Tailored nanomedicines to overcome biological barriers for targeted drug delivery

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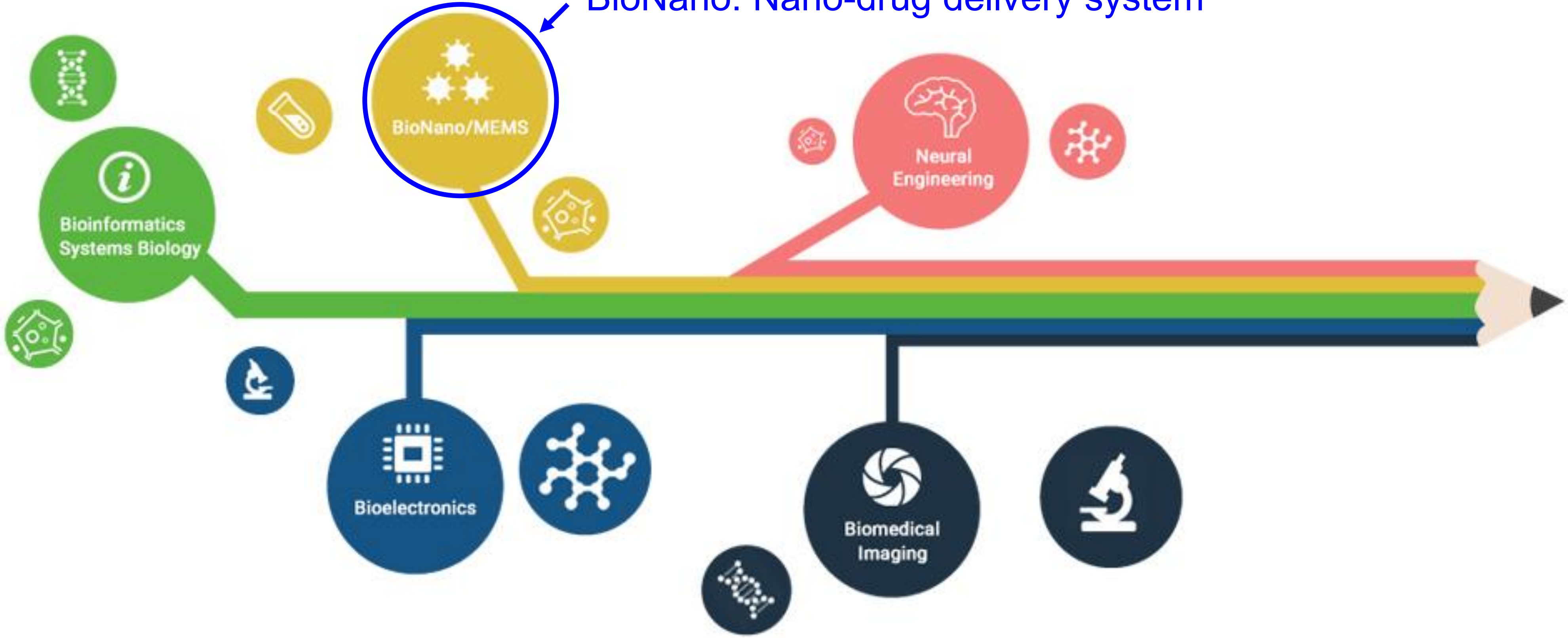
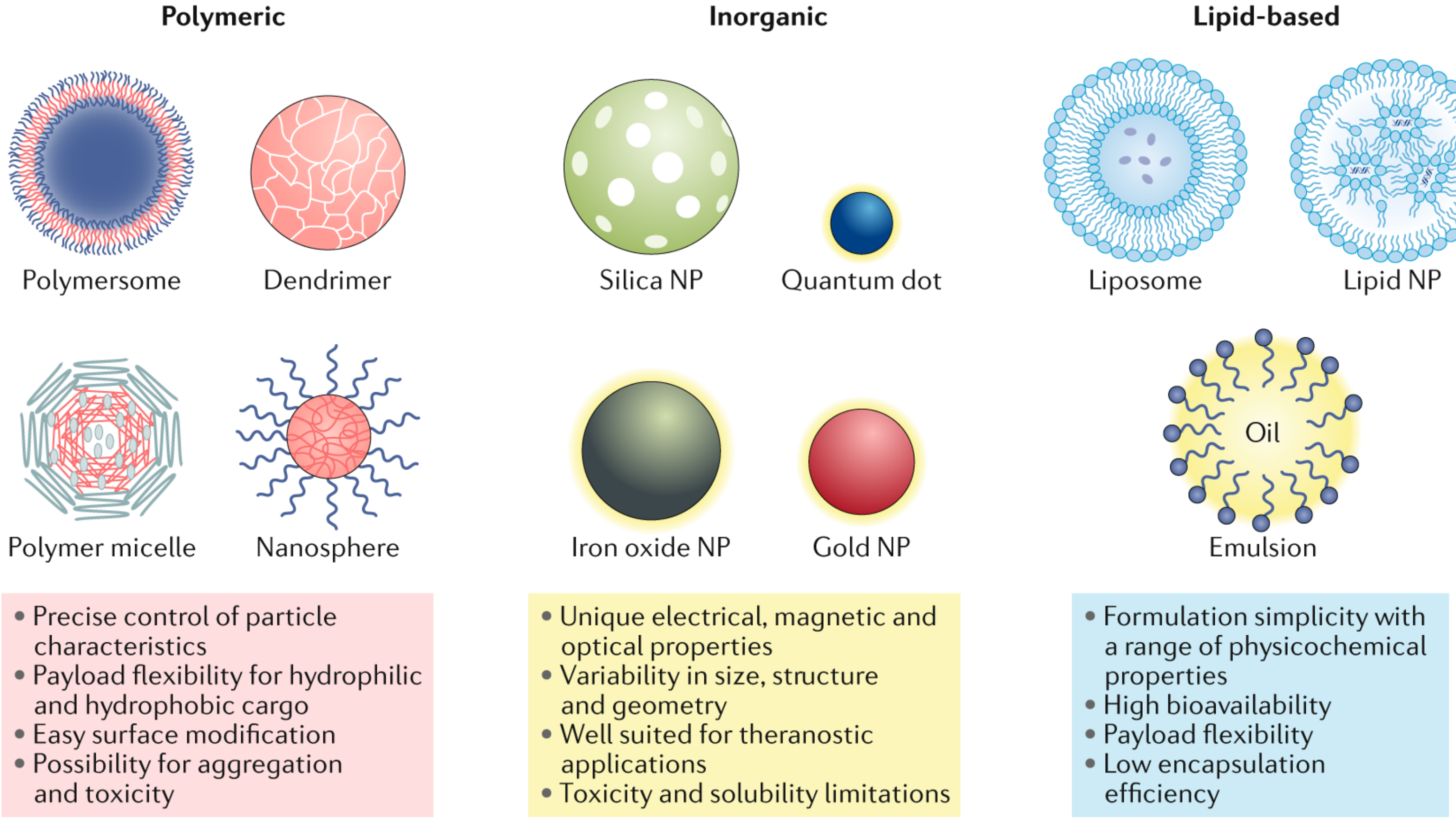
Dept. of
Bio and Brain
Engineering

Creating innovative bio-convergent technologies for better human life

BioNano: Nano-drug delivery system



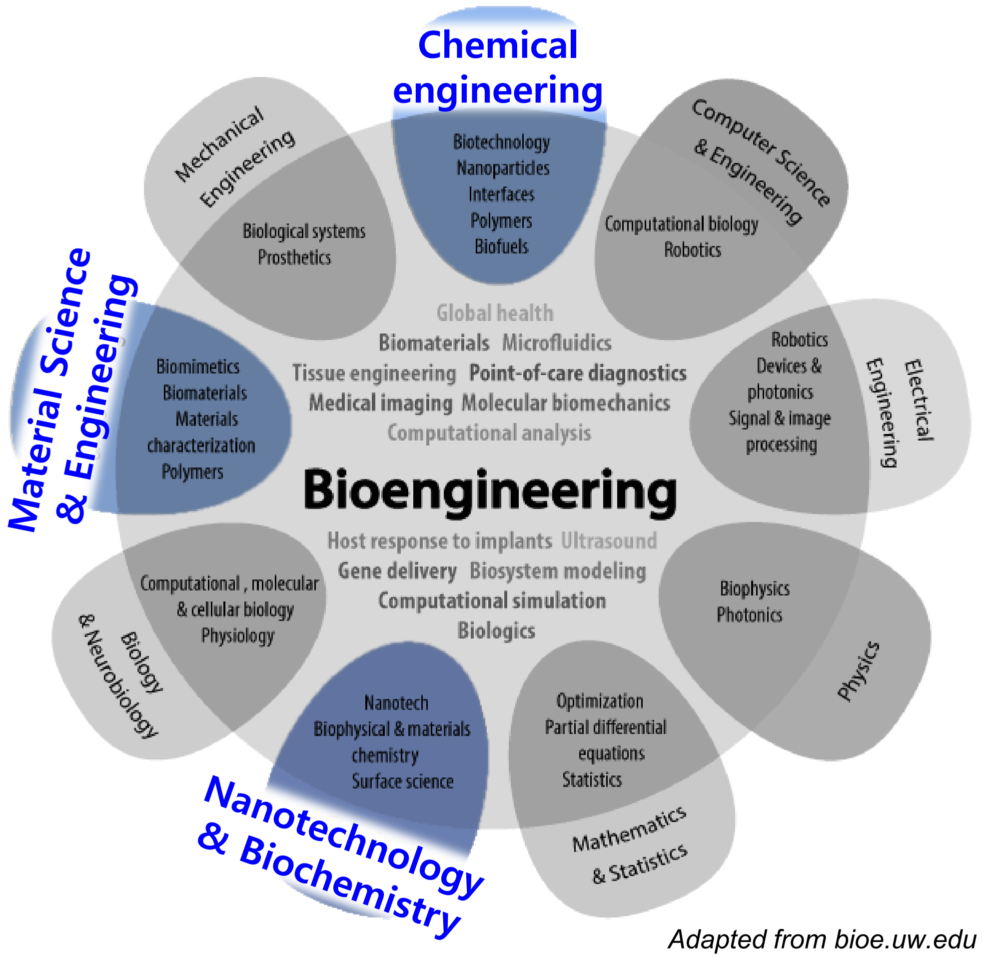
Cancer nanomedicines



- Nano-sized particles, designed to deliver therapeutic agents to tumor tissues.

