Nanoparticles-Mediated Inhibition of DPP4 for Improved Cancer Immunochemotherapy

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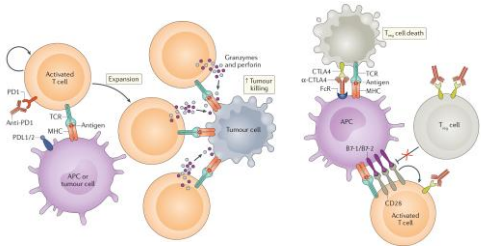
University of Pittsburgh
School of Pharmacy

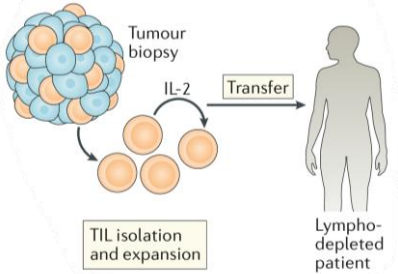
NEXT-GENERATION DELIVERY INNOVATIONS

Chemokine in Immunotherapy

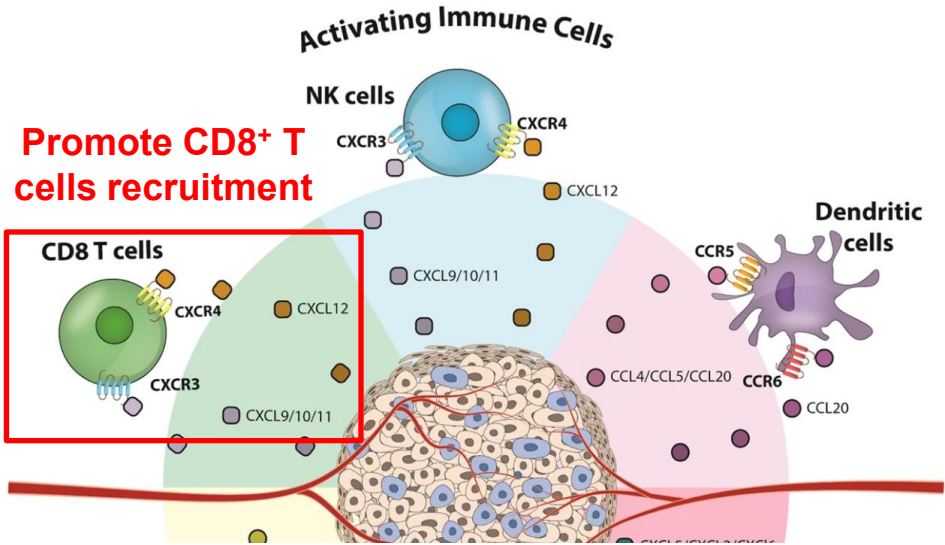
Checkpoint blockade



Adoptive T-cell therapy



Chemokine-guided migration (e.g., **CXCL10**)



Emerging immunotherapeutic strategies:

1. Checkpoint blockade
2. Adoptive T-cell therapy
3. Cytokine-based therapy
4. Combination therapies
5. …

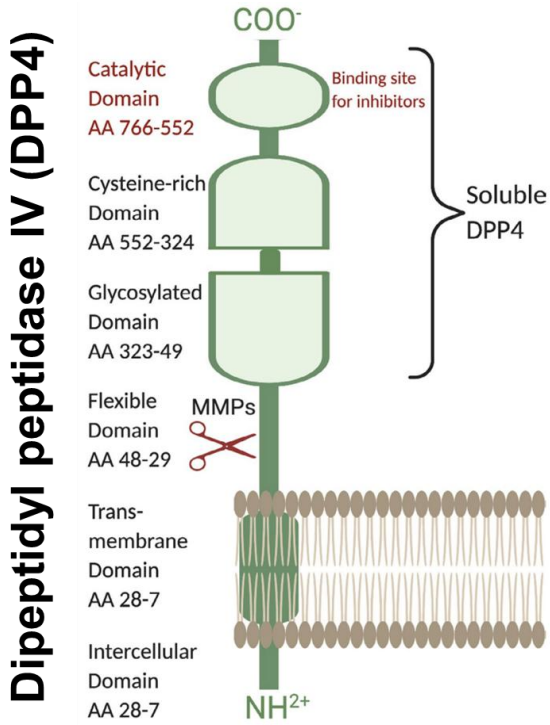
Effector T cells infiltration → **Tumor killing**

Cancer Gene Therapy 29 (**2022**) 10-21.

Immunotherapy harnesses the power of the immune system to fight cancer

Limitations

The degradation of T-cell-recruiting chemokines (CXCL10) by **dipeptidyl peptidase IV** (**DPP4**)



DPP4 (CD26)

- Widely distributed
- 110 kDa **membrane-anchored** glycoprotein
- **Removes first two amino acids** from proteins with proline/alanine in second N-terminal position

Pharmacology & Therapeutics 198 (**2019**) 135–159.
Experimental Dermatology 30 (**2021**), 304-318.
Science 381, 501 (**2023**), eadd5787.

