Targeting Serpinb9 via Gemcitabine-based siRNA/drug Dual-Nanocarrier for Improved Pancreatic Cancer Therapy

Yiqing Mu[1,2], Haozhe Huang[1,2], Jingjing Sun[3] and Song Li[1,2]

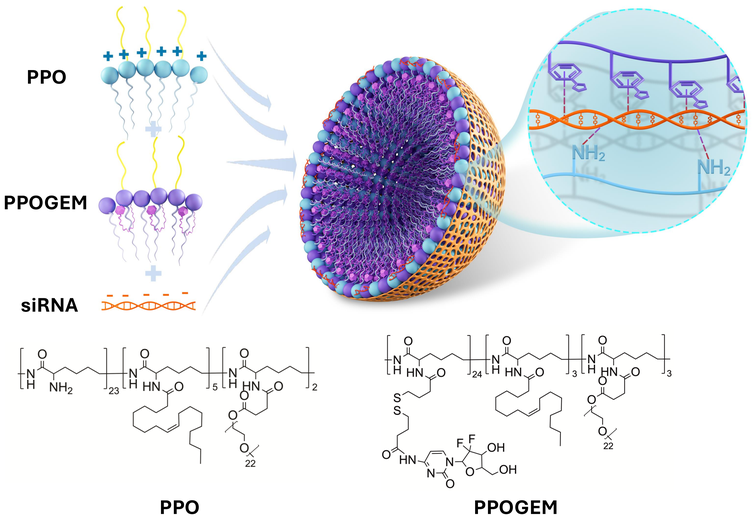
1. Center for Pharmacogenetics, Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA 15261, USA
2. UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA 15261, USA
3. Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE 68198, USA

INTRODUCTION

- SERPINB9 (SPB9), an endogenous inhibitor of granzyme B (GzmB), has emerged as a critical factor in the resistance to immunotherapy, attributed to its protective mechanism against GzmB-mediated killing of cancer cells. However, its role in chemosensitivity remains unknown.
- In this study, we show that gemcitabine (GEM) treatment leads to significant upregulation of SPB9 in vitro and in vivo. Interestingly, GEM also induces the expression of GzmB and knockout (KO) or knockdown (KD) of SPB9 results in enhanced response of tumor cells to GEM, suggesting a new role of GzmB/SPB9 axis in regulating chemosensitivity.
- To facilitate the therapeutic translation of these findings, we have engineered a 'POEM-like' nanocarrier that is highly effective in codelivery of built-in GEM and loaded SPB9 short interfering RNA (siSPB9). Codelivery of GEM and siSPB9 leads to significantly enhanced antitumor activity and improved tumor immune microenvironment in several pancreatic cancer models.

METHODS

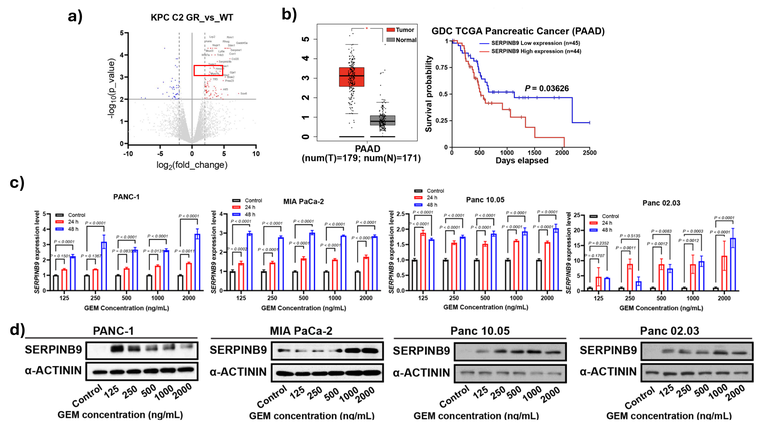
Design of the siRNA/drug Dual-Nanocarrier



