Targeted chemoradiotherapy of prostate cancer using gold nanoclusters with protease activatable monomethyl auristatin E

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Advanced Delivery Science

Prostate Cancer

1 in **9** American men will have prostate cancer during his life

No.1 most commonly diagnosed cancer for men (268, 490 estimated new cases in 2022)

nearly **3.1** million American men living with prostate cancer

No.2 #2 leading cause of cancer death among American men (34, 500 estimated death in 2022)

Treatment Options

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Localized Prostate Cancer

The cancer is only inside the prostate (78%).

High-risk Localized Prostate Cancer

The cancer has started to break out of the prostate or has spread to the area just out of it (15%).

Metastatic Prostate Cancer

The cancer has spread from the prostate to other parts of the body (7%).

Active Surveillance

Metastatic cancer may develop and curative treatment may not be an option

Radical Prostatectomy

About 48% have residual tumor (about half of these will develop biochemical or clinical recurrence). Side effects include infertility, erectile dysfunction, and urinary incontinence.

Radiotherapy

Tumor recurrence rate is high (>35). Side effects include infertility, erectile dysfunction, urinary incontinence and bowel problems.

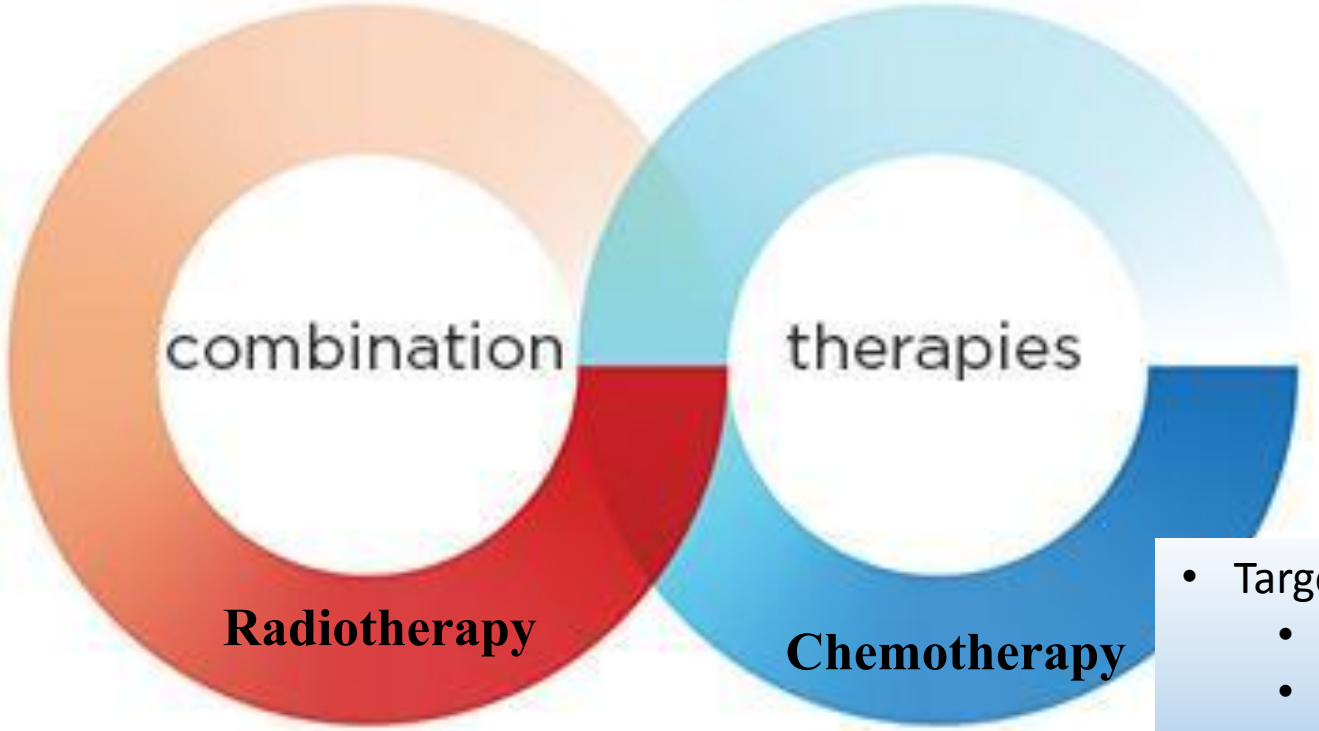
Hormone Therapy

Side effects include hot flashes, sexual dysfunction and skeletal mobility. All patients will ultimately develop resistance.

Chemotherapy

Usage is limited by severe toxicity and development of drug resistance.

Our Approach-combination therapy



- Targeted Nanotechnology
  - Radiosensitizer
  - Drug delivery
    - Chemotherapy
    - Radiosensitizer

- Synergistic effect
- overcome chemo-resistance

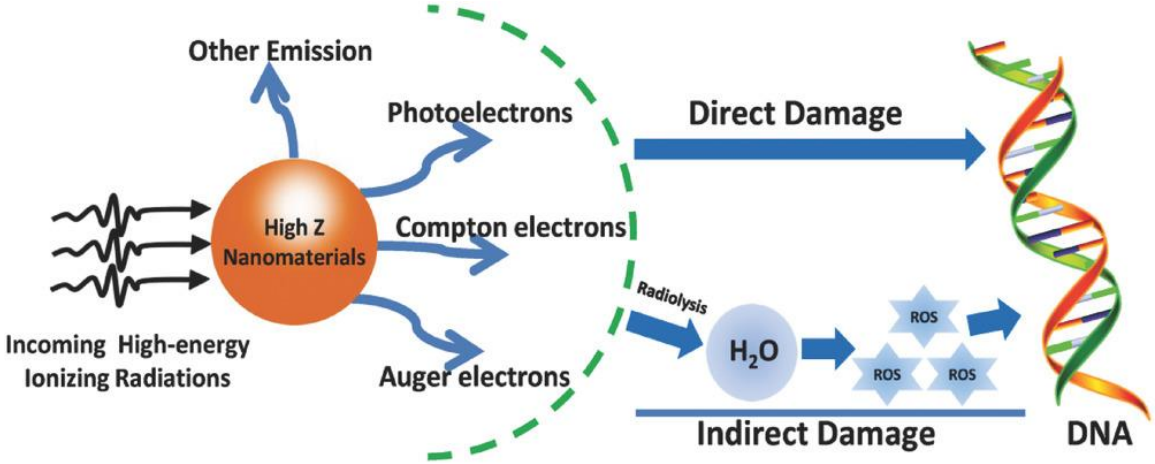
- Off-target toxicity
- Separate drug administration

Radiosensitizers

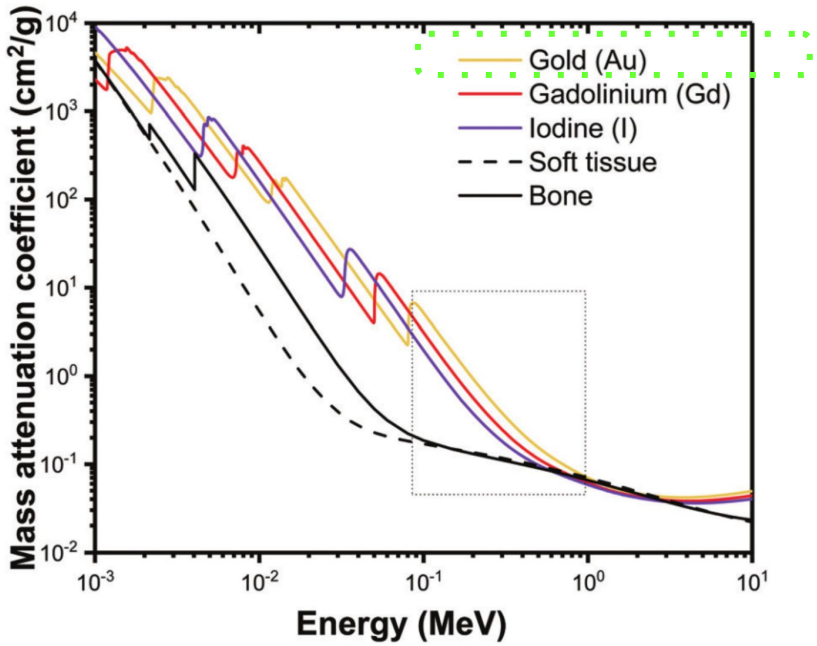
Radiosensitizer: compounds that increase the cytotoxicity of ionizing radiation

Heavy-metal nanomaterials with high atomic number (Z) values

absorb, scatter, and emit radiation energy



Xie, J. et al. *Adv. Mater.* 2019, 31, 1802244



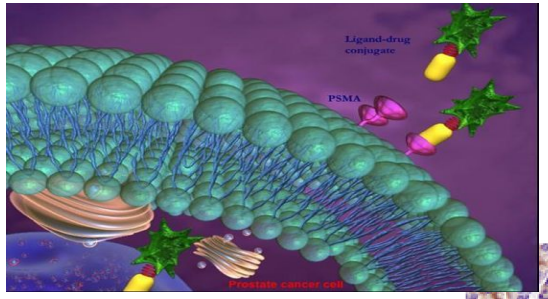
Goswami, N. et al. *Mater. Horiz.* 2017, 4, 817-831

Need to deposit the High Z nanomaterials efficiently to tumor !