Challenges & Hypothesis

1. Systemic DPP4 inhibition (**DPP4i**) may cause off-target effects.

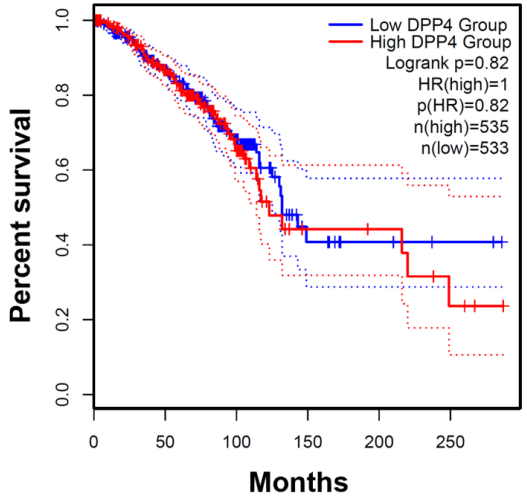
2. The interplay between **DPP4** and **chemotherapy** remains largely unexplored.

Chemotherapy + DPP4i = Synergy

DPP4 inhibitor (DPP4i, e.g., FDA-approved Sitagliptin)

GEPIA2 Data—Clinical Prognosis

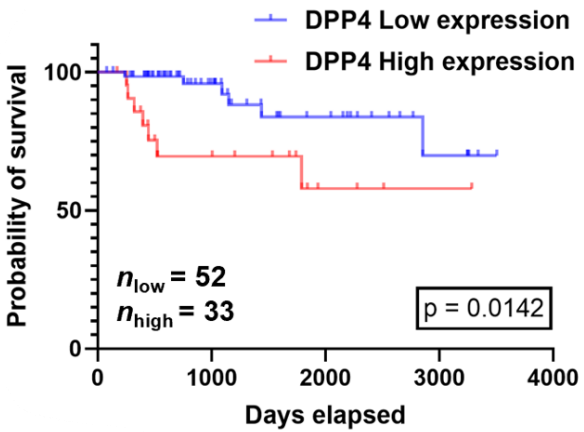
BRCA



No significance

Unpublished data

BRCA-TNBC-Chemo