Nature Reviews Materials 2021, 6, 766–783

Research field in Bioengineering

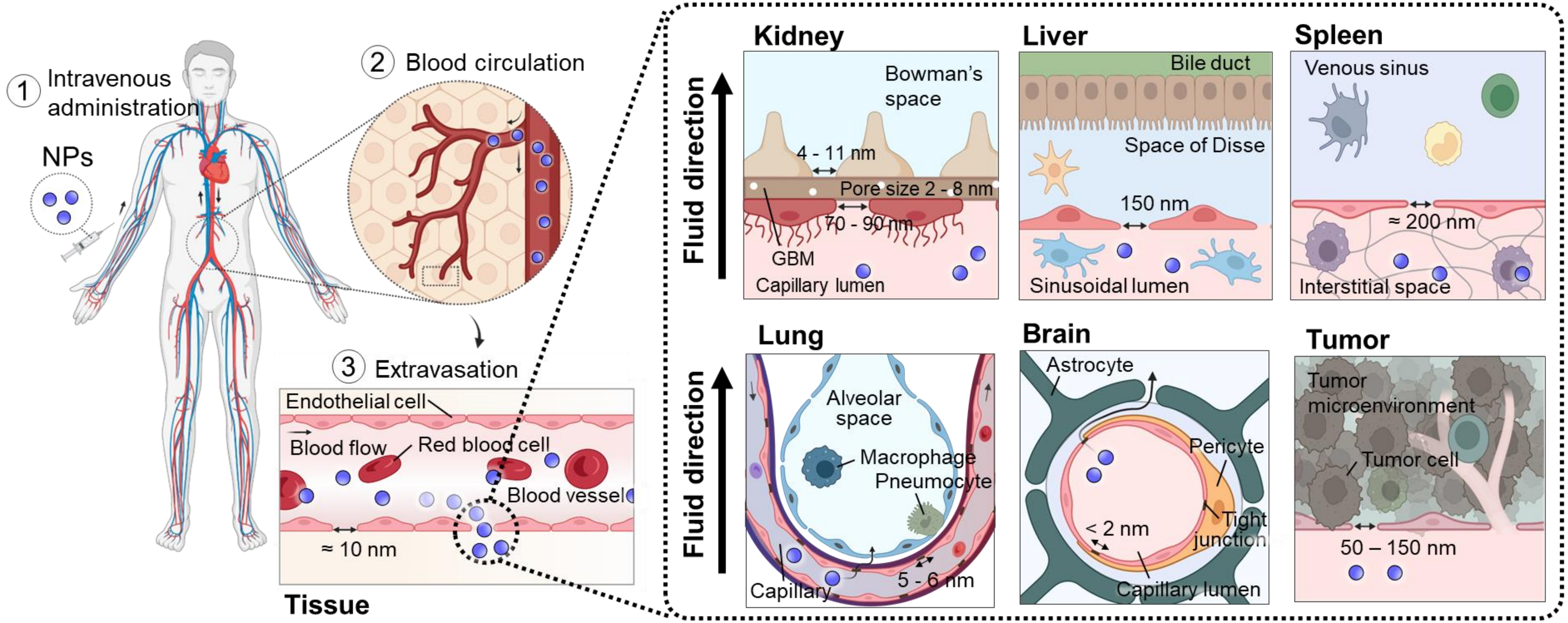


Adapted from bioe.uw.edu

❖ Chemical engineering of

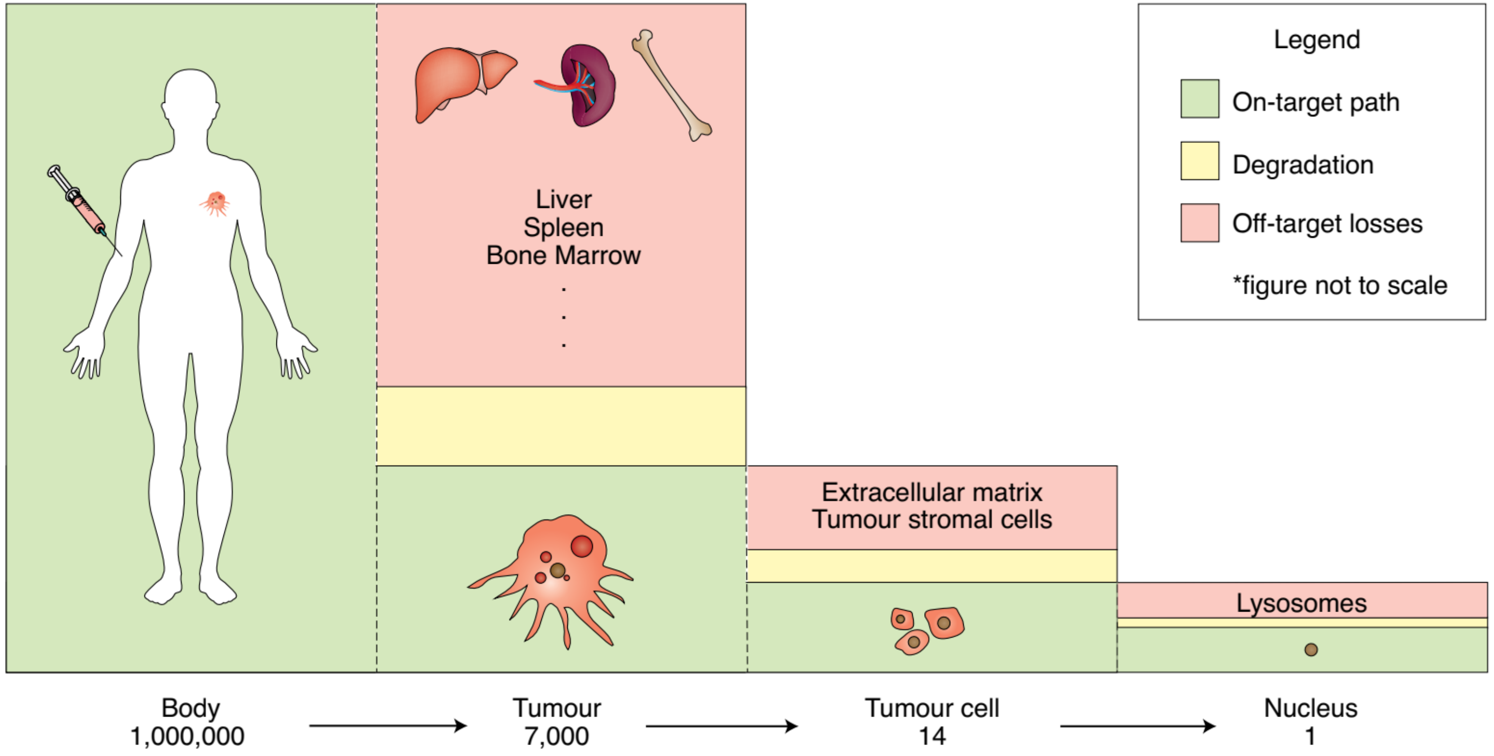
1. **Organic nanocarriers**
   - Targeted drug and contrast agent delivery
2. **Organic fluorophores**
   - Early disease diagnosis
   - Image-guided surgery & phototherapy
3. **Delivery systems for prime editors**
   - Gene therapy

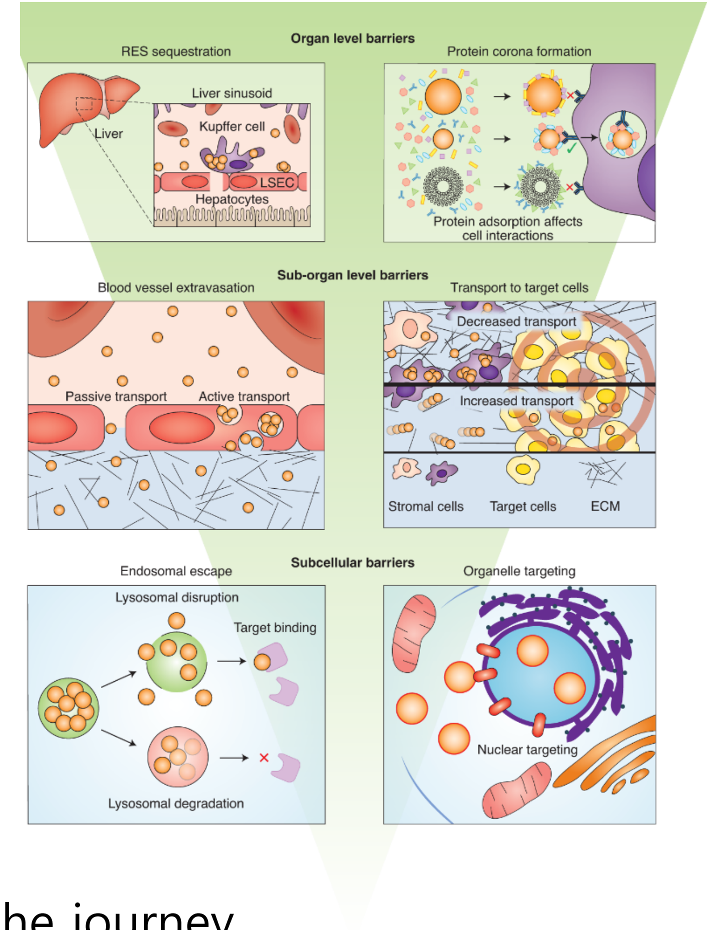
Controlling in vivo fate of nanoparticles