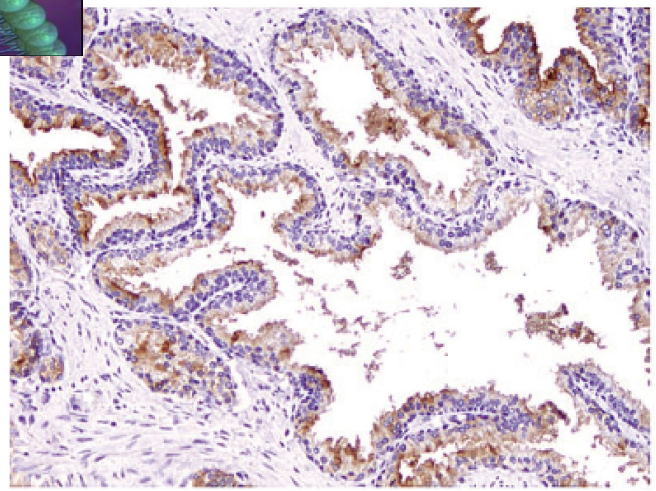
Targeting

Prostate Specific Membrane Antigen (PSMA)

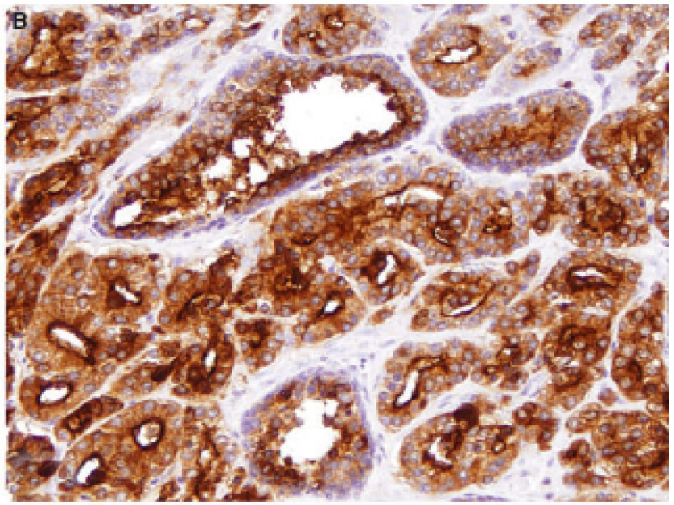
Expression of Prostate Specific Membrane Antigen (PSMA)



Benign prostate hyperplasia (BPH)

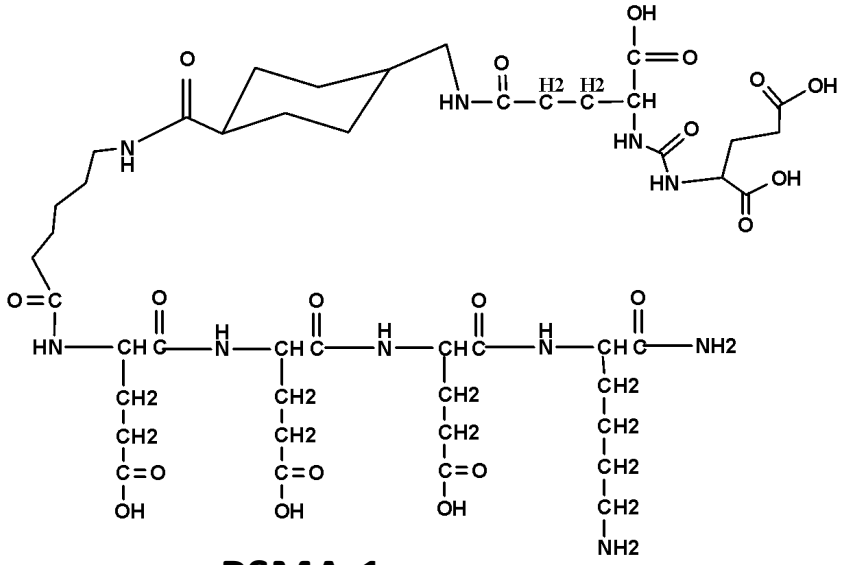


Prostate cancer



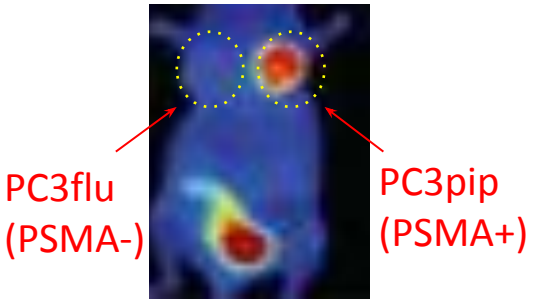
Mhawech-Fauceglia P, Zhang S, Terracciano L et al, *Histopathology*, 2007, 50, 472-483.

PSMA targeted ligand and nanoclusters

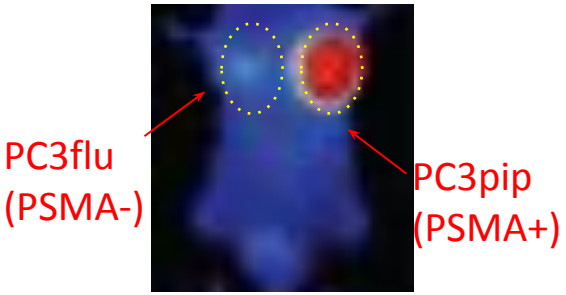


PSMA-1

IC_{50}=2.30 nM

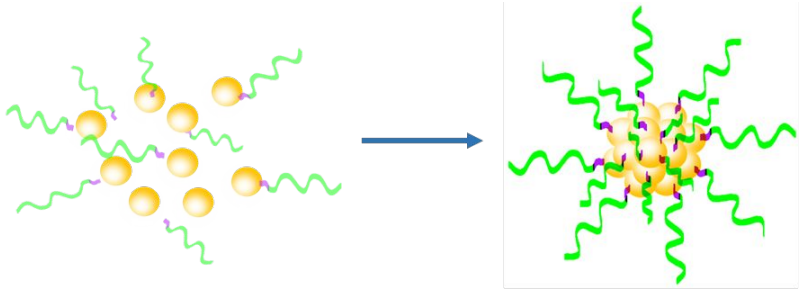


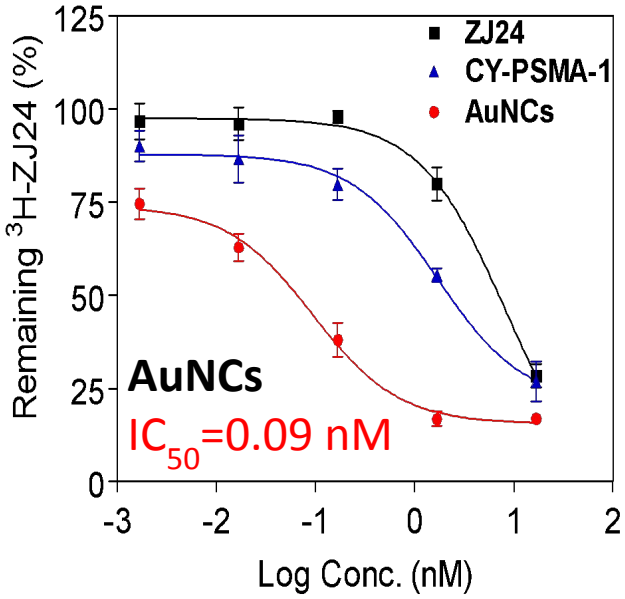
PSMA-1-IR800



PSMA-1-Cy5.5

Wang X., et al. *Mol Cancer Ther*, 2014, 13, 2595.





Luo, D., et al. *Small*, 2019, 15, 1900968.