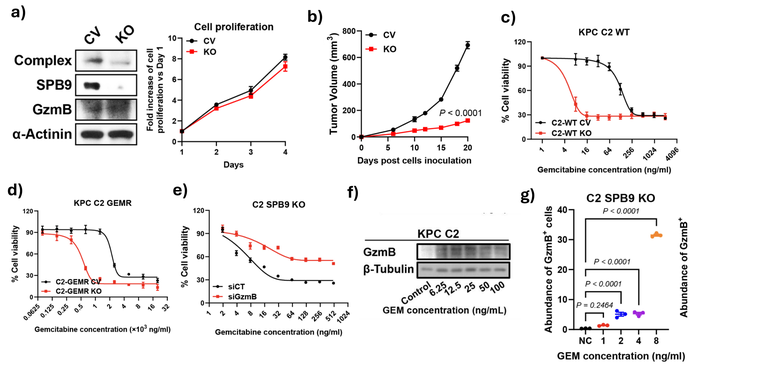
- Structure of synthesized polymer was confirmed by ^{1}H NMR.
- Bulk RNAseq
- qPCR, Western blot.
- CRISPR/Cas9 Genome Knockout
- MTT cytotoxicity assay.
- Near-infrared fluorescence optical imaging.
- In vivo therapeutic study.

RESULTS

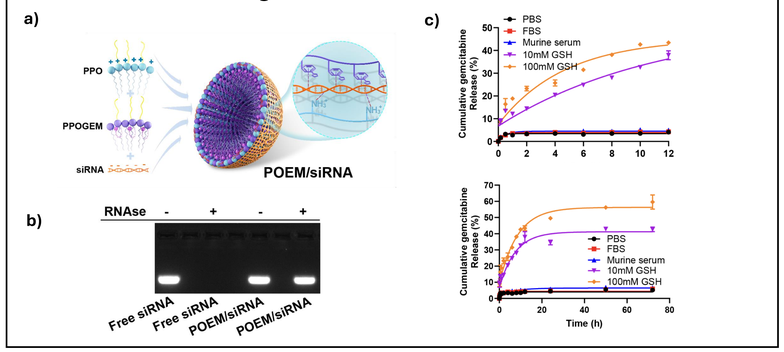
Gemcitabine induced the expression of SPB9 in pancreatic cancer



Disruption of SPB9 sensitized tumor to gemcitabine treatment through induction of GzmB

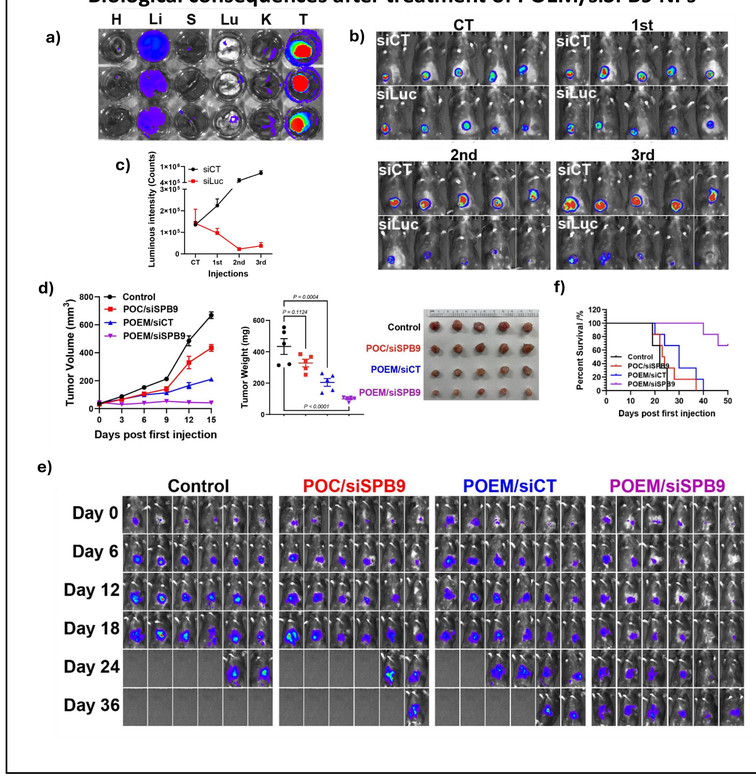


Development of POEM(PPO/PPOGEM) nanocarrier for co-delivery of gemcitabine and siSPB9



RESULTS, cont'd

Biological consequences after treatment of POEM/siSPB9 NPs



CONCLUSIONS

- SPB9, an endogenous inhibitor of GzmB, is induced following gemcitabine treatment in pancreatic cancer.
- SPB9 knockout or knockdown enhances gemcitabine sensitivity, highlighting its potential as a therapeutic target.
- Co-delivery of siSPB9 and gemcitabine via POEM nanoparticles significantly improved anti-tumor effects in multiple pancreatic cancer models. This suggests a promising combination treatment strategy for future pancreatic cancer therapies.

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