Baek et al., *ACS Nano 19, 15, 14605-14626* (2025)

Off-target effect of NPs

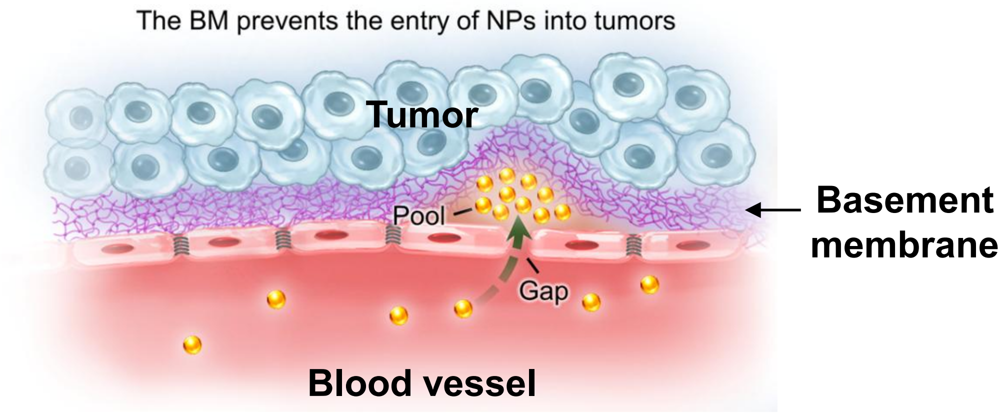


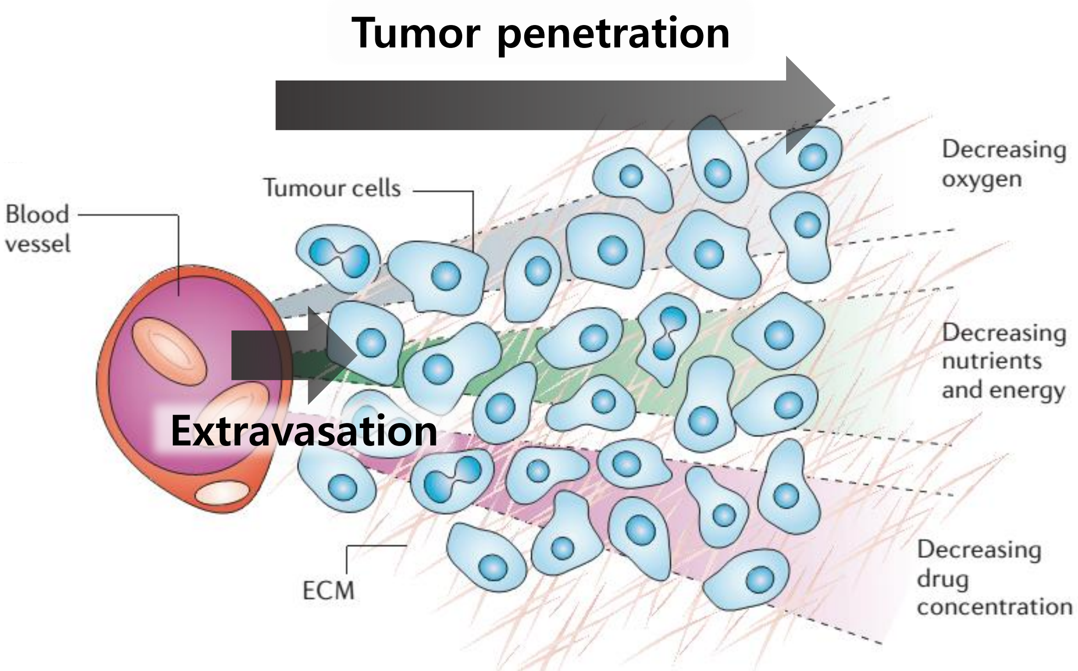


- Many biological barriers remove nanoparticles from the journey.
- **Less than 1%** of NPs can reach target (**tumour**).
- More than **99% of NPs** are distributed to **off-target sites.**

Adv Drug Deliv Rev 2015, 91, 7-22.
Nat Nanotechnol 2020, 15, 819-829.

Limited extravasation and penetration of NPs in tumor





- The **basement membrane (BM) prevents the entry of NPs into tumors.**
- BM pore size of **~50 nm.**

- **High interstitial fluid pressure (IFP)**
- **Dense extracellular matrix (ECM)**

Nature Reviews Cancer 6, 583–592 (2006)
Nature Nanotechnology 19 95-105 (2024)

Tailored nanoparticles to overcome various biological barriers in tumors

Focus I. **Renal clearable nanocarriers for tumor selective drug delivery**

: Overcoming off-target effect of NPs

nature nanotechnology

Article

https://doi.org/10.1038/s41565-023-01381-8

Tailoring renal-clearable zwitterionic cyclodextrin for colorectal cancer-selective drug delivery

Received: 24 October 2022

Accepted: 21 March 2023

Min-Jun Baek[1], Duy-Thuc Nguyen[1], Dahan Kim[1], So-Yeol Yoo[2], Sang Min Lee[2], Jae-Young Lee[2] & Dae-Duk Kim[1]

Focus II. **Photobleaching-harnessing nanoparticles for deep tumor penetration**

: Overcoming limited tumor penetration of NPs

nature nanotechnology

Article

https://doi.org/10.1038/s41565-024-01757-4

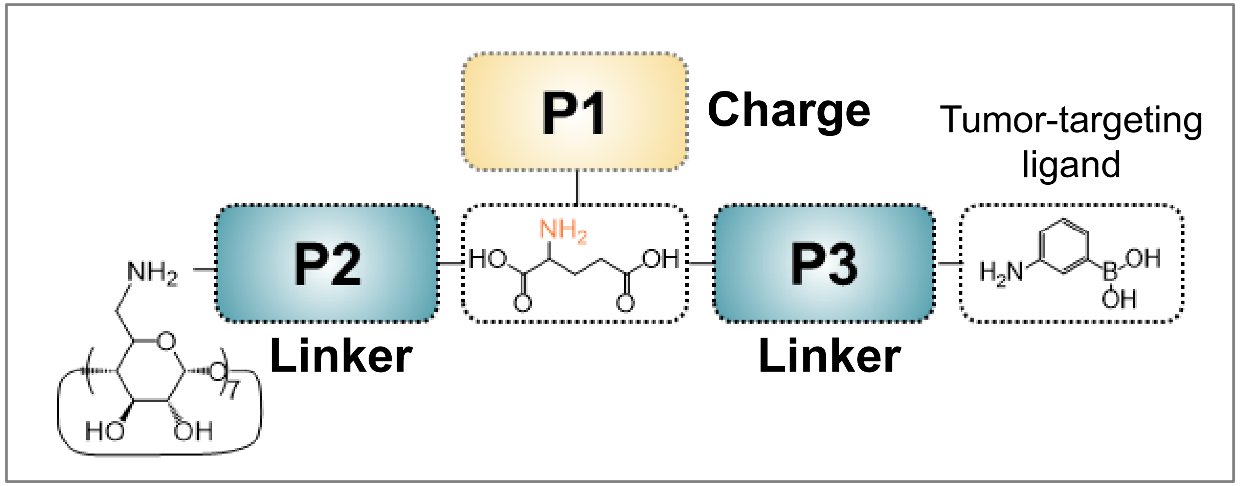
Photobleaching-mediated charge-convertible cyclodextrin nanoparticles achieve deep tumour penetration for rectal cancer theranostics

Received: 14 November 2023

Accepted: 15 July 2024

Duy-Thuc Nguyen[1,4], Min-Jun Baek[1,4], Sang Min Lee[1], Dahan Kim[1], So-Yeol Yoo[2], Jae-Young Lee[1,3] & Dae-Duk Kim[1,3]

Design considerations for renal-clearable nanocarriers



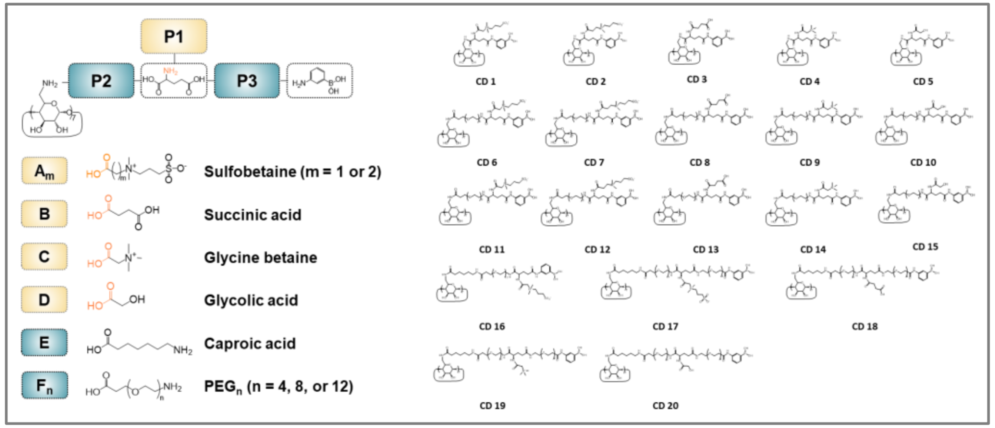
Structure optimization
- Linker length
- Linker position
- Charge