AuNCs-MMAE for chemoradiotherapy

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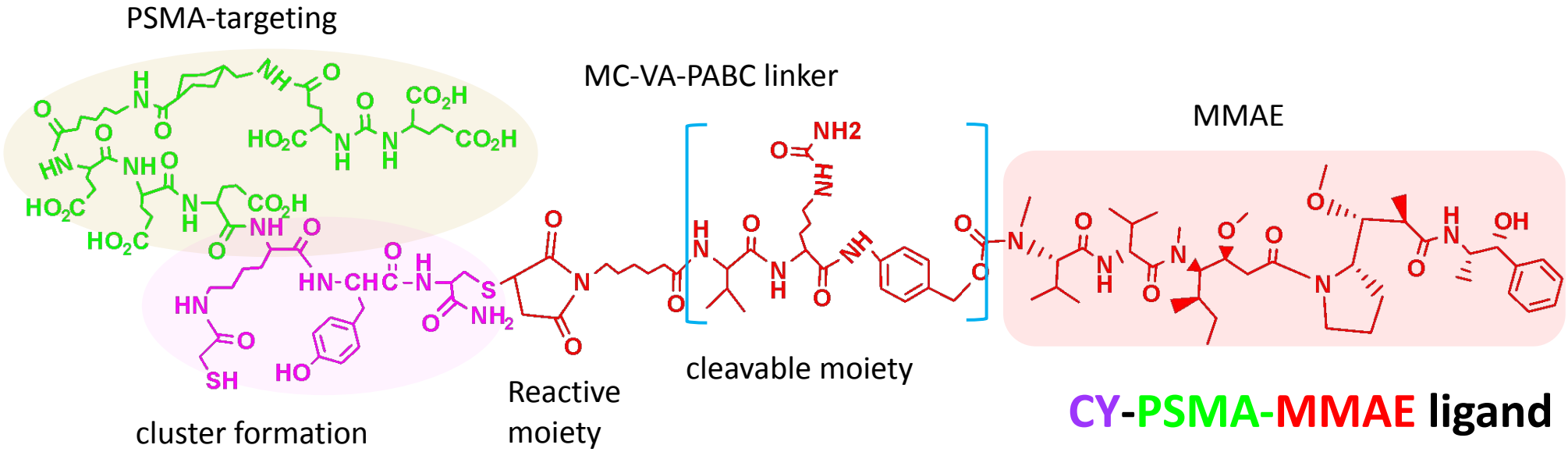
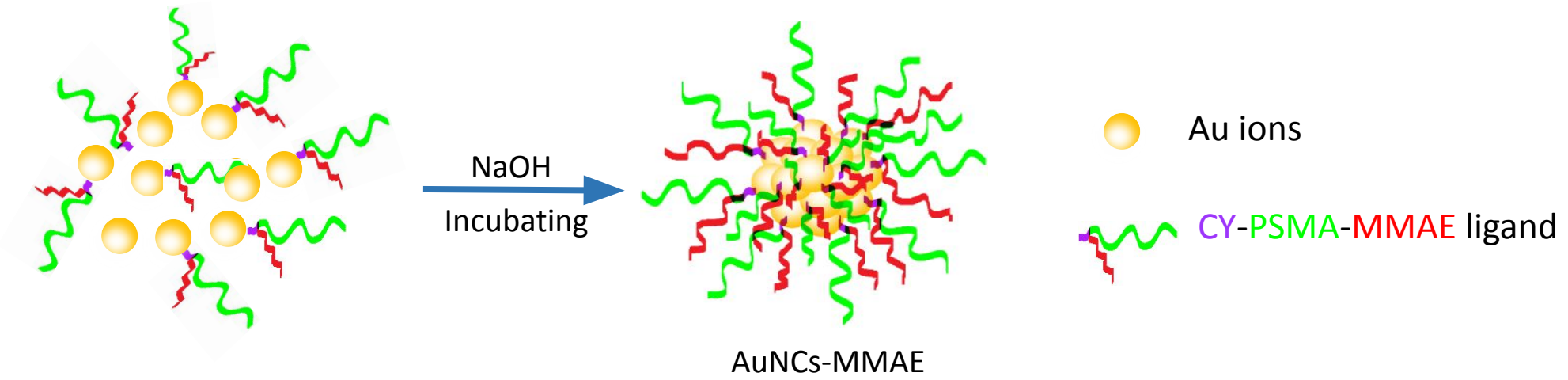
Molecule structure



Nano structure



MMAE release and *in vitro* uptake

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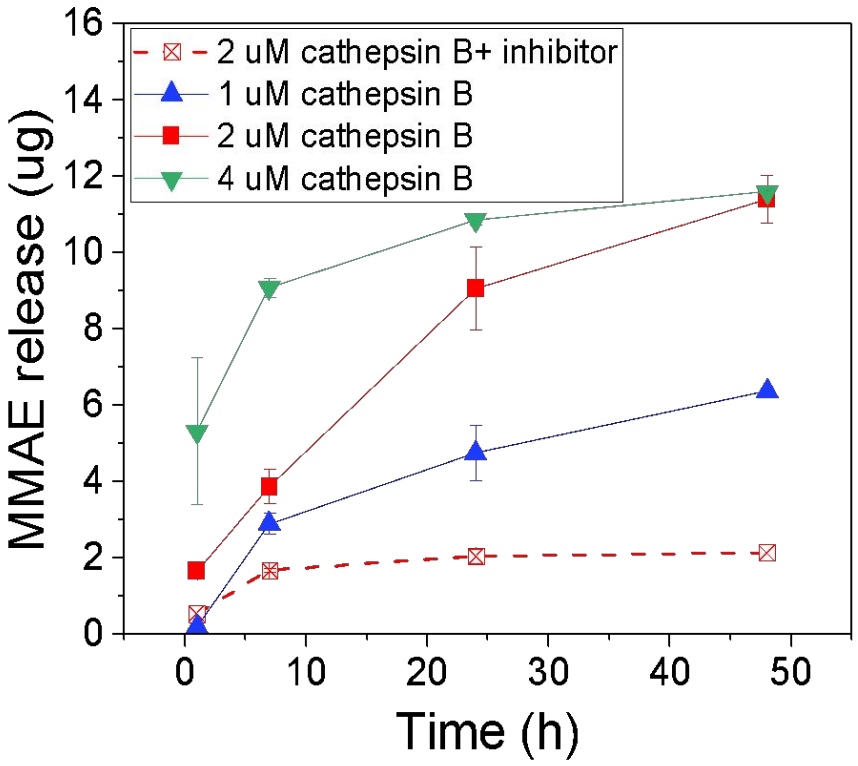
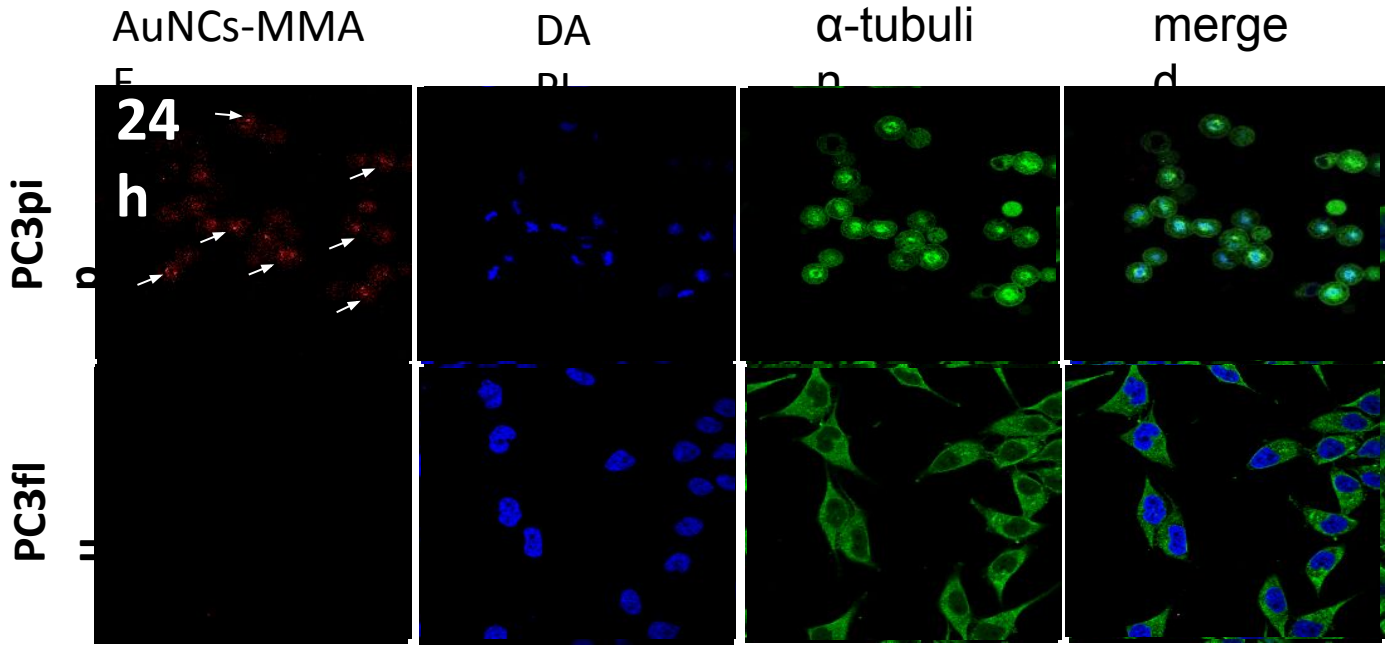
Cathepsin activated MMAE release