Patient cohorts **receiving chemotherapy**

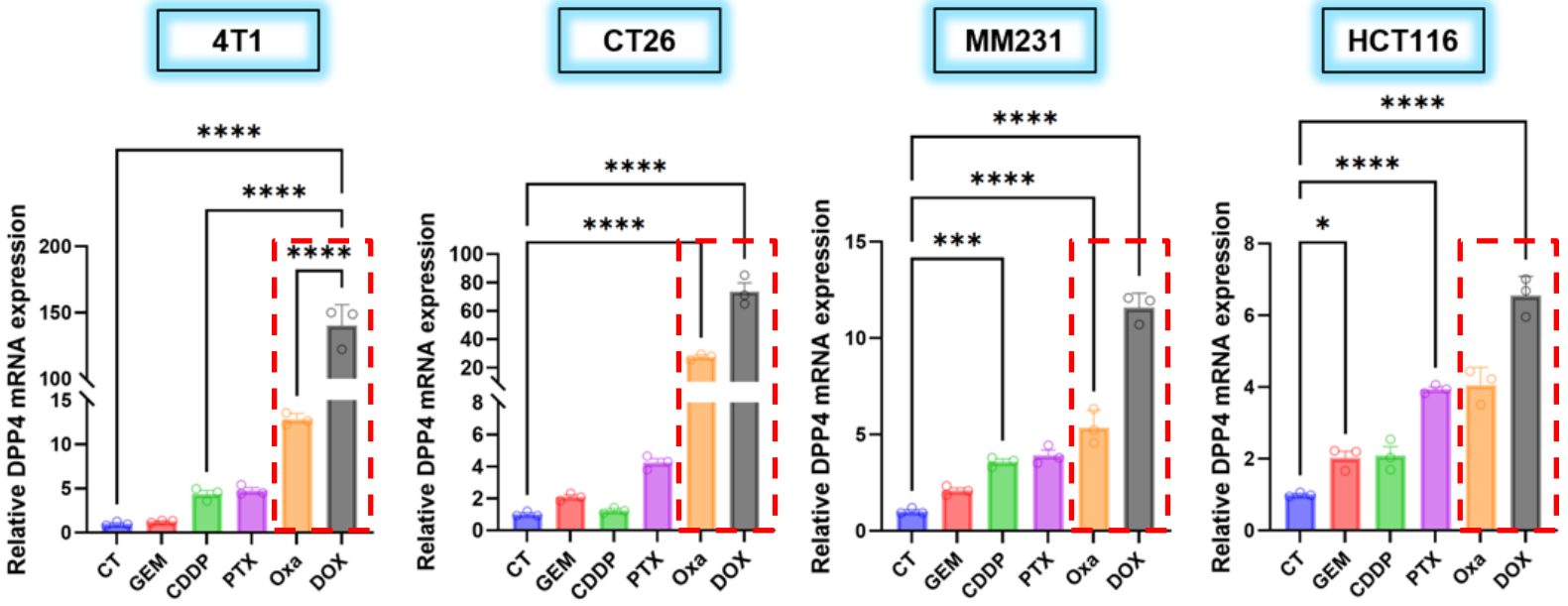
High DPP4 → **Poorer prognosis**

Clinical relevance of DPP4 in chemotherapy

Unpublished data

BRCA: Breast cancer
COAD: Colon adenocarcinoma

DPP4 Induction by Chemodrugs

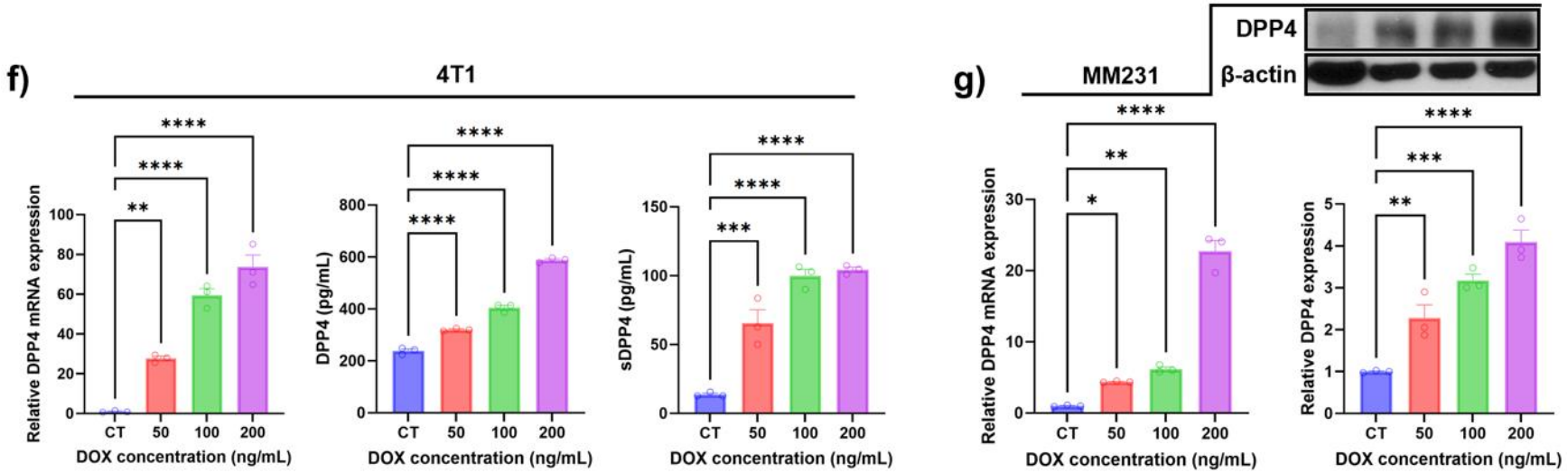


A **negative feedback mechanism** to limit the level of **CXCL10**

Immunogenic cell death (**ICD**) inducer (e.g., Doxrubicin (**DOX**))