Materials	Size	Surface Charge	Tumor selective retention
▪ Biocompatible - Cyclodextrin - Amino acid - PEG	▪ 6 ~ 8 nm (renal clearable) - Renally clearable - Efficient extravasation - RES uptake↓	▪ Zwitterionic surface - Non-specific uptake↓ - Serum protein binding↓	▪ Tumor-targeting ligand

Baek et al., Nature Nanotechnology, 18, 945–956 (2023)

KAIST Dept. of Bio and Brain Engineering

Screening of Renal-Clearable CD Derivatives



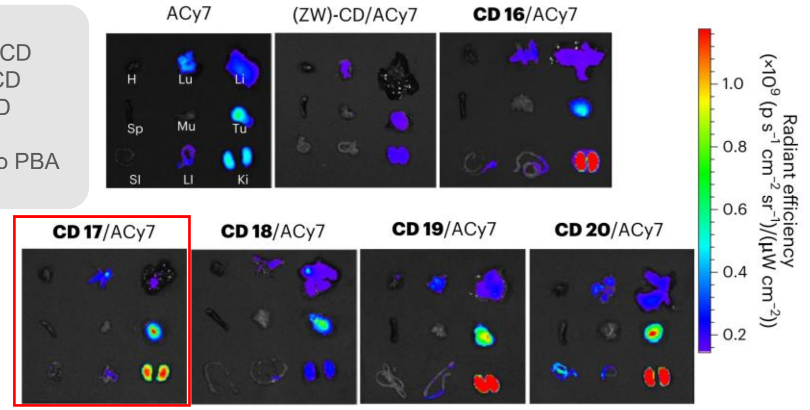
Schematic view of CD derivatization

	P1	P2	P3
CD 1	A_1		
CD 2	A_2		
CD 3	B		
CD 4	C		
CD 5	D		
CD 6	A_1	F_4	
CD 7	A_2	F_4	
CD 8	B	F_4	
CD 9	C	F_4	
CD 10	D	F_4	
CD 11	A_1	F_8	
CD 12	A_2	F_8	
CD 13	B	F_8	
CD 14	C	F_8	
CD 15	D	F_8	
CD 16	A_1	F_{12}	
CD 17	A_1	$E\text{-}F_8$	F_4
CD 18	B	$E\text{-}F_8$	F_4
CD 19	C	$E\text{-}F_8$	F_4
CD 20	D	$E\text{-}F_8$	F_4

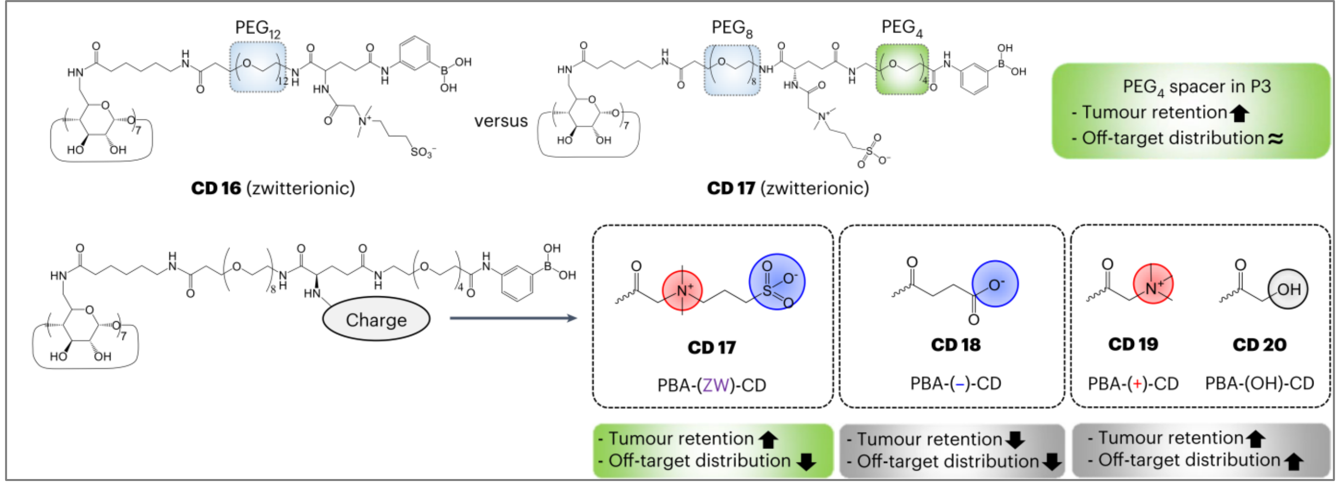
Insoluble in FBS and PBS
Soluble in FBS, insoluble in PBS
Soluble in FBS and PBS

1st Screening:
Colloidal stability

ACy7: Near-infrared dye
CD 16 & **CD 17**: Zwitterionic CD
CD 18: Negatively-charged CD
CD 19: Positively-charged CD
CD 20: Neutral CD
(ZW)-CD: Zwitterionic CD w/o PBA
PBA-(ZW)-CD: CD 17



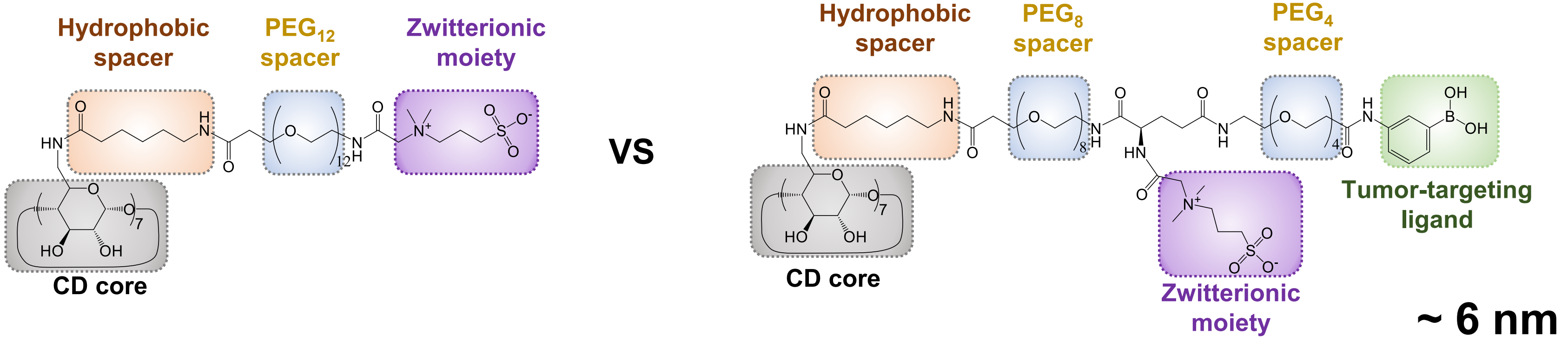
2nd Screening:
Tumor selectivity



Structure-Biodistribution Relationship (SBR)-based tailoring

Baek et al., Nature Nanotechnology, 18, 945–956 (2023)

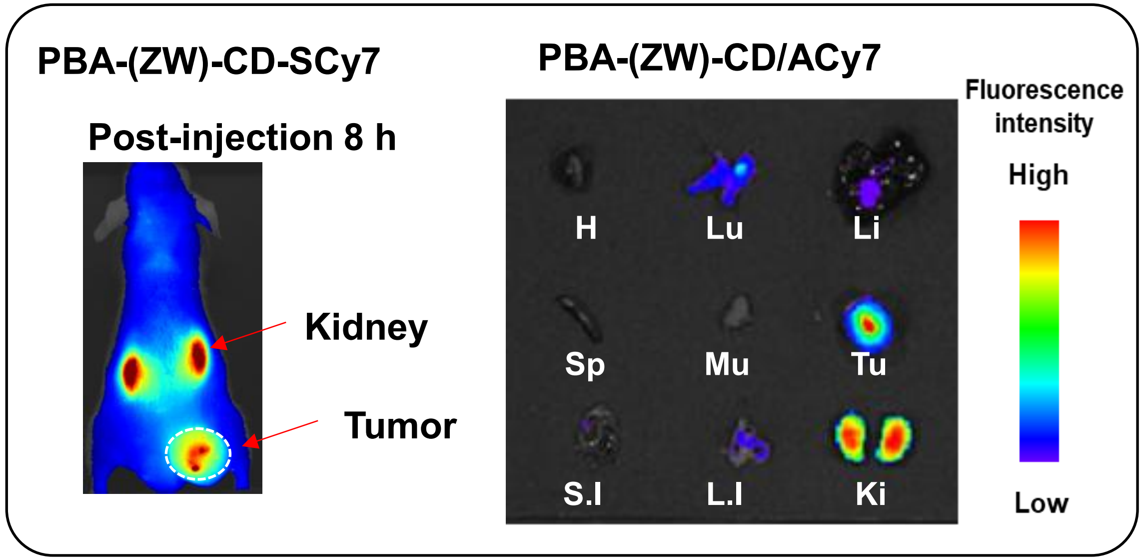
Tumor targetability of renal-clearable nanocarriers



(ZW)-CD
(without tailoring)