Selective uptake and chemotherapy *in vitro*



MMAE is delivered as a prodrug: If synthesized with a non-cleavable linker there is no effect

In vivo tumor targeting

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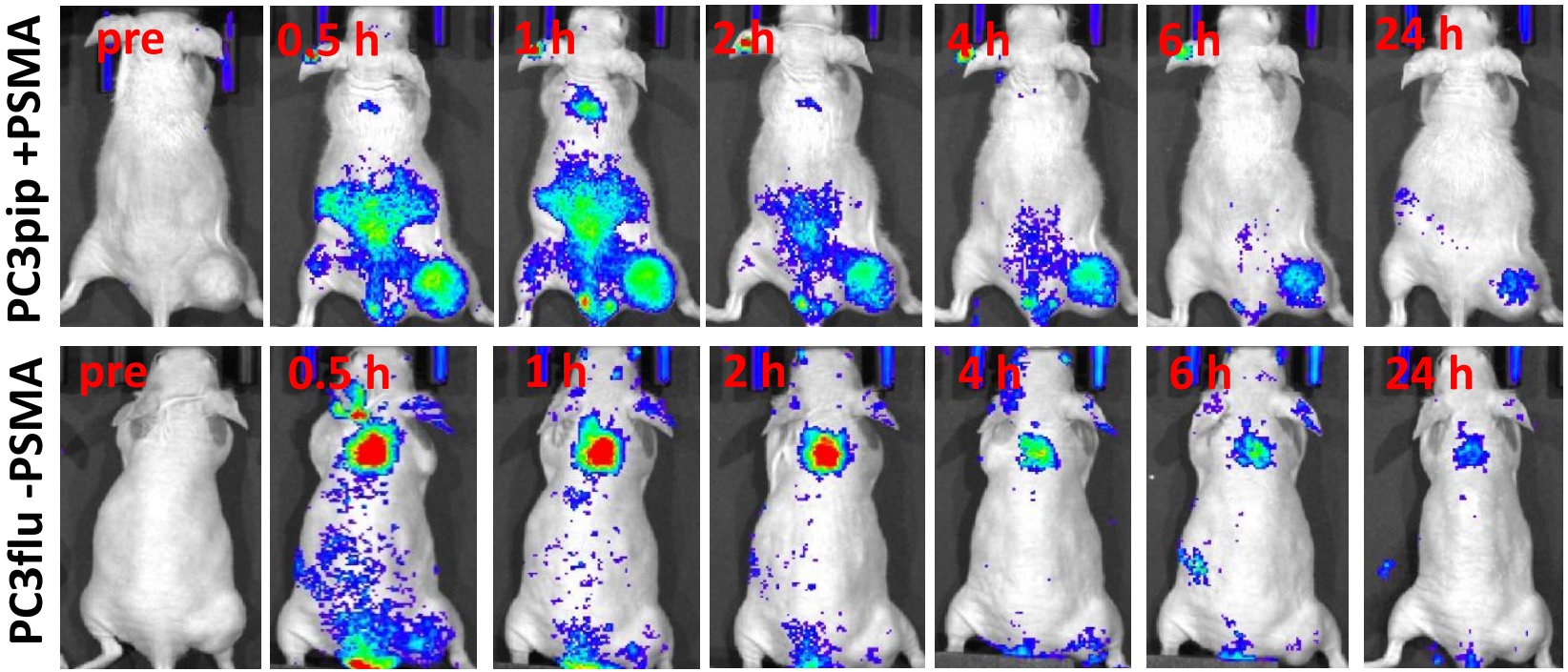
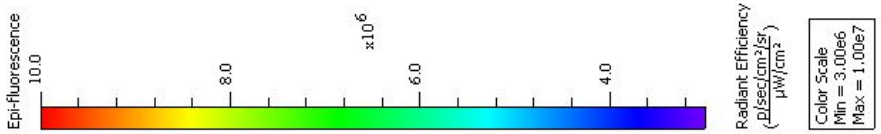
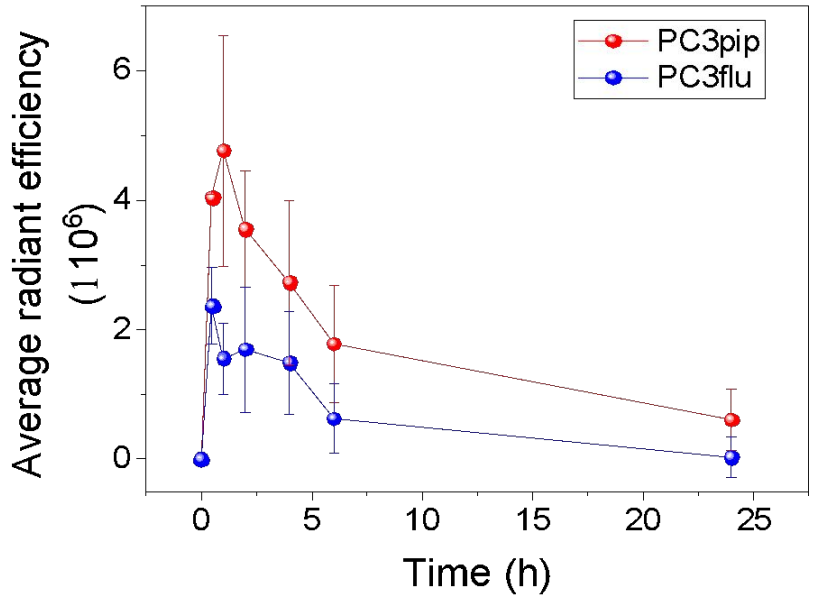
Selective to tumor



