Nanoparticles-mediated codelivery of cell cycle blockers for the treatment of prostate cancer

Shichen Li[1,2], Shangyu Chen[1,2], Haozhe Huang[1,2], Wenxiao Zheng[3], Song Li[1,2] and Qiming Jane Wang[3]
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 Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15260, USA

INTRODUCTION

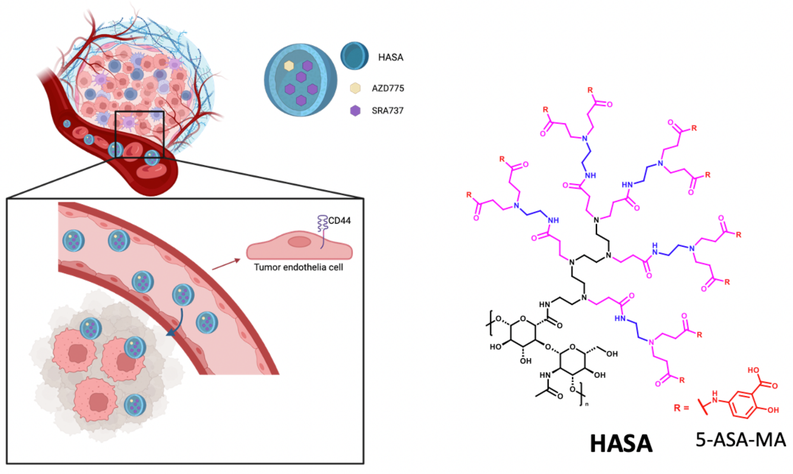
- Genomic alterations in tumor suppressor genes are common in prostate cancers, particularly in castration-resistant prostate cancer (CRPC), making them vulnerable to therapeutic strategies targeting the G2/M checkpoint, a critical regulator of cell cycle progression.
- This checkpoint is primarily controlled by the ATR/CHK1/WEE1 tri-kinase pathway, and co-inhibition of WEE1 and CHK1 has emerged as a promising approach to induce mitotic catastrophe in CRPC cells.
- However, the clinical translation of this strategy is limited by low efficacy and toxicity, highlighting a need of strategy to overcome these limitations.
- To address this, we developed a CD44-targeted hyaluronic acid-stearic acid (HASA) nanoparticle capable of co-delivering the CHK1 inhibitor SRA737 and the WEE1 inhibitor AZD1775, enabling synergistic G2/M checkpoint abrogation while reducing systemic toxicity.
- This nanocarrier exhibits high tumor selectivity via CD44 targeting and significantly enhances antitumor efficacy in prostate cancer models, providing a compelling therapeutic strategy for overcoming resistance and improving outcomes in CRPC.

METHODS

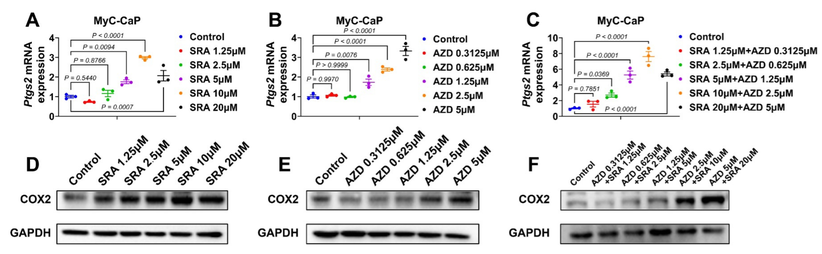
- A CD44-targeted nanocarrier was developed using hyaluronic acid (HA) conjugated with 5-aminosalicylic acid (5-ASA), a COX inhibitor, for the co-delivery of:
  - SRA737 (CHK1 inhibitor)
  - AZD1775 (WEE1 inhibitor)
- Various molecular weights of HA and different chemical conjugation strategies were screened to optimize tumor targeting through CD44.
- A CD44 knockout (KO) cancer cell line was generated to assess targeting specificity.
- In vitro uptake and in vivo biodistribution studies were performed using both wild-type and CD44 KO cells to evaluate the CD44-dependent targeting of HASA.
- The optimal synergistic ratio of SRA737 and AZD1775 was determined using MTT assays.
- The induction of COX by SRA737 and AZD1775 was evaluated at both:
  - mRNA level (e.g., RT-qPCR)
  - protein level (e.g., Western blot)
- The anti-tumor efficacy of the combination therapy was assessed in a mouse tumor model.

RESULTS

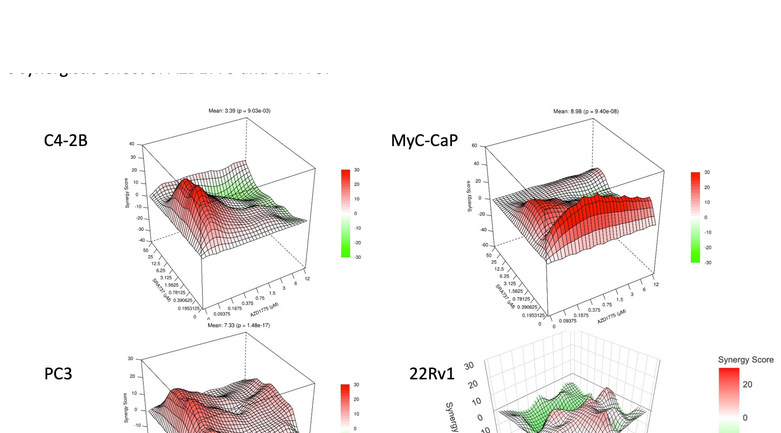
Design of the novel therapy



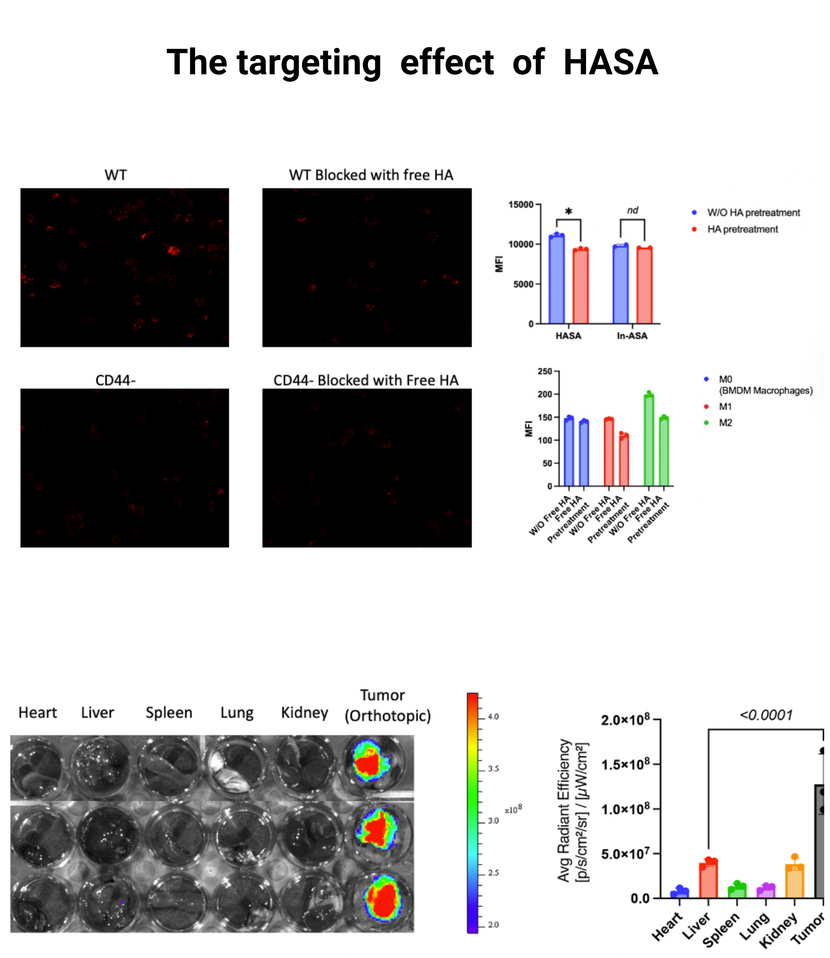
COX-2 induced by chemotherapeutic agents



The synergistic effect of Cell cycle check points inhibitors

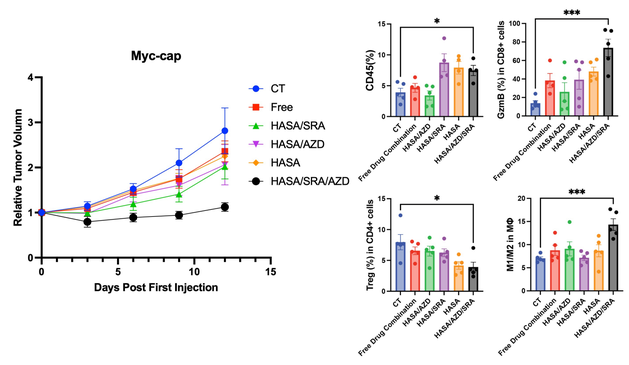


The targeting effect of HASA



RESULTS

In vivo therapeutic effect and impact on immune microenvironment



CONCLUSION

- SRA737 and AZD1775 were readily co-loaded into HASA nanoparticles, which had a uniform particle size of approximately 120 nm and demonstrated high drug loading efficiency (>80%) for both agents.
- Ex vivo biodistribution and fluorescence imaging confirmed efficient tumor targeting and deep tumor penetration by HASA. Furthermore, MTT assays demonstrated that co-delivery of SRA737 and AZD1775 via HASA nanoparticles resulted in synergistic cytotoxicity.
- Systemic delivery of the combination therapy using HASA significantly enhanced antitumor efficacy in a murine prostate cancer model. These results support the potential of CHK1/WEE1 co-inhibition via CD44-targeted nanocarriers as a promising therapeutic strategy to improve outcomes and reduce toxicity in CRPC treatment.

ACKNOWLEDGEMENTS

This work was supported by NIH Grants No. R01CA219399 and R01CA223788.