 40% in PDAC patients.

Therefore, KRAS G12D has remained the most crucial targeting substrate for PDAC

*Buscail L, Bournet B, Cordelier P. Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. Nature reviews Gastroenterology & hepatology. 2020 Mar;17(3):153-68.*

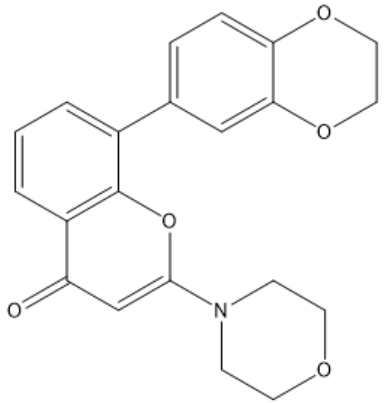
# Innovative Therapeutics in PDAC: A Comparative Overview of MRTX1133 and MDP5

**MRTX1133**

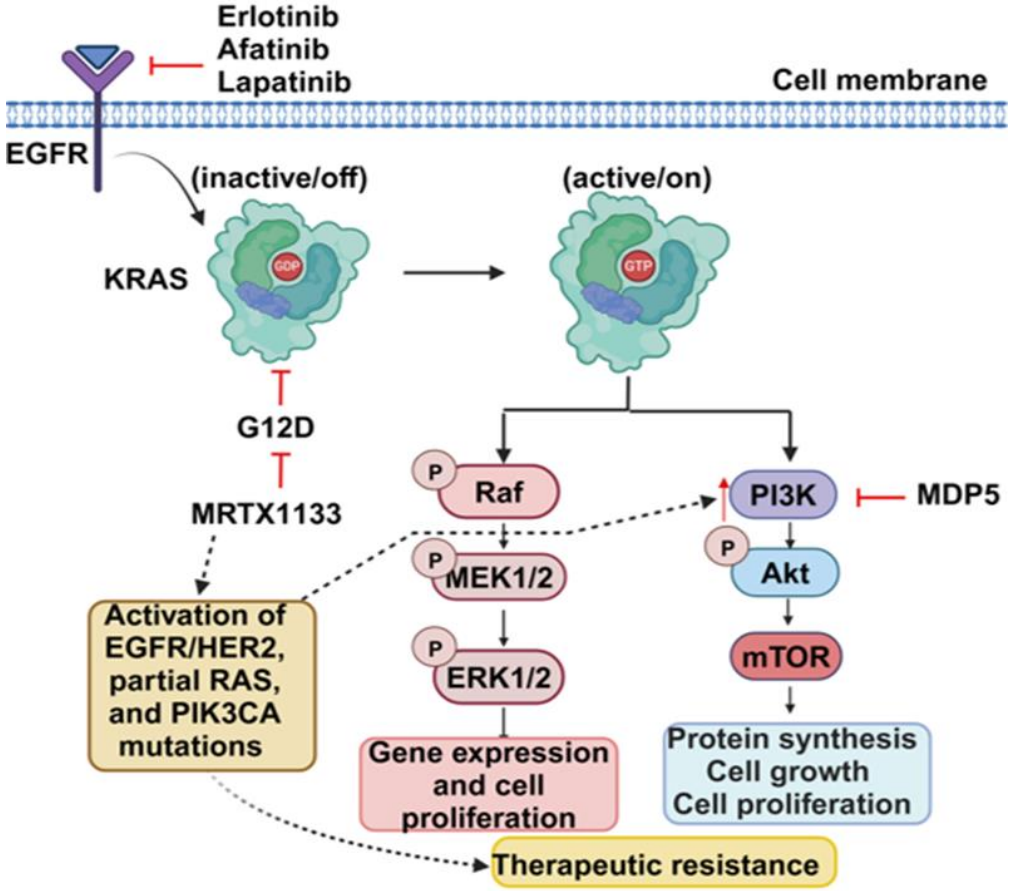


- Selective, non-covalent KRAS G12D inhibitor
- Ongoing clinical evaluation (NCT05737706)
- MRTX1133 develops chemoresistance via YAP1 activation, reactivation of RAS/MAPK and EGFR/HER2 pathways.