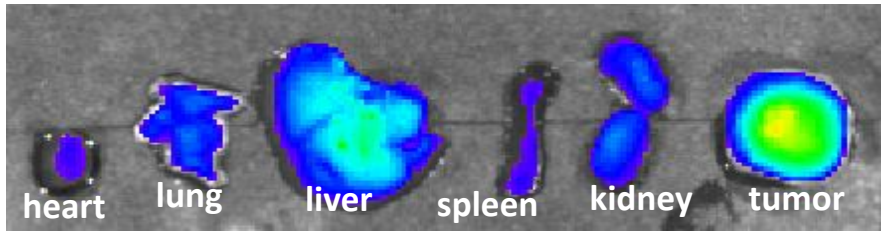


Fluorescence signal of tumor

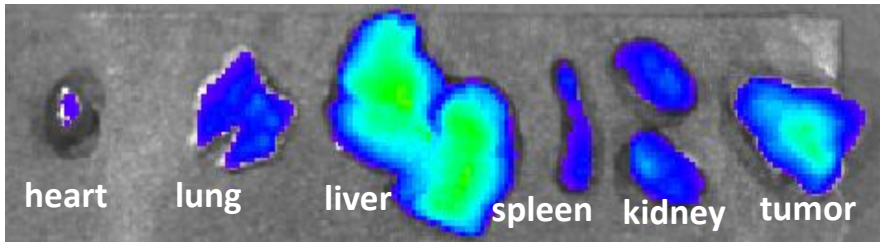


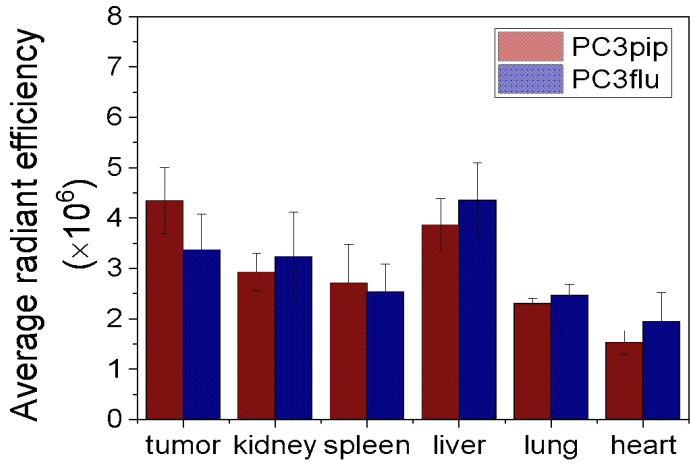
Biodistribution and clearance

Mouse with PC3pip tumor



Mouse with PC3flu tumor





AuNCs in urine

In vivo chemoradiotherapy

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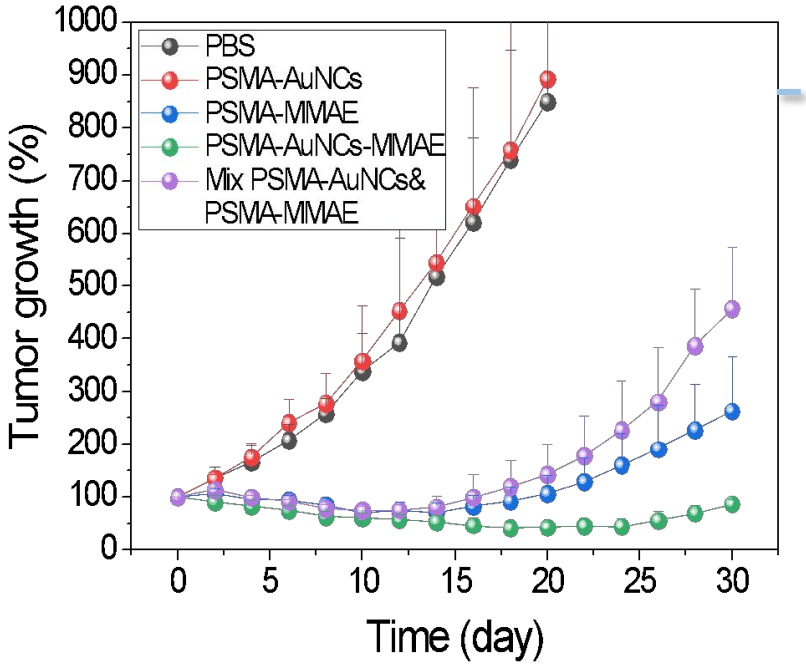
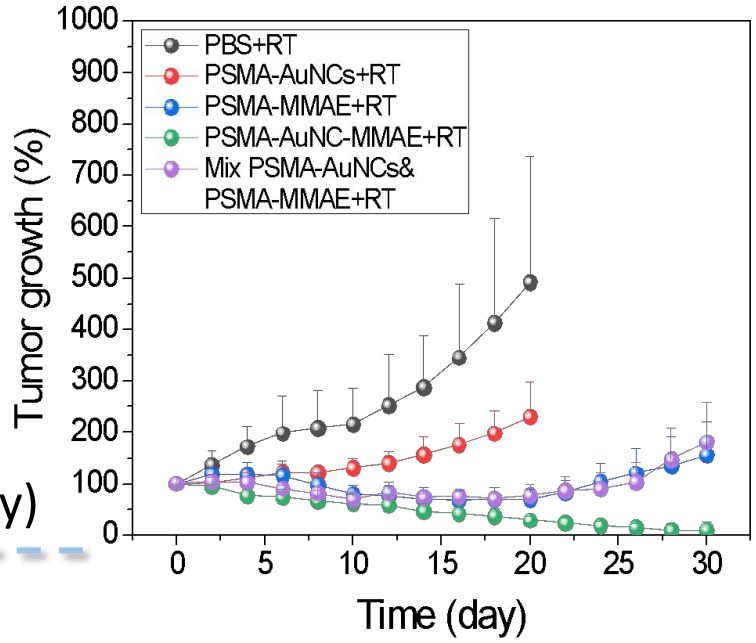
Tumor growth kinetics

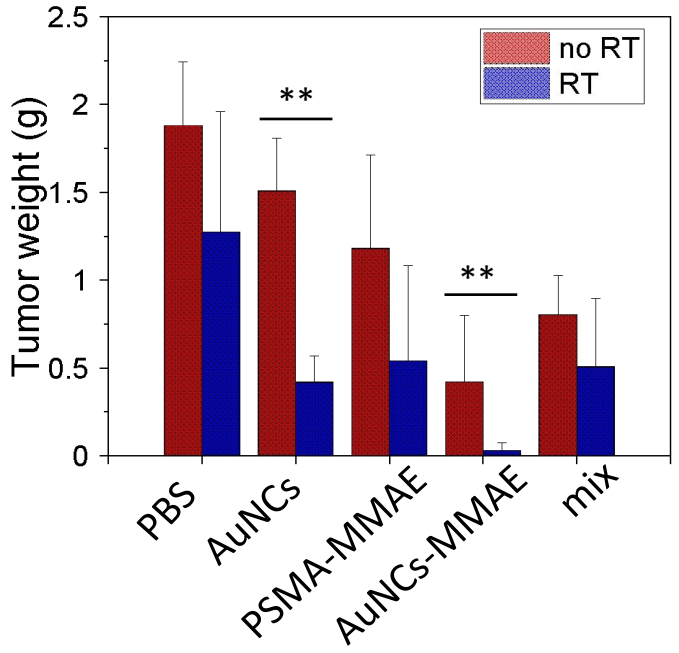
With no radiation



With radiation (6 Gy)



Tumor weight
at end of observation



Tumor staining – with radiation

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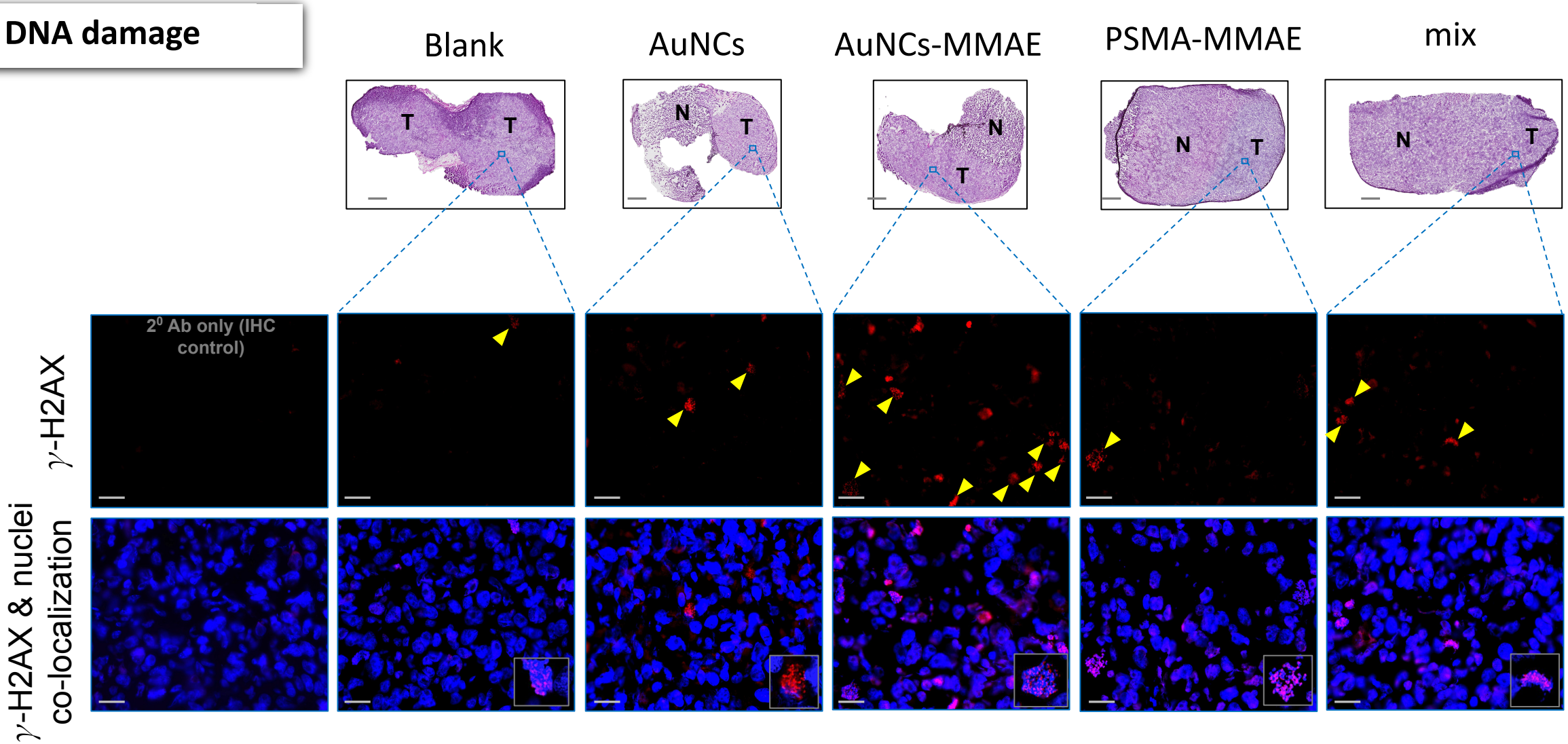
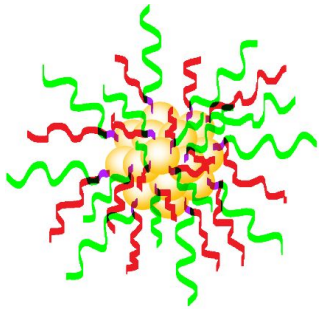
DNA damage