Unpublished data

DPP4 Induction by DOX



DPP4 was **induced by DOX** at both mRNA and protein levels

Unpublished data

Aims

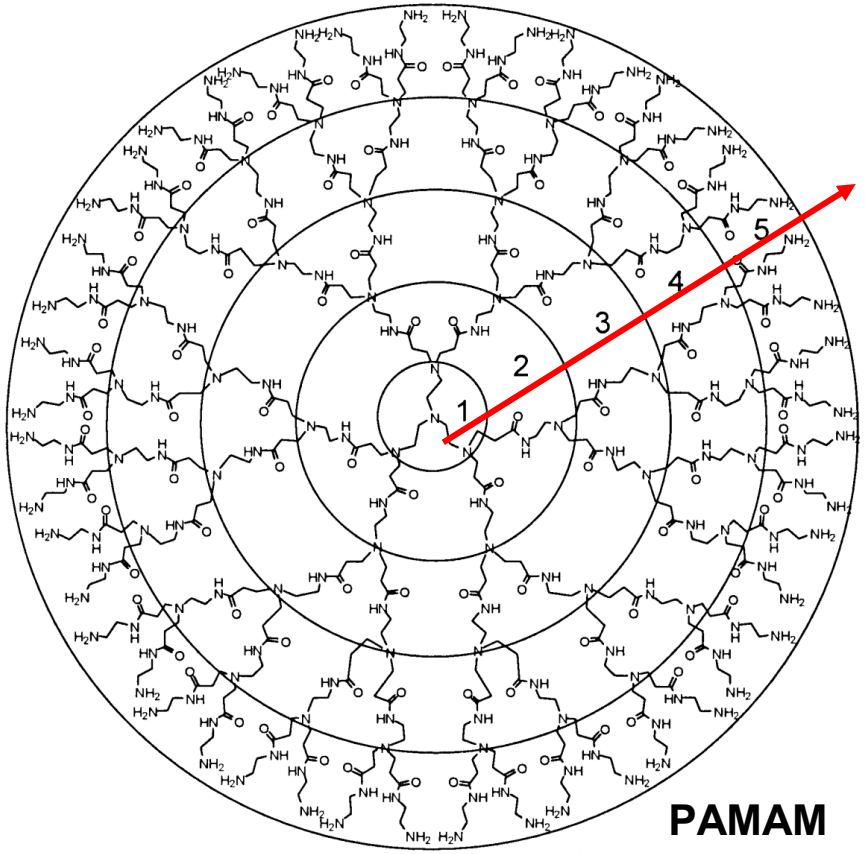
Aim 1: To construct a nanocarrier for the **efficient and targeted codelivery of chemodrug and DPP4i** specifically to tumor tissues.

Aim 2: To evaluate whether this combination strategy can **improve anti-tumor efficacy**.

Dendrimer_Drug Delivery

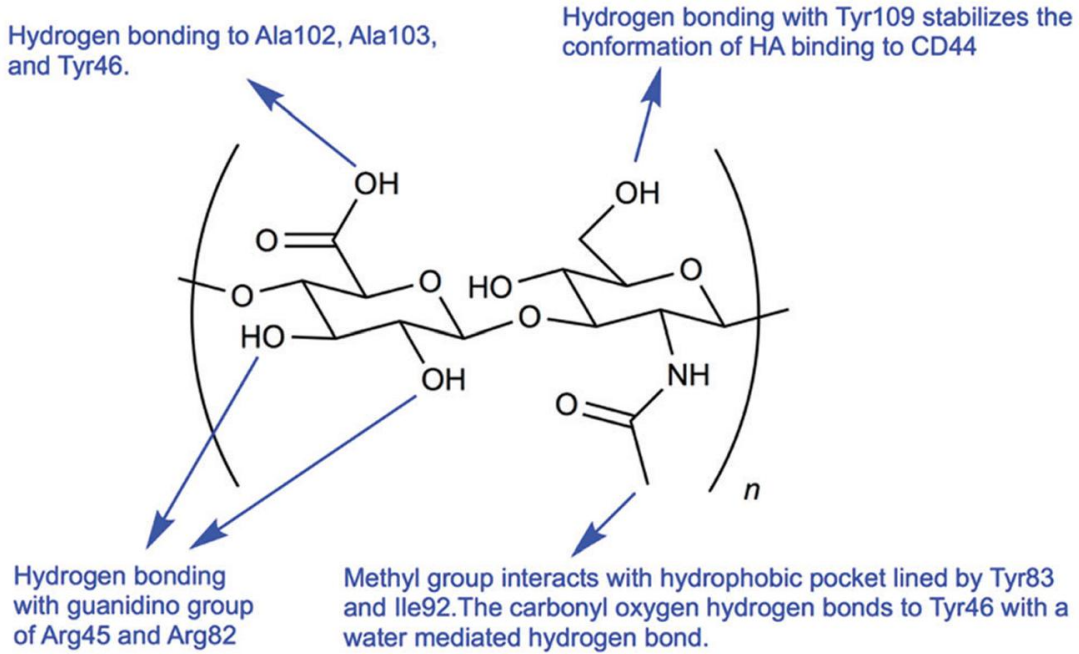
PAMAM

- A mix of polyamides and amines
- Biodegradable
- Highly branched
- Efficient drug & gene delivery