**MDP5**

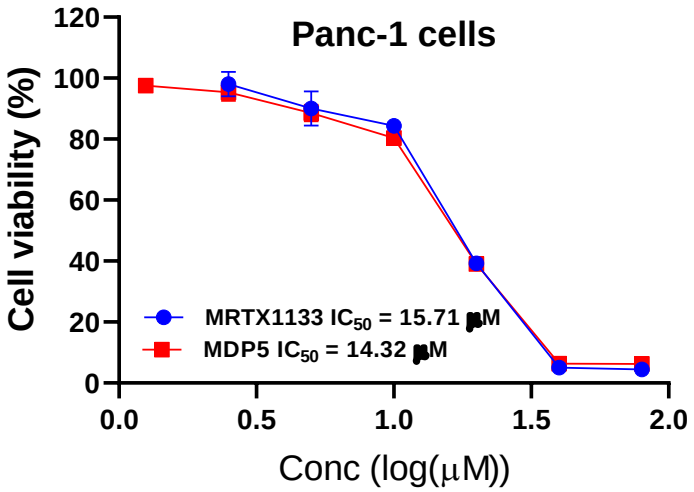


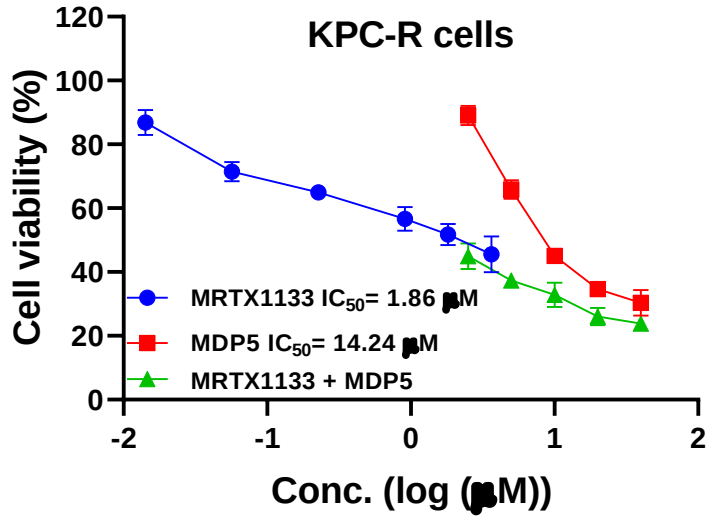
- Dual functional PI3K and BRD4 inhibitor
- Promotes MYC degradation by simultaneous inhibition of AKT function

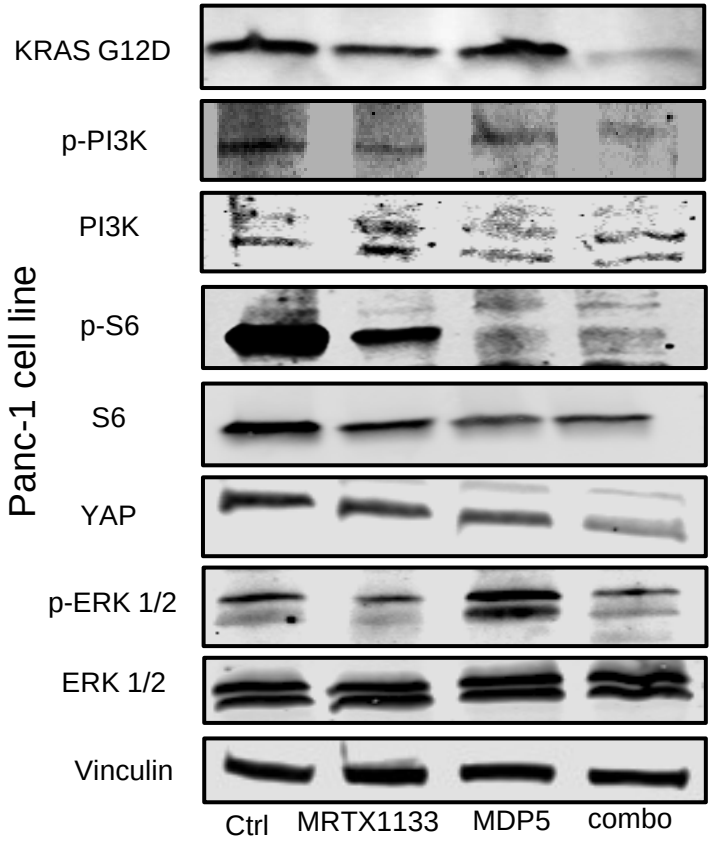



*Wei D, Wang L, Zuo X, Maitra A, Bresalier RS. A small molecule with big impact: MRTX1133 targets the KRASG12D mutation in pancreatic cancer. Clinical Cancer Research. 2024 Feb 16;30(4):655-62.*