Summary

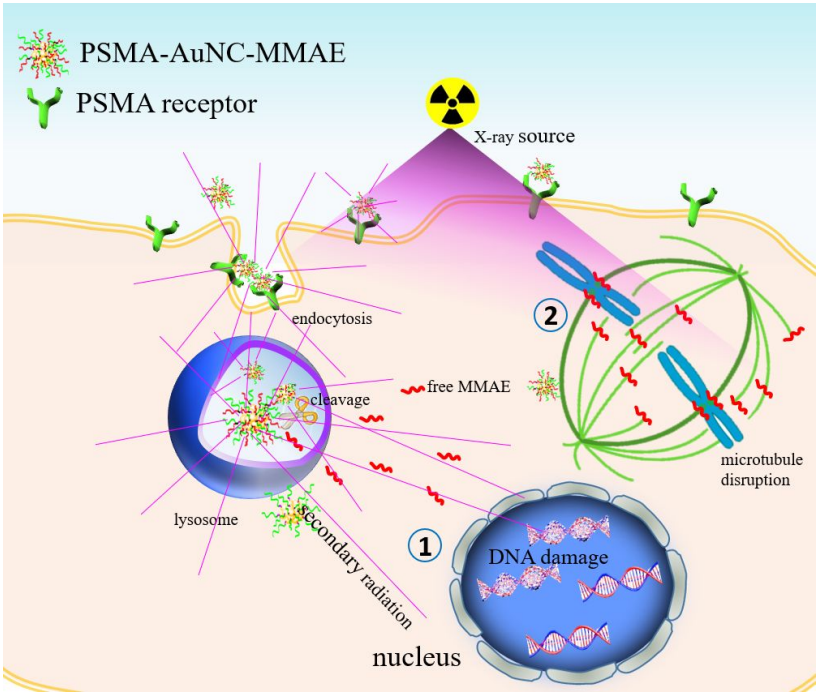
PSMA-targeted AuNCs-MMAE conjugates :



- Fluorescent and renal clearable size
- Selectively targeting to PSMA positive cells
- Protease based MMAE release
- Synergetic therapy effect by Au and MMAE

Chemoradiotherapy of prostate cancer:

- Selective targeting to prostate tumor by PSMA
- Renal clearable and Low accumulation in main organs
- Chemotherapy by MMAE and Radiosensitizing by both Au and MMAE



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Dr. Lifang Zhang
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Prof Clemens Burda
Sarah Springer
Zoe Lockwood

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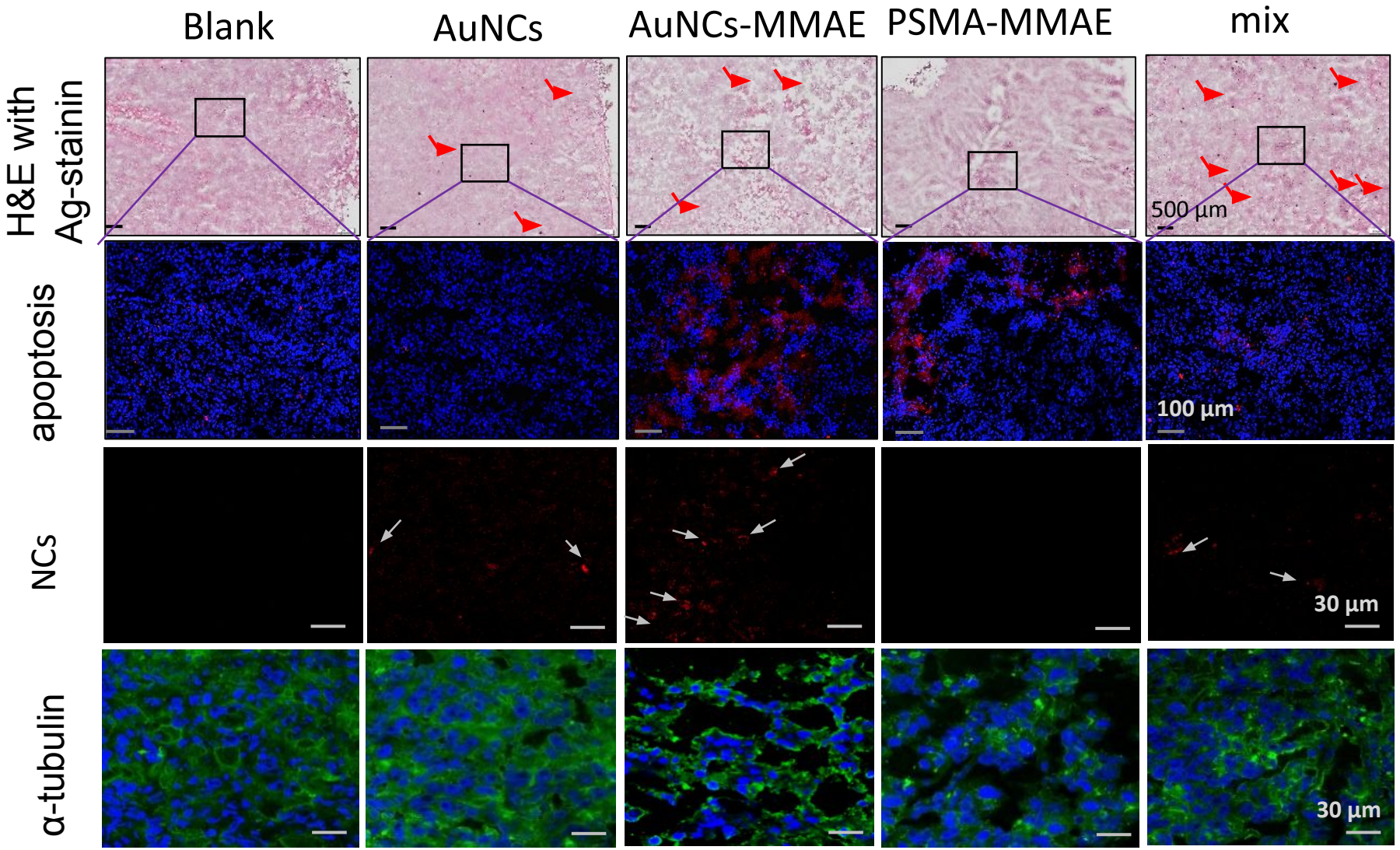
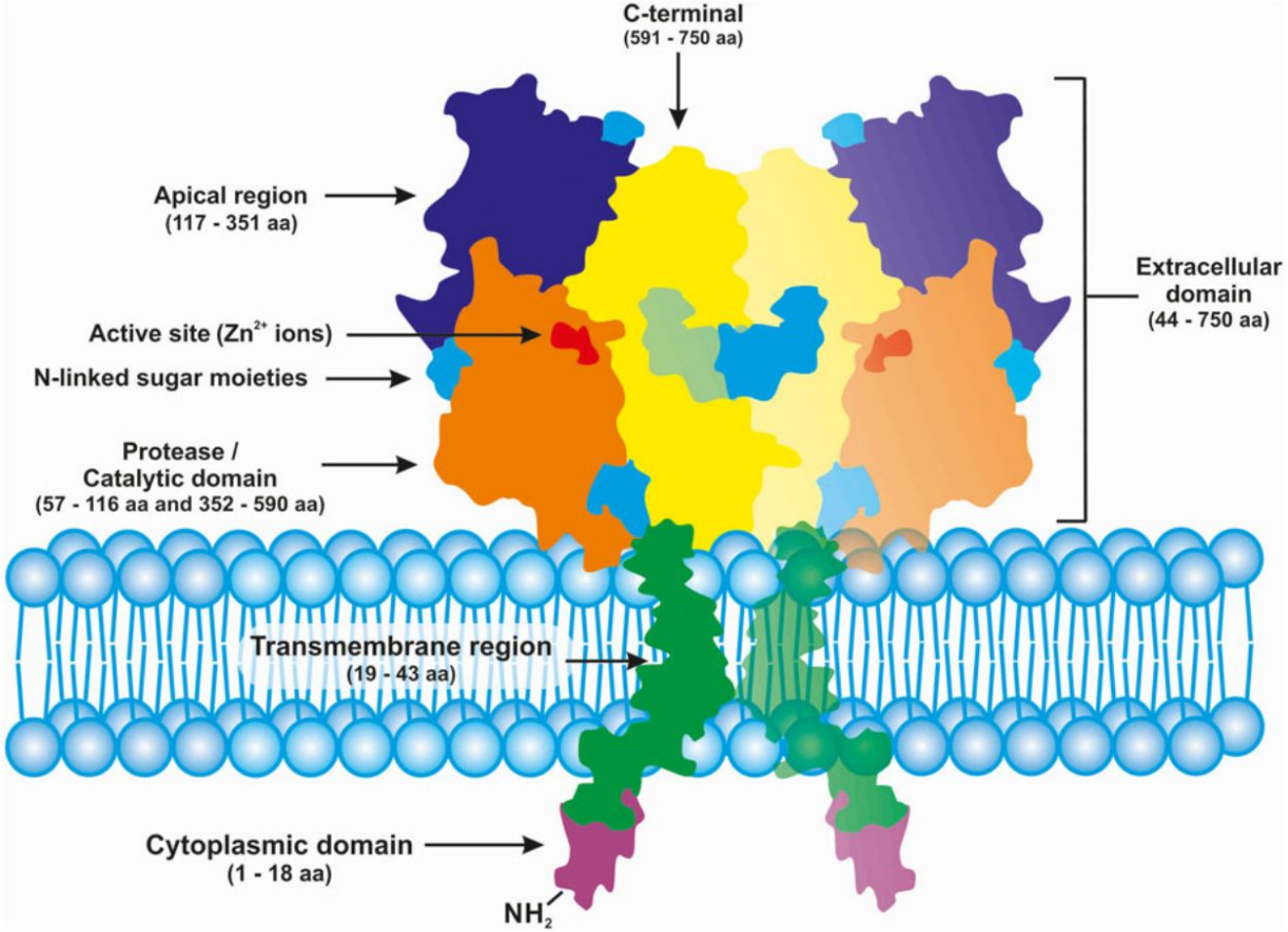
Tumor staining – with no radiation