PAMAM

Hyaluronic Acid (HA)_Tumor Targeting



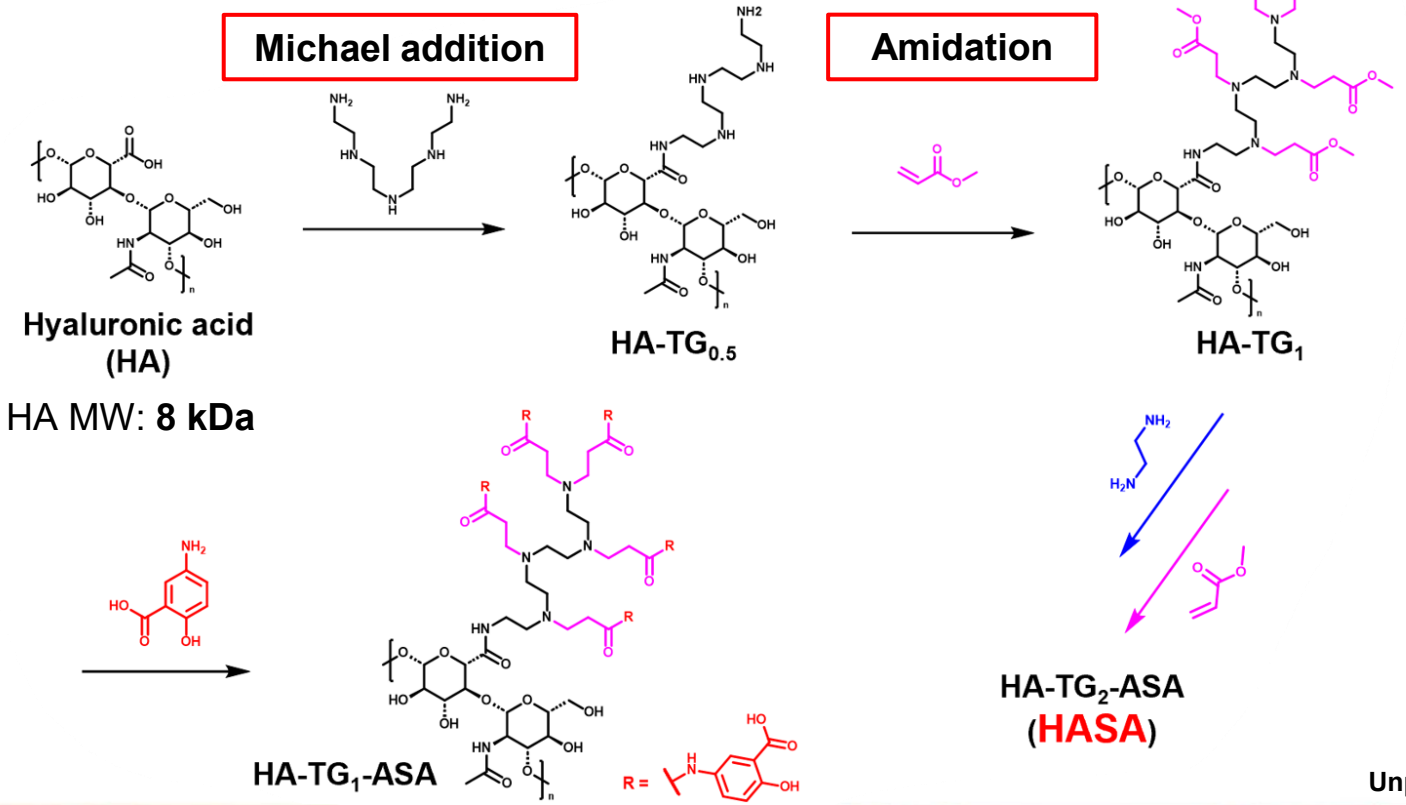
J. Mater.Chem. B, 5 (**2017**) 8183.

Hyaluronic acid (HA)

- Biocompatible & biodegradable
- CD44 targeting
- **Tumor-specific delivery**

(**CD44** is overexpressed in both **tumor endothelial cells** and **tumor cells**.)

Synthesis of HA-based Dendrimer



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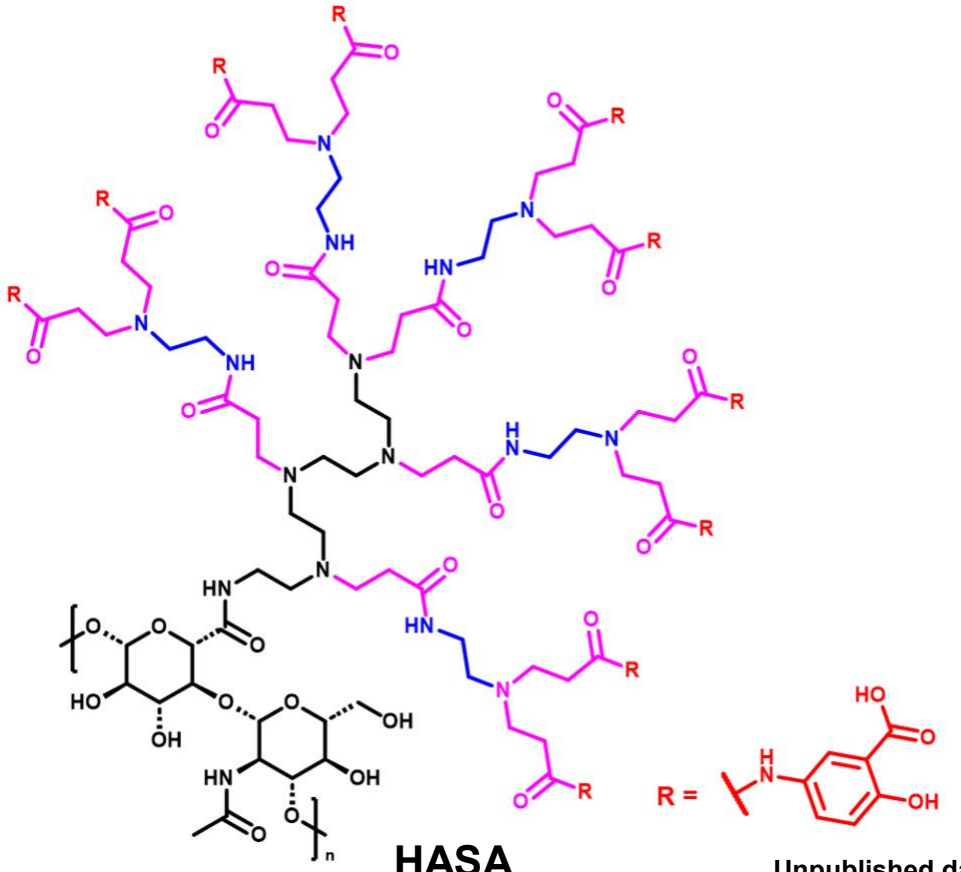
Structure of HASA