# Synergy of MRTX1133 and MDP5 Reverses Resistance in KRAS-Driven Pancreatic Cancer



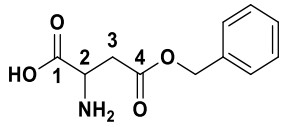




- MRTX1133-resistant Panc-1 and KPC/Y cell lines show reduction in viability with a combination approach demonstrating synergistic efficacy.
- In Panc-1 resistant cells, the combination treatment inhibits upregulated KRAS downstream effectors, thus reversing resistance mechanisms.

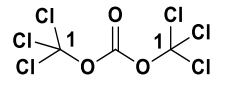
Combining MDP5 with MRTX1133 overcomes resistance in KRAS-driven cancers by restoring pathway inhibition.

# Formulation characterization

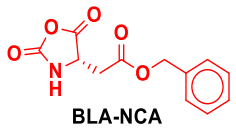
A



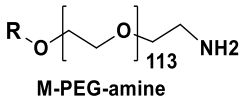
2-amino-4-(benzyloxy)-4-oxobutanoic acid



bis(trichloromethyl) carbonate



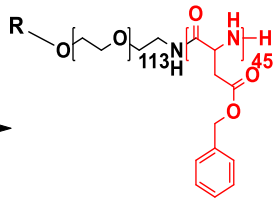
BLA-NCA



M-PEG-amine

ROP, DMF

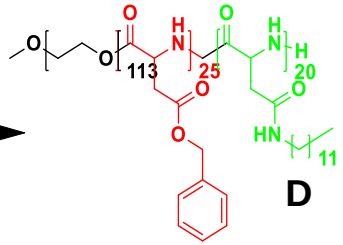
BLA-NCA



Methoxy-PEG-PBLA

Dodecylamine

A



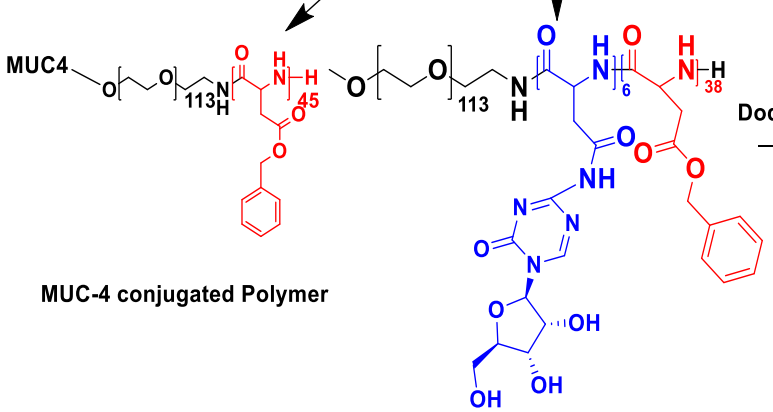
D

m-PEG[113]-p-[Asp-BLA]-p-g[Asp-DA]