Prostate Specific Membrane Antigen (PSMA)

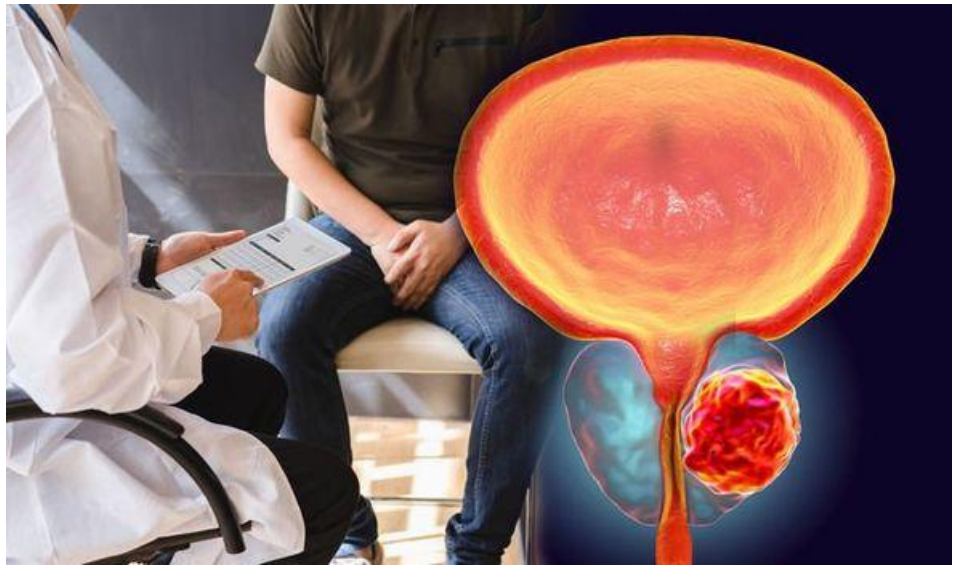


- Well validated target
- Expressed on >95% of prostate tumors
- Expression increases as the prostate cancer progresses
- Minimal expression on normal tissue
- Expressed on blood vessels in most solid tumors

(lung, kidney, colon, stomach, breast and brain cancers)

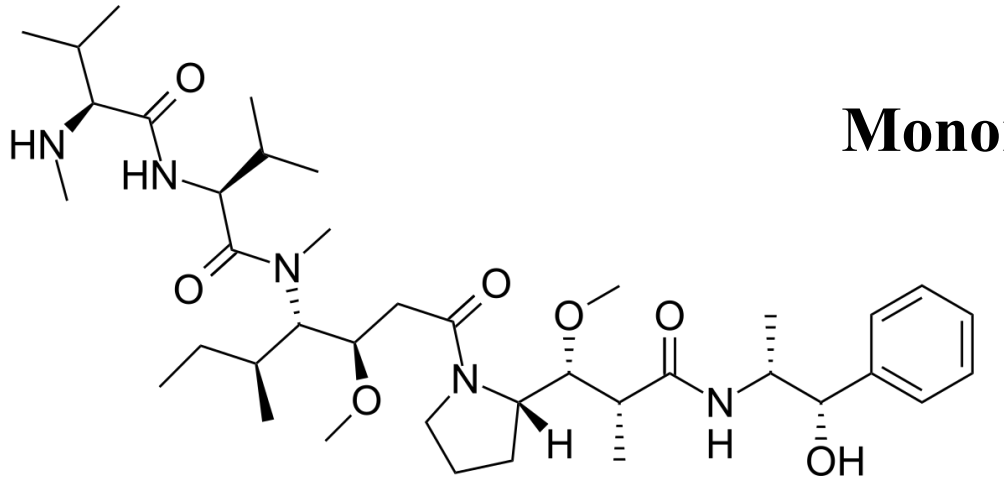
Evans, J. et al. Br. J. Pharmocol., 2016, 173, 3041

Treatment Options

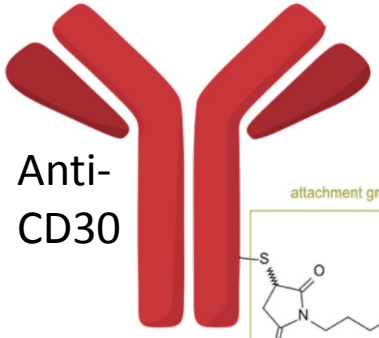


- Watchful waiting or active surveillance
- Surgery
- **Radiation therapy** and radiopharmaceutical therapy
- Hormone therapy
- **Chemotherapy**
- Cryosurgery
- High-intensity–focused ultrasound therapy
- Proton beam radiation therapy
- Photodynamic therapy