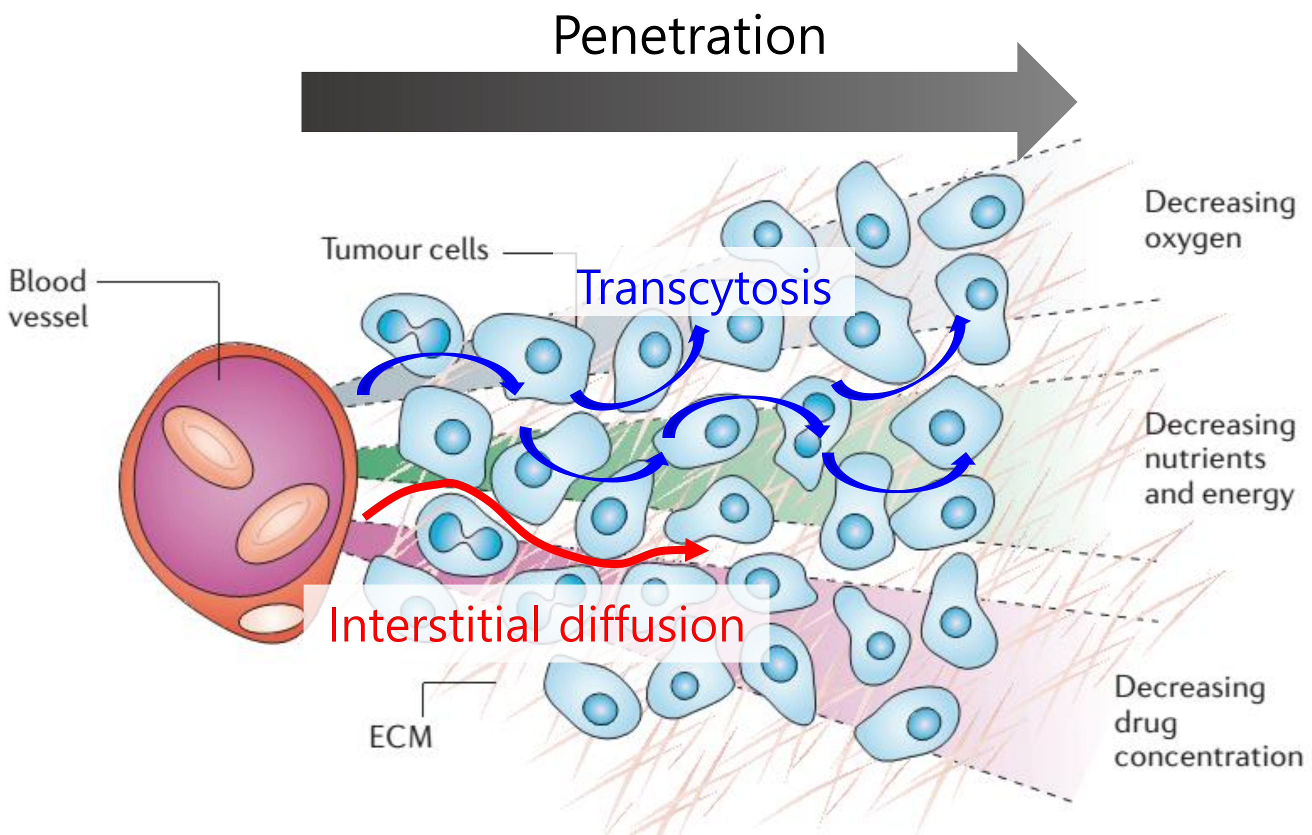
PBA-(ZW)-CD
(Tailored renal clearable nanocarrier)

- **PBA-(ZW)-CD** improved tumor distribution
  - **14.8-fold** higher **tumor accumulation** compared to **(ZW)-CD.**



Baek et al., Nature Nanotechnology, 18, 945–956 (2023)

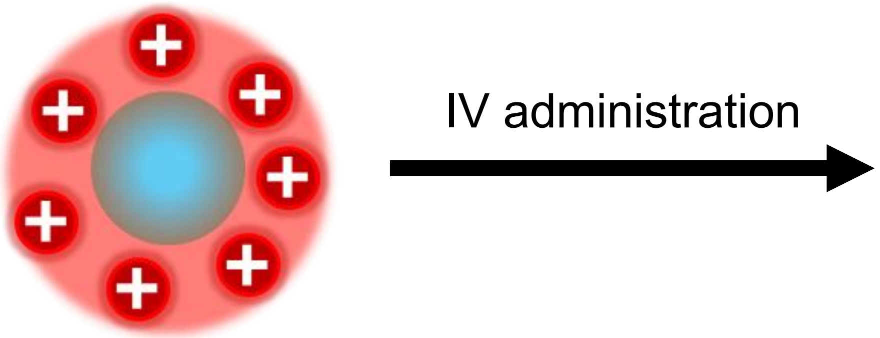
Tumor penetration via transcytosis



Positively charged NPs can penetrate via transcytosis

Nano Lett. 2019, 19, 11, 8010–8020

Problems of positive surface charge

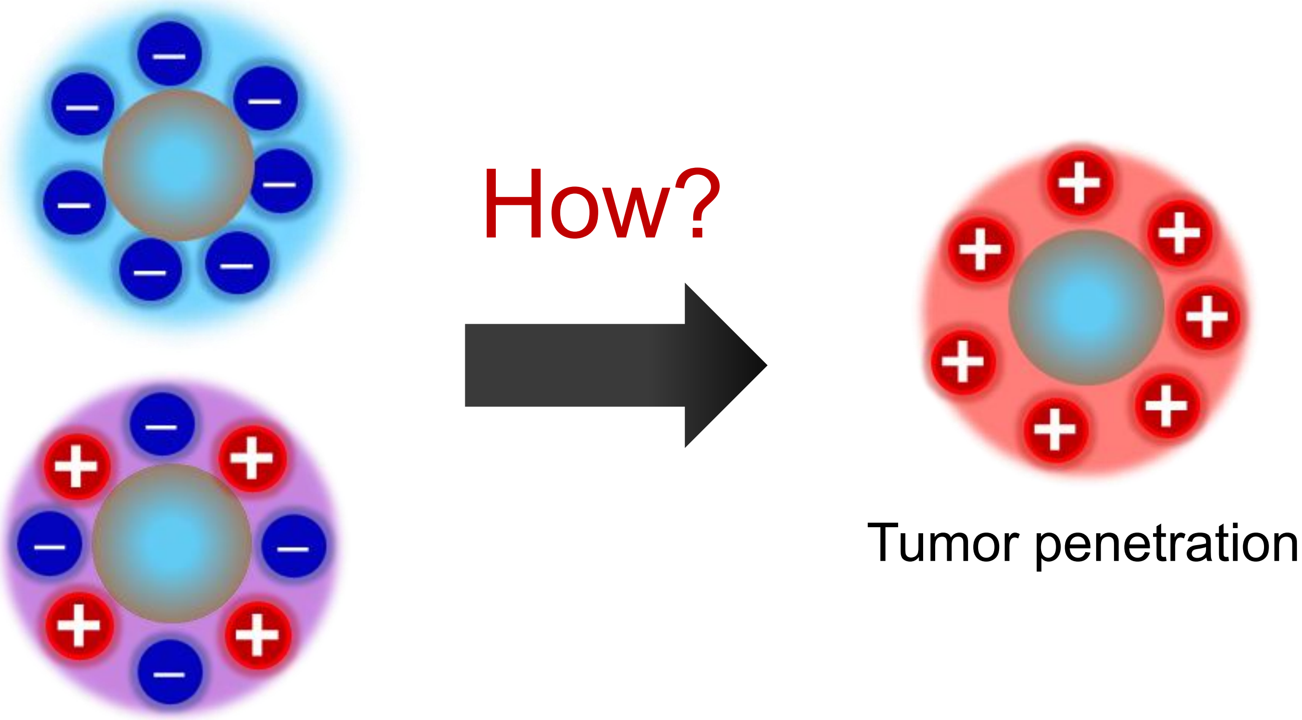


- Serum protein aggregation.
- Rapid opsonization.
- High reticuloendothelial system (RES) uptake.
- Nonspecific adsorption to normal cells and tissues.

➔ Unsuitable for systemic injection and tumor targeting

Nano Today 11.2 (2016): 133-144.
Theranostics. 2020 May 17;10(15):6629-6637.