Maleimide-Thiol conjugation

Gemcitabine

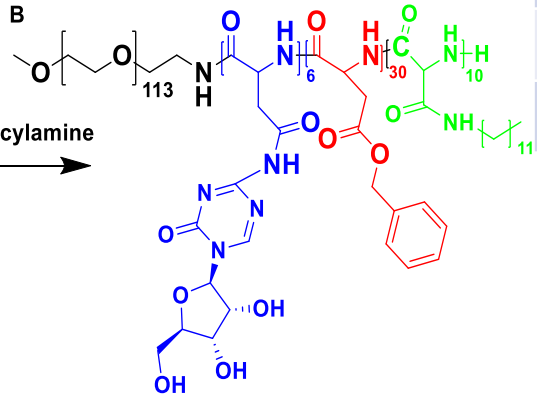
C



MUC-4 conjugated Polymer

Dodecylamine

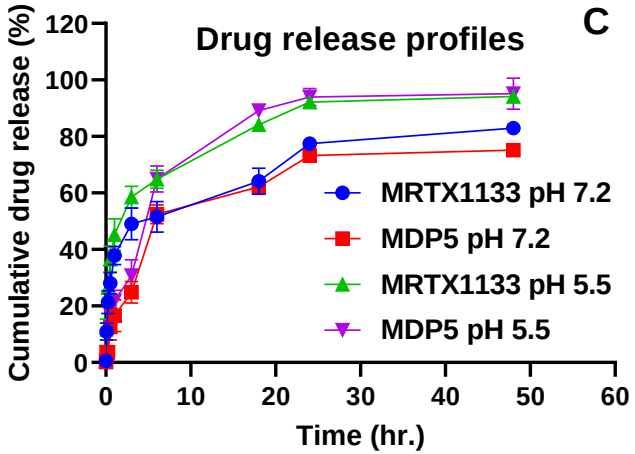
B



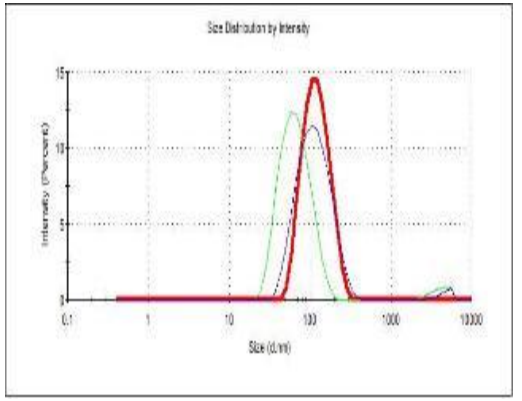
m-PEG[113]-p-[Asp-GEM]-p-[Asp-BLA]-p-g[Asp-DA]

Where R-Methoxy for A,B and Maleimide for C

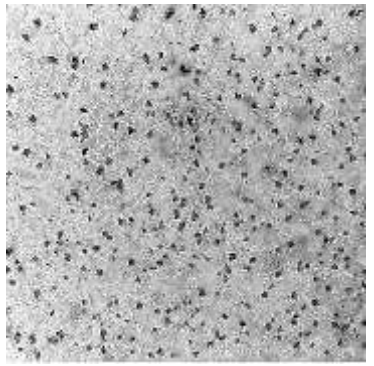
B



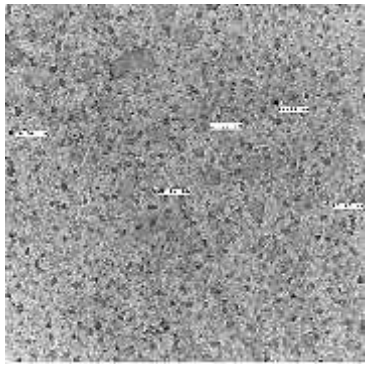

C



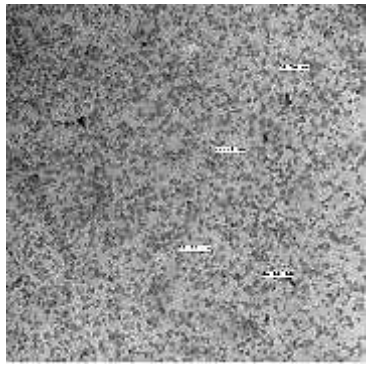
| Groups | Size | PDI |
|---|---|---|
| Blank NPs | 63.01±0.71 | 0.219±0.005 |
| MRTX1133 NPs | 112.1±0.76 | 0.163±0.003 |
| MDP5 NPs | 103.9±0.306 | 0.218±0.003 |