Second-generation_HASA

- CD44-mediated tumor targeting
- Improved drug loading capacity and stability in circulation

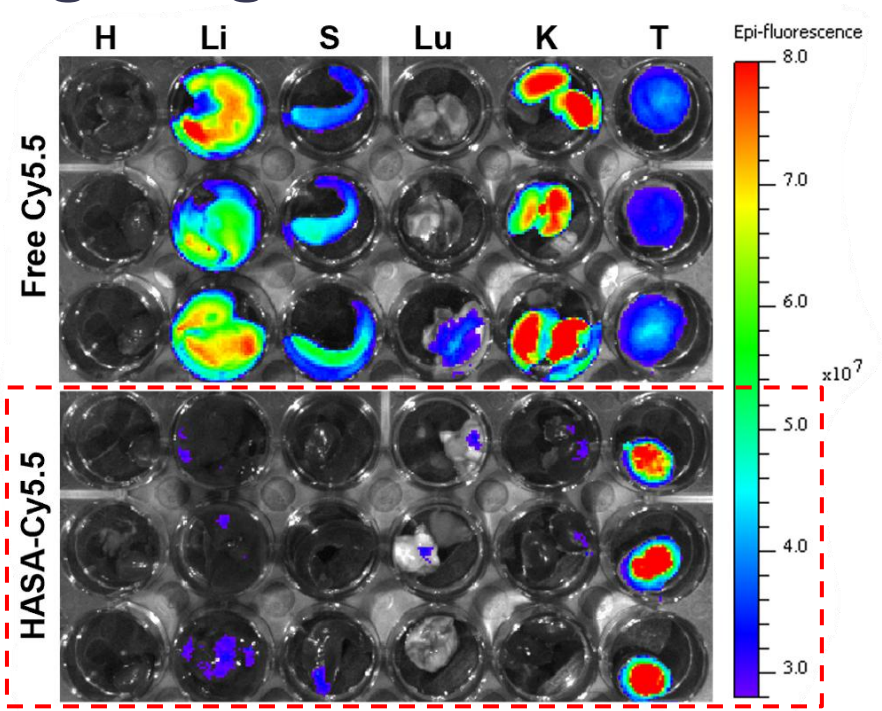


HASA

Unpublished data

IVIS_Tumor Targeting

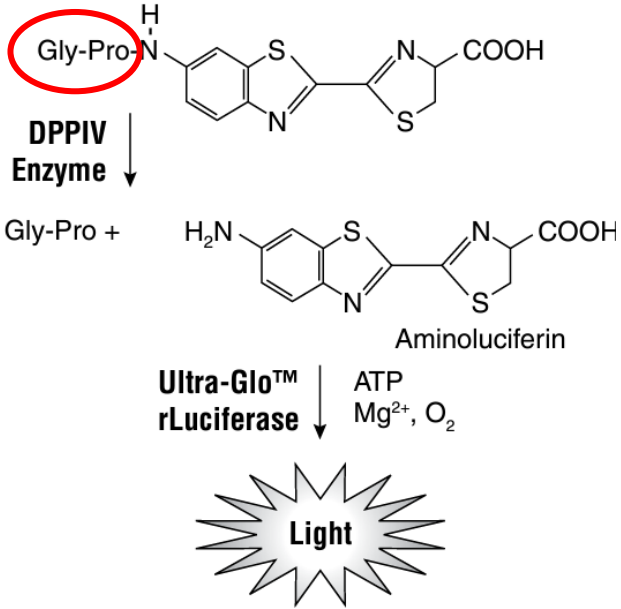
H: Heart
Li: Liver
S: Spleen
Lu: Lung
K: Kidney
T: Tumor