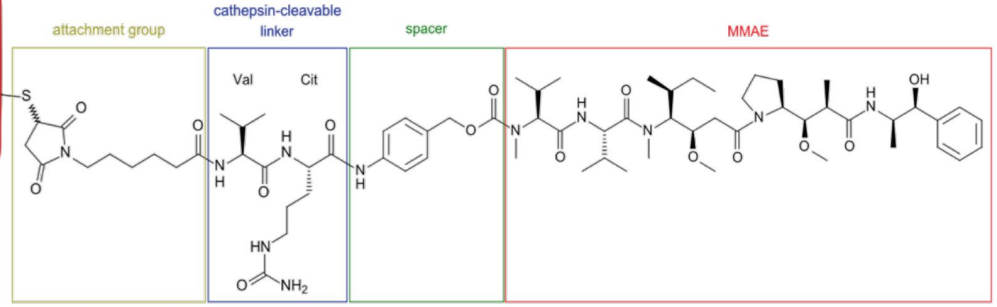
Chemotherapy drug- MMAE

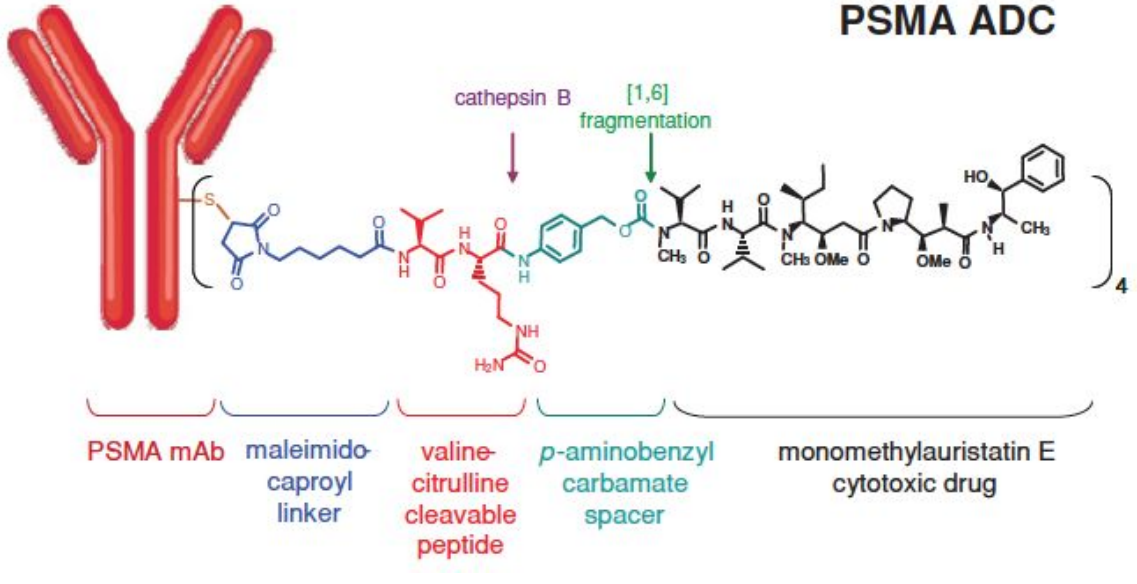


Monomethylauristatin E (MMAE)

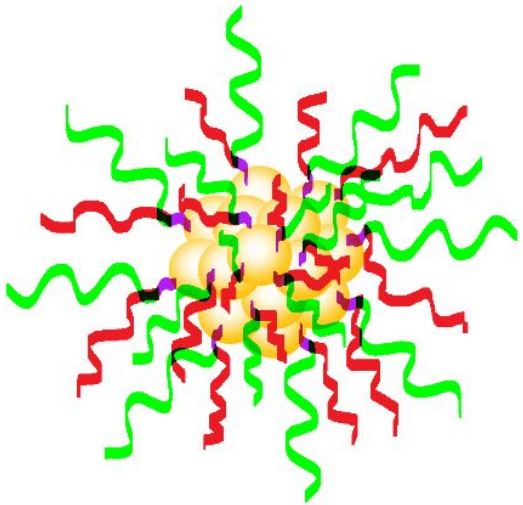


Brentuximab vedotin
(Adcetris®)
(Seattle Genetics)





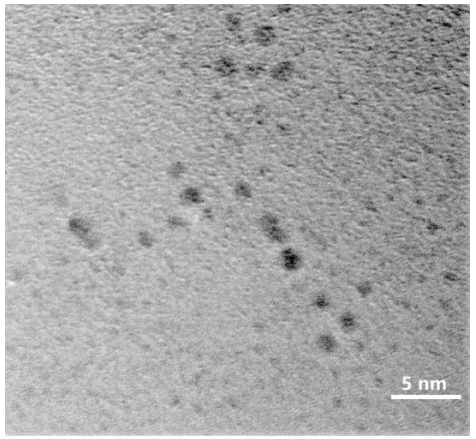
AuNCs-MMAE characterization



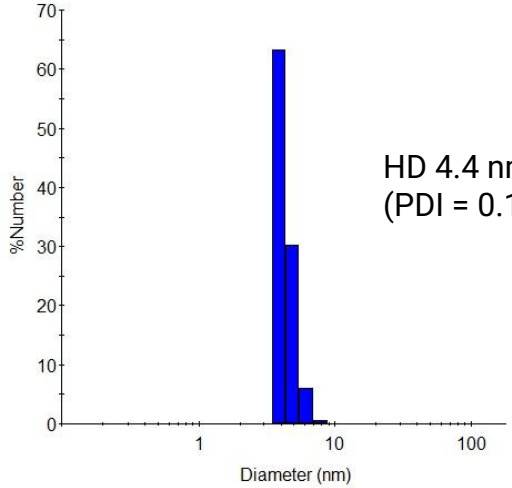
AuNCs-MMAE

Nano size

TEM



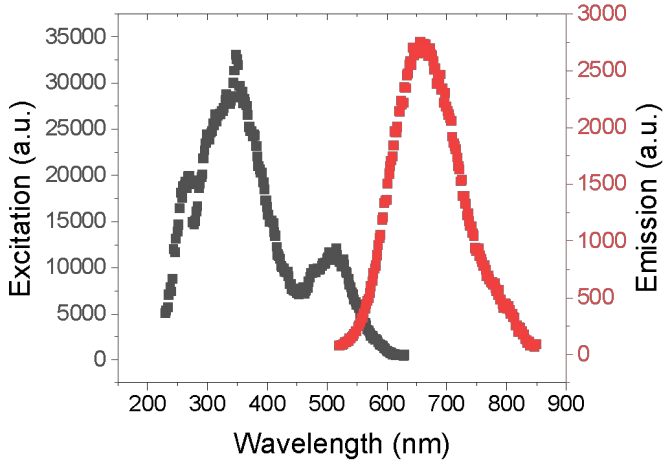
DLS



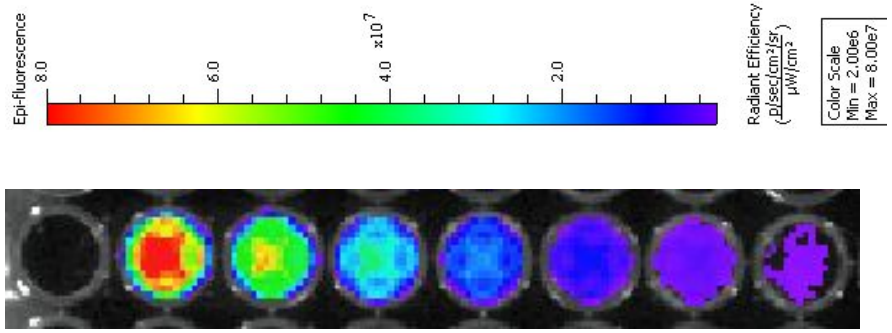
HD 4.4 nm
(PDI = 0.16)

Optical

Ex/Em



Fluorescence



0 5 2.5 1.25 0.625 0.313 0.156 0.078 mg/ml

In vitro chemoradiotherapy

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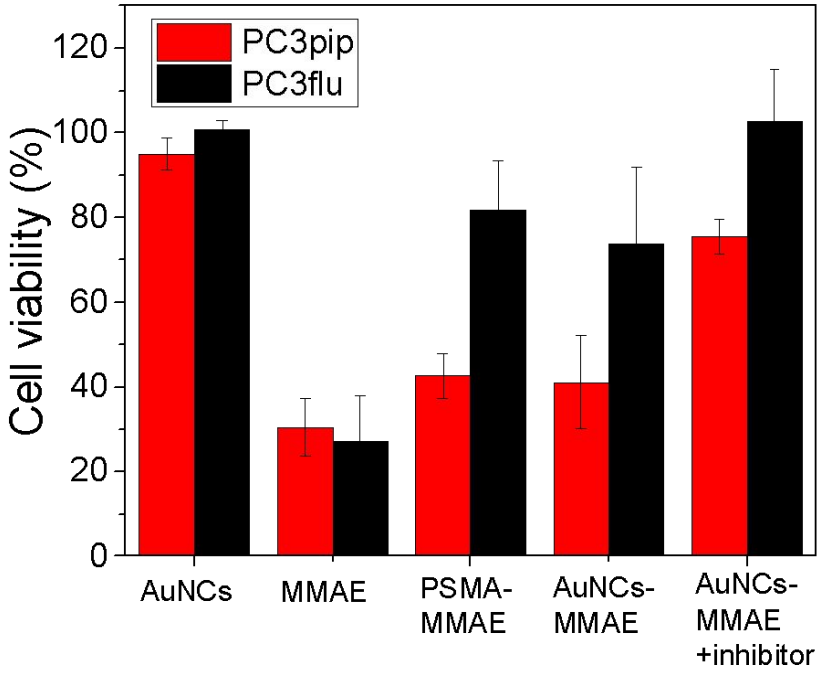
Cathepsin activated MMAE release



Radiation therapy