Blank NPs

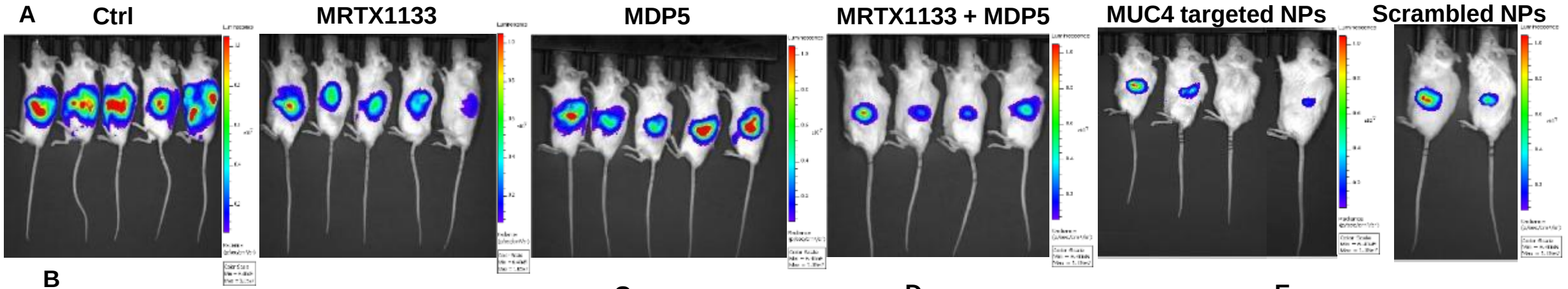


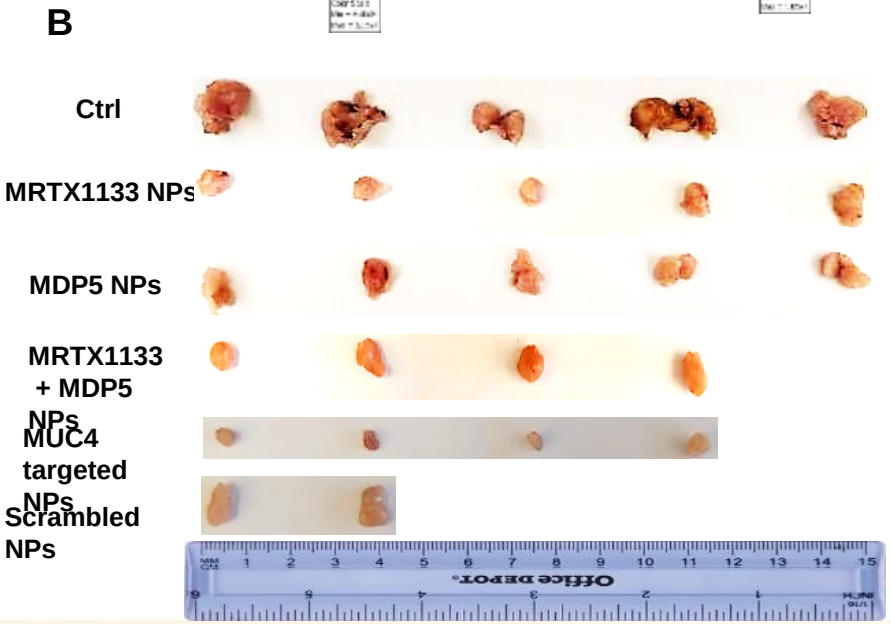
MRTX1133 loaded NPs

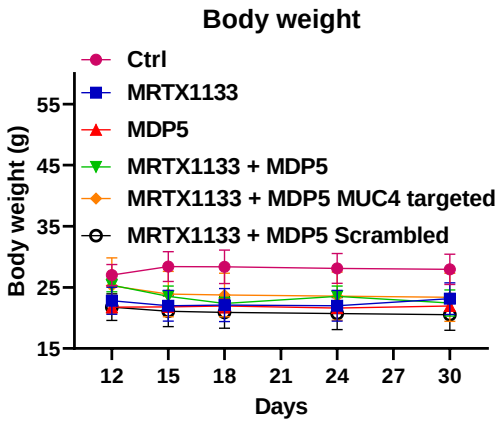


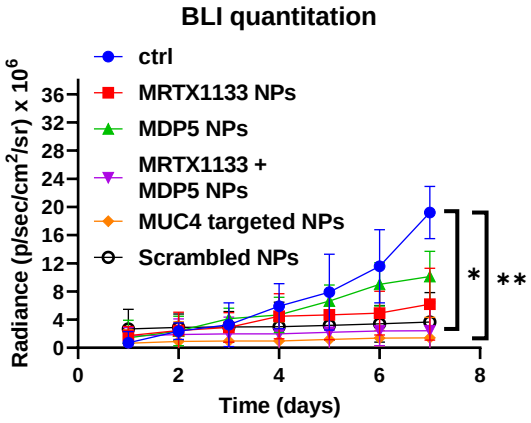
MDP5 loaded NPs

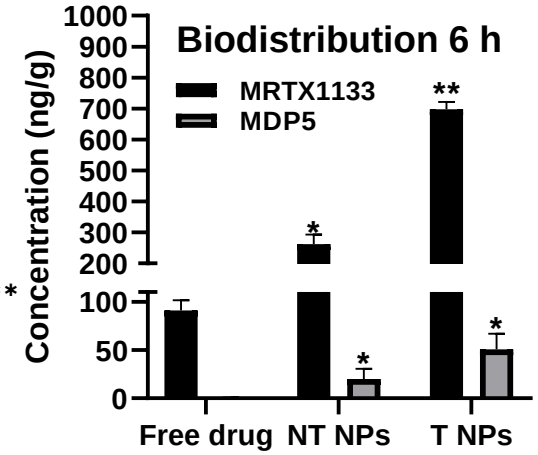
# *In vivo* therapeutic efficacy studies