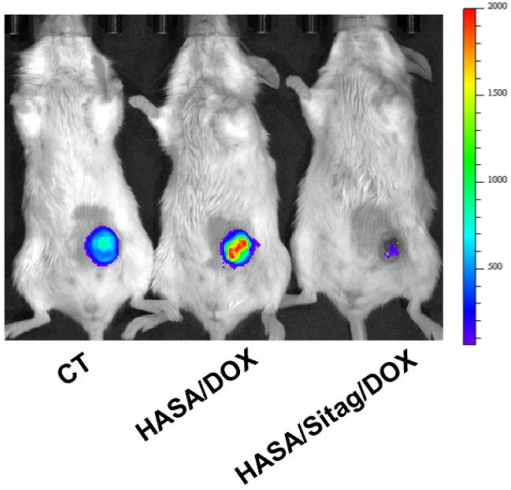
HASA was **stable and highly effective** in targeting tumor tissues

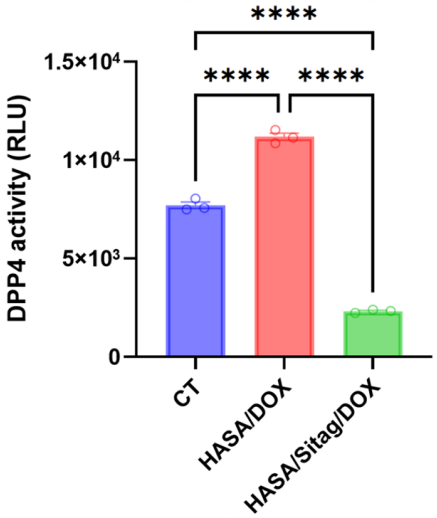
Unpublished data

In vivo DPP4 Activity



Gly-Pro-aminoluciferin imaging

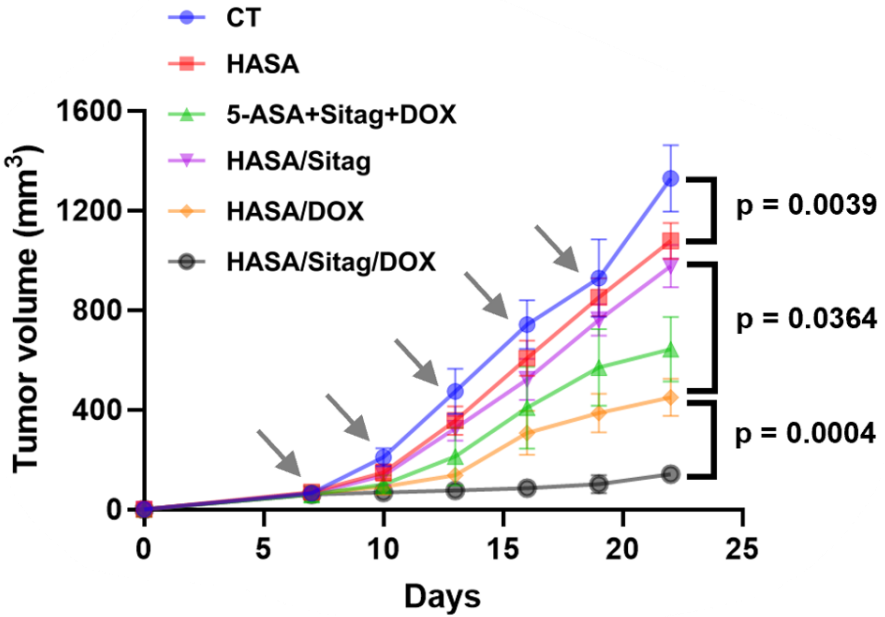


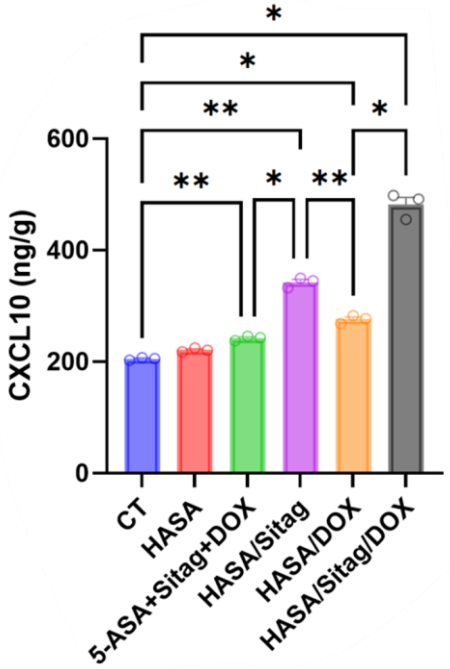


Both **basal** and **DOX-induced** DPP4 activity can be inhibited

Unpublished data

Anti-Tumor Efficacy



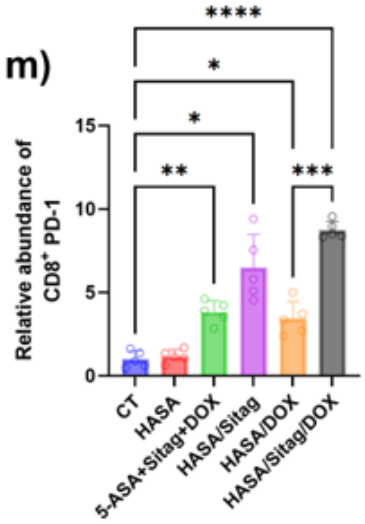


Increased CXCL10 levels and enhanced anti-tumor efficacy

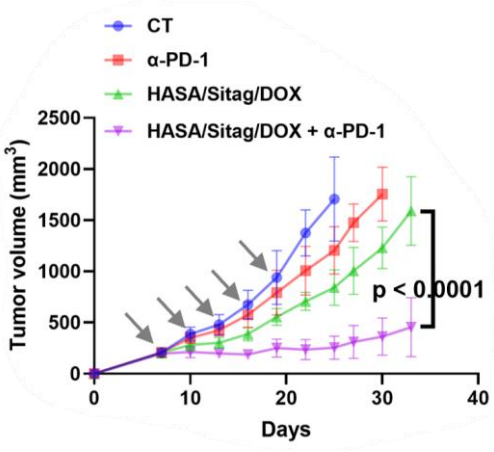
Unpublished data

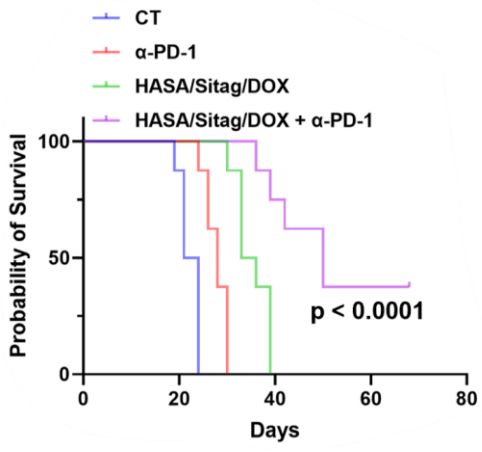
Synergy with Immune Checkpoint Blockade