Charge conversion in tumor for penetration

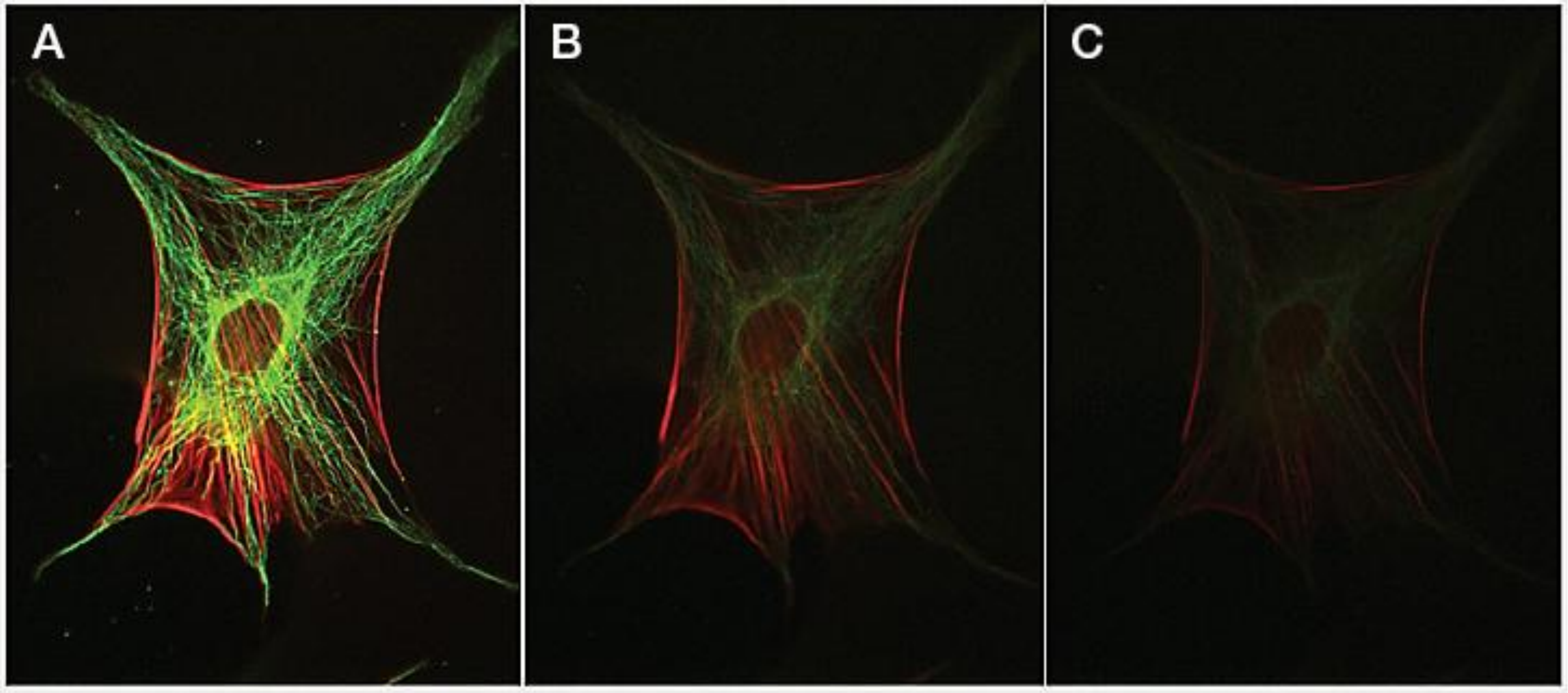


Tumor targeting

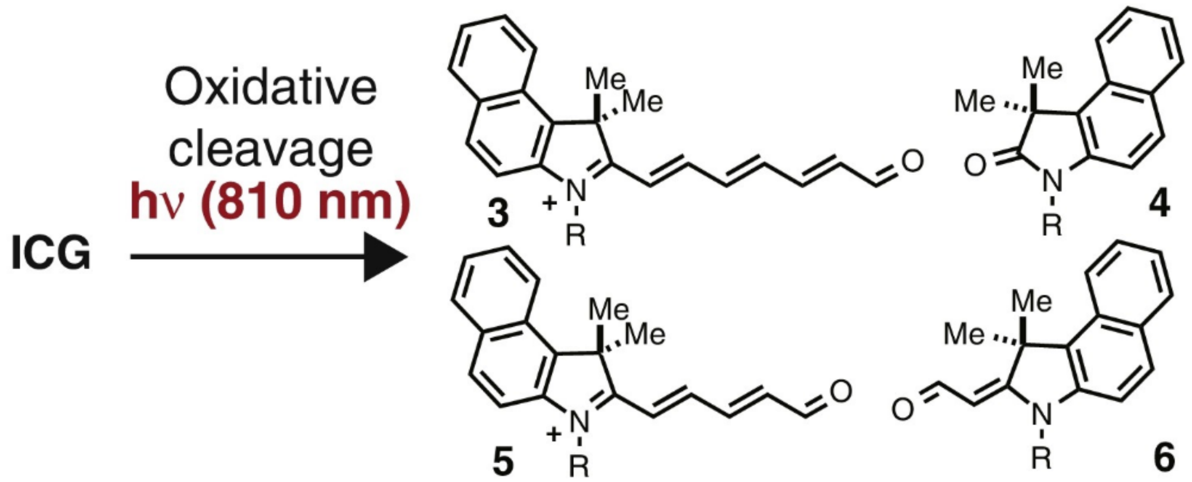
Tumor penetration

New charge conversion strategy: photobleaching

Laser irradiation time



Idea inspired by photobleaching



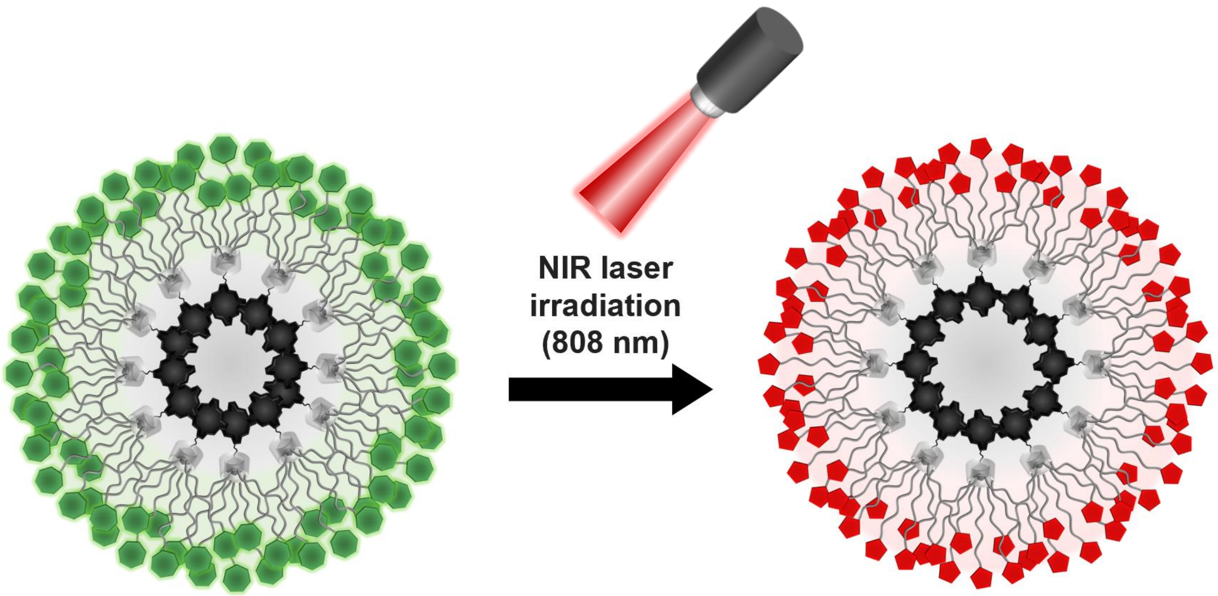
Asymmetric degradation

→ From a balanced to an imbalance structure

Current Opinion in Chemical Biology 33, 117-125 (2016)

Photobleaching-mediated charge convertible NPs

Conjugation of NIR fluorophore to the NP surface



P-ZWNIR NPs
(zwitterionic)

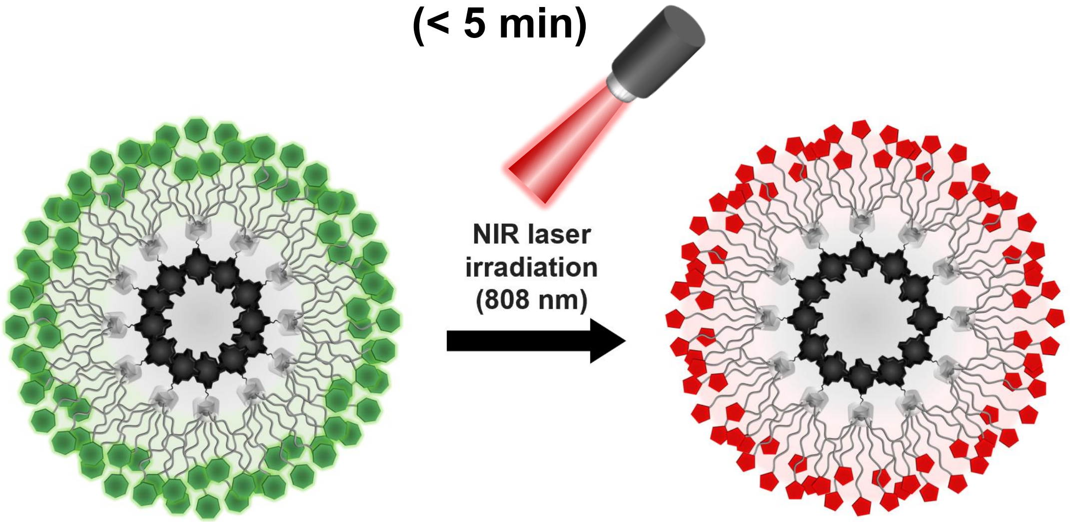
Charge-converted NPs
(cationic)

Photobleaching-mediated charge conversion

P-ZWNIR NPs [Cyclodextrin nanocarrier + Organic NIR fluorophore]

Photobleaching-mediated charge conversion

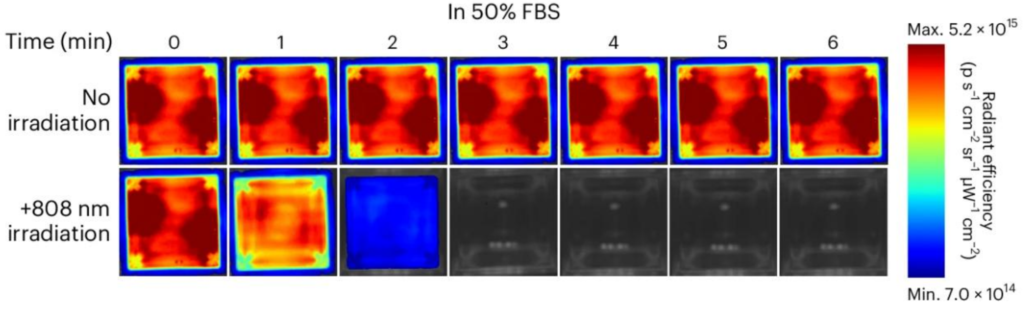
(< 5 min)