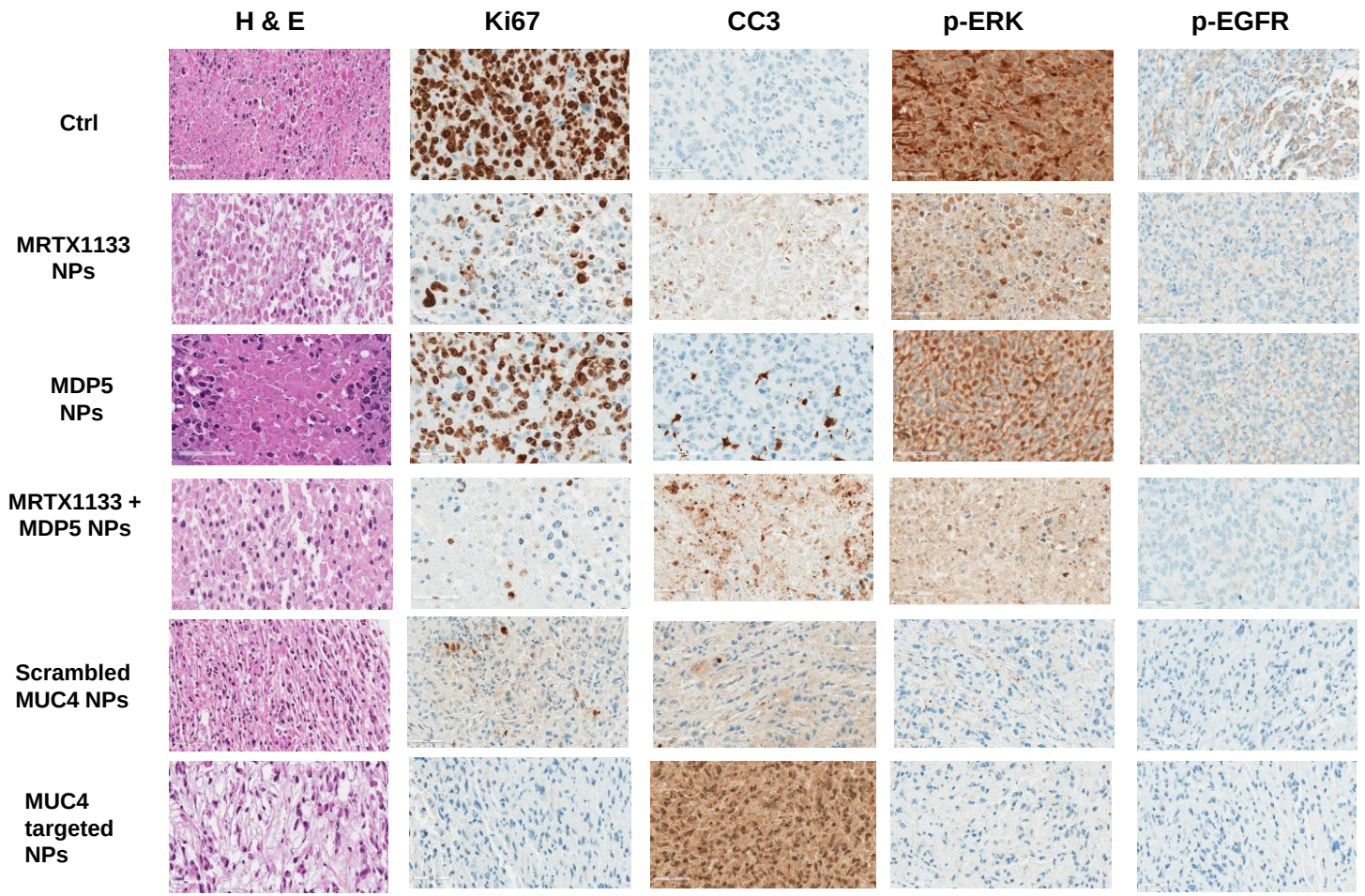



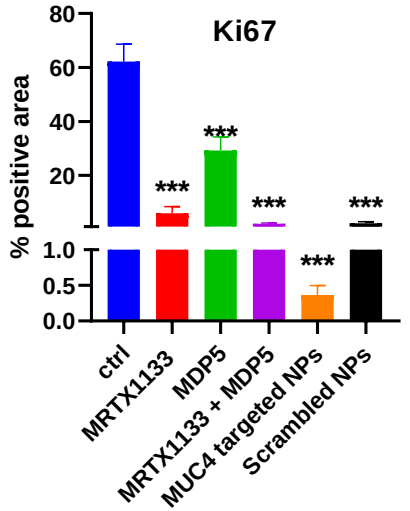



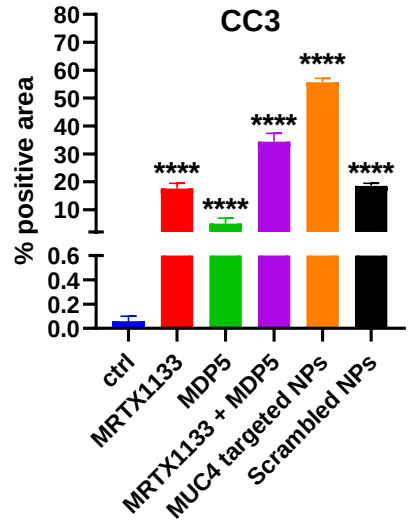



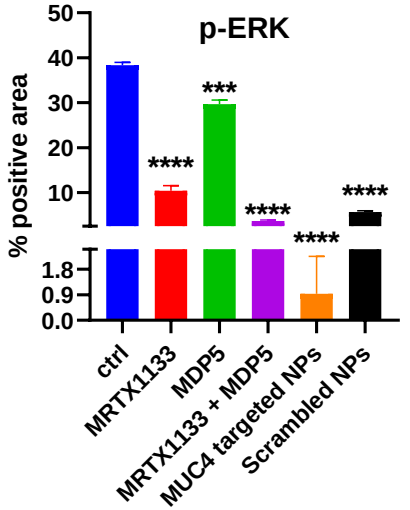



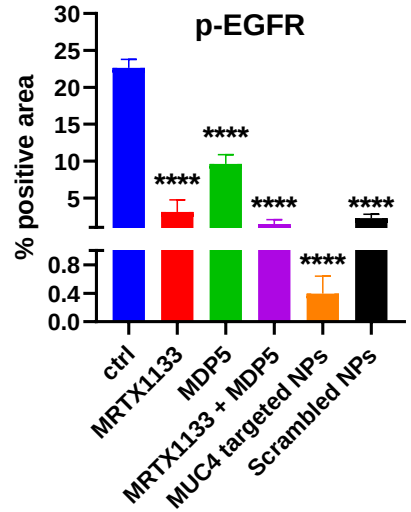
# Immunohistochemical analysis




MUC4-targeted nanoparticles suppress pancreatic tumor growth by inhibiting proliferation pathways and activating apoptosis, offering a promising multi-mechanistic therapy.

# Conclusion

- Combining MRTX1133 with MDP5 synergistically inhibits oncogenic signaling, induces apoptosis, and reverses immune evasion in KRASG12D-mutant pancreatic ductal adenocarcinoma.
- Nanoparticle-based co-delivery systems overcome pharmacological limitations, enhancing targeted therapy efficacy in solid tumors.
- MDP5 enhances the efficacy of MRTX1133, overcoming chemoresistance and reinforcing its therapeutic potential.
- These findings not only advance our mechanistic understanding of KRAS-driven PDAC but also provide a clinically actionable strategy to improve outcomes in this intractable disease.

# Future Directions

- Evaluate combination treatment impact on cancer stem cells and immune activation ($CD8^+$ T cells, TAMs, etc.).
- Overcome NSG model limitations by testing efficacy in syngeneic and GEMMs to capture immune dynamics and desmoplastic stroma.
- Conduct pharmacokinetic and biodistribution studies for these compounds.

## Acknowledgements

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Ajaykumar Chittipolu
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