Upregulated PD-1 on CD8⁺ T cells



Improved anti-tumor activity/survival

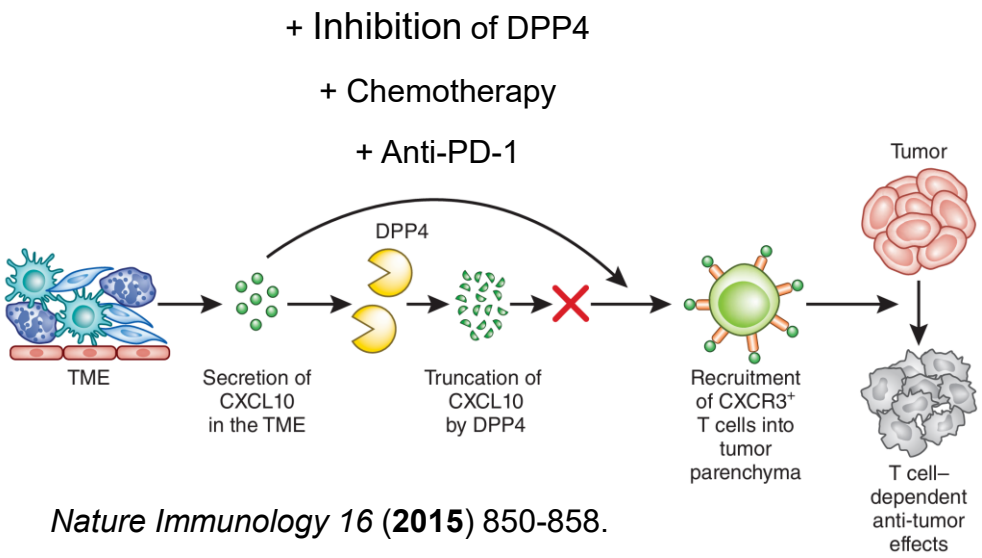




Anti-PD-1 therapy further improves the outcome of treatment

Unpublished data

Summary of Findings



Nature Immunology 16 (**2015**) 850-858.

- DPP4 **limits T-cell infiltration** by degrading CXCL10.
- Chemotherapy (e.g., **DOX**) induces DPP4 expression.
- Our **CD44-targeted nanocarrier** (HASA) enables co-delivery of chemodrug and DPP4i.
- Triple therapy (**DOX** + **DPP4i** + **anti-PD-1**) greatly improves anti-tumor efficacy.

A promising strategy for improving immunochemotherapy

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