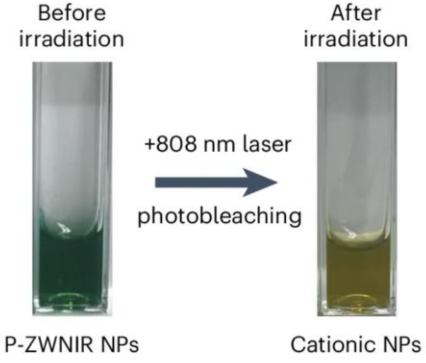
P-ZWNIR NPs (zwitterionic)

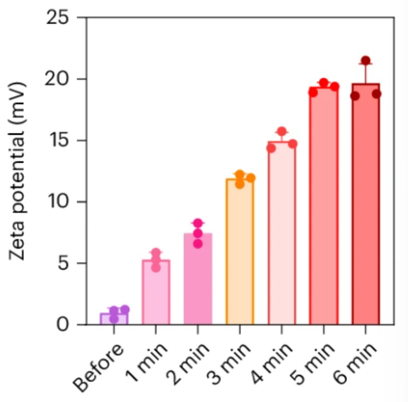
Charge-converted NPs (cationic)

Fluorescence change upon radiation



Charge conversion

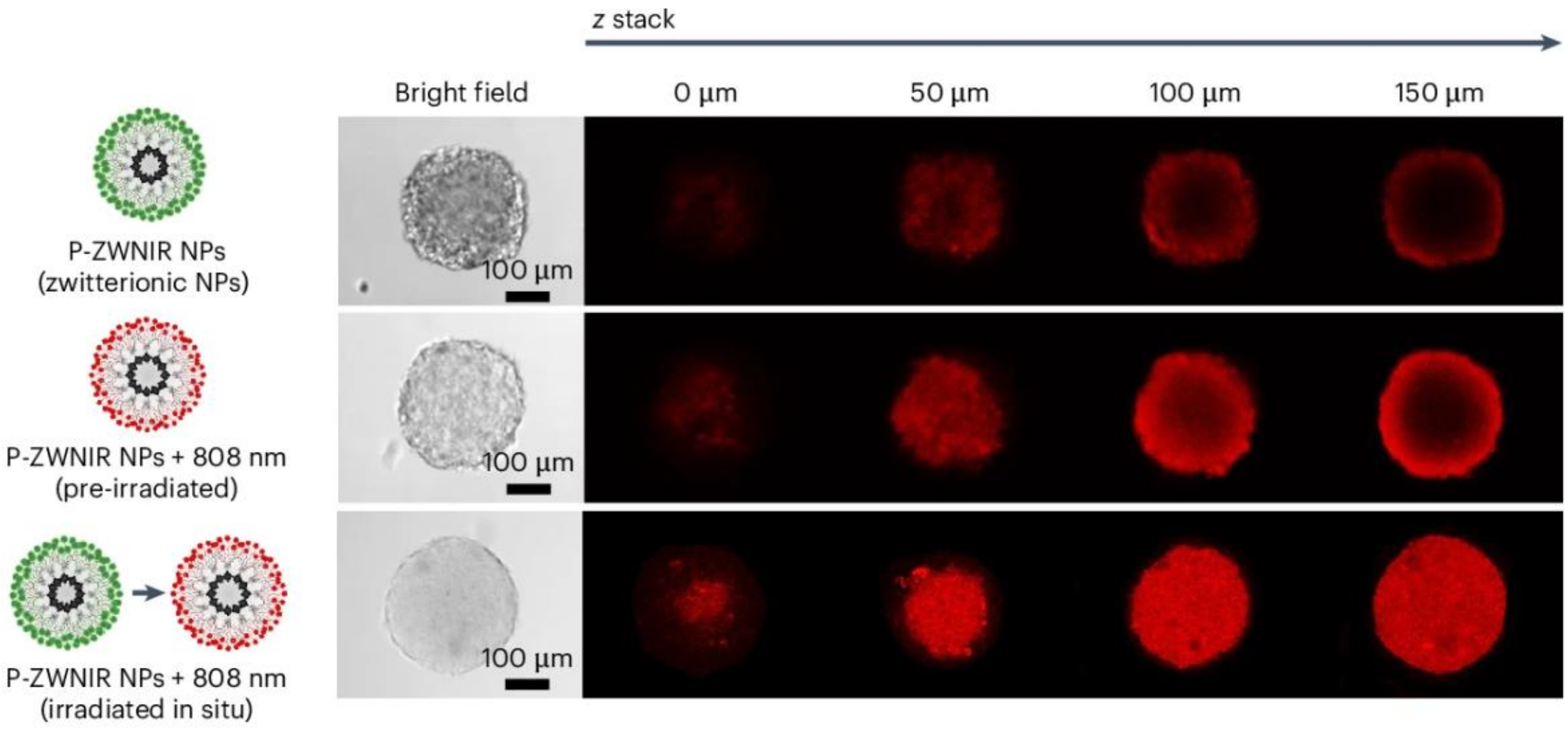




Nat. Nanotechnol. **19**, 1723-1734 (2024)

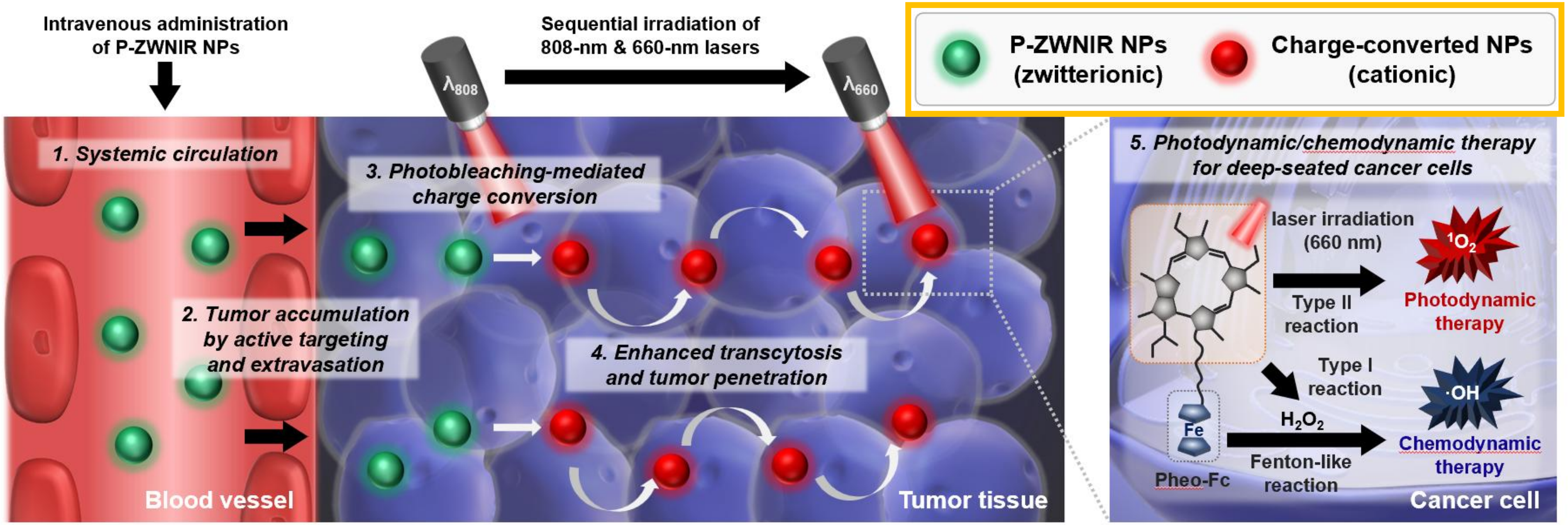
Photobleaching-mediated deep tumor penetration

Tumor penetration of the P-ZWNIR NPs in the HT-29 spheroid model



Nat. Nanotechnol. **19**, 1723-1734 (2024)

Delivery cascade and phototherapy mechanism of P-ZWNIR NPs



IV injection → Tumor targeting → Photobleaching → NPs penetration
→ Photodynamic therapy

Nat. Nanotechnol. **19**, 172-1734 (2024)

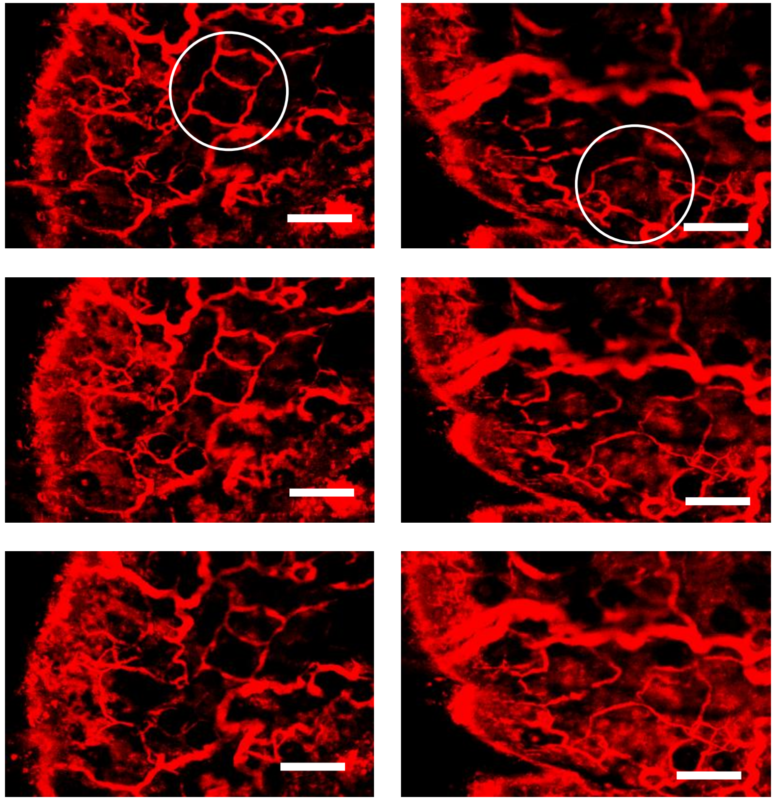
Deep tumor penetration of NPs

Without laser | After 808 nm irradiation

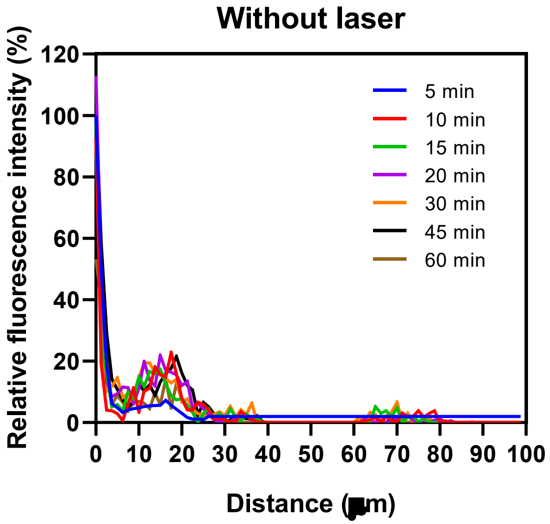
5 min

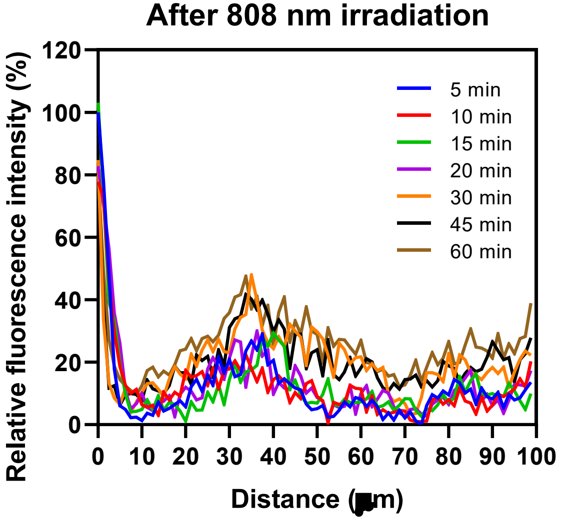
30 min

60 min



Scale bar: 200 μm





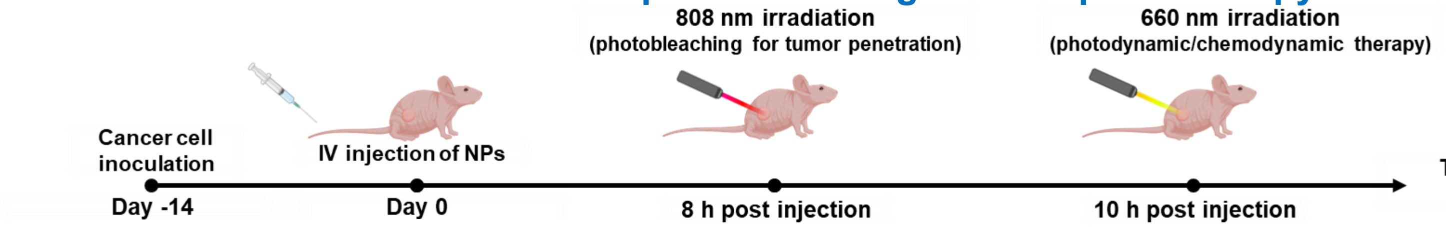
Nat. Nanotechnol. **19**, 172-1734 (2024)

Impact of deep tumor penetration on PDT efficacy

1st irradiation: **photobleaching**

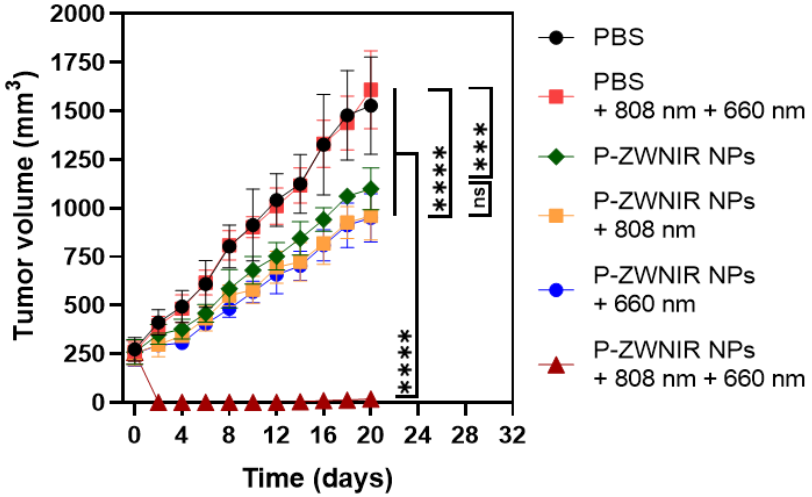
2nd irradiation: **phototherapy**

808 nm: 0.8 W/cm^2
660 nm: 2 mW/cm^2



* The therapy was applied only one time at Day 0.

Tumor volume ≈ 250 mm^3



PBS

PBS + 808 nm + 660 nm

P-ZWNIR NPs

P-ZWNIR NPs + 808 nm

P-ZWNIR NPs + 660 nm ← **PDT w/o penetration**

P-ZWNIR NPs + 808 nm + 660 nm ← **PDT w penetration**

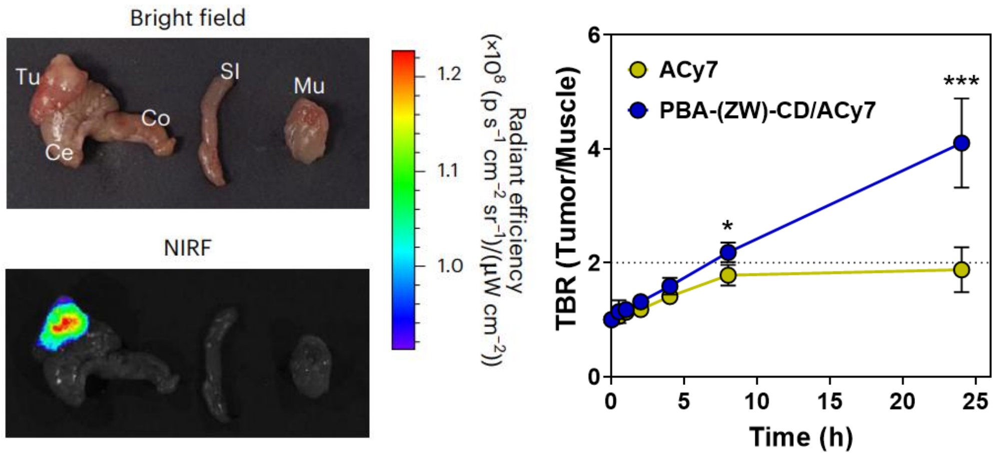
P-ZWNIR NPs + 808 nm + 660 nm eradicated ~ 250 mm^3 tumor

Nat. Nanotechnol. **19**, 172-1734 (2024)

Application of highly tumor selective NPs

Renal clearable NPs

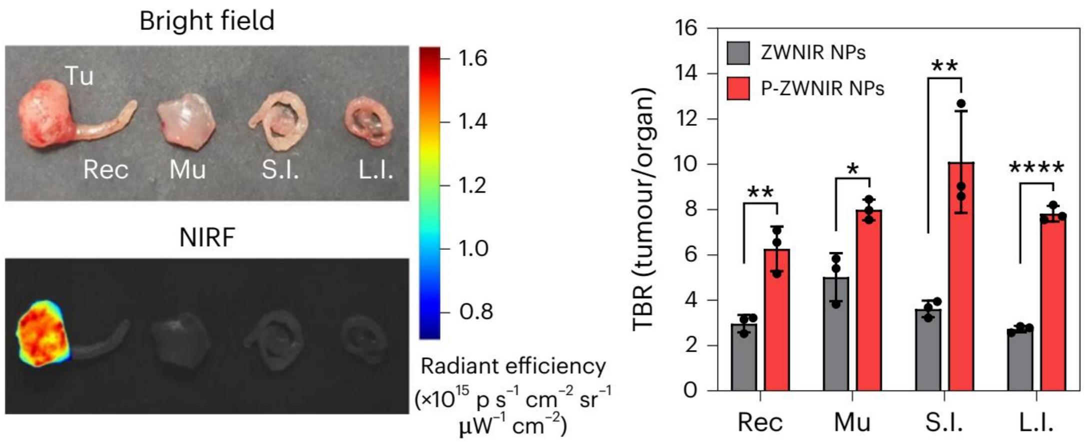
ex vivo NIRF imaging at 24 h post injection



Colon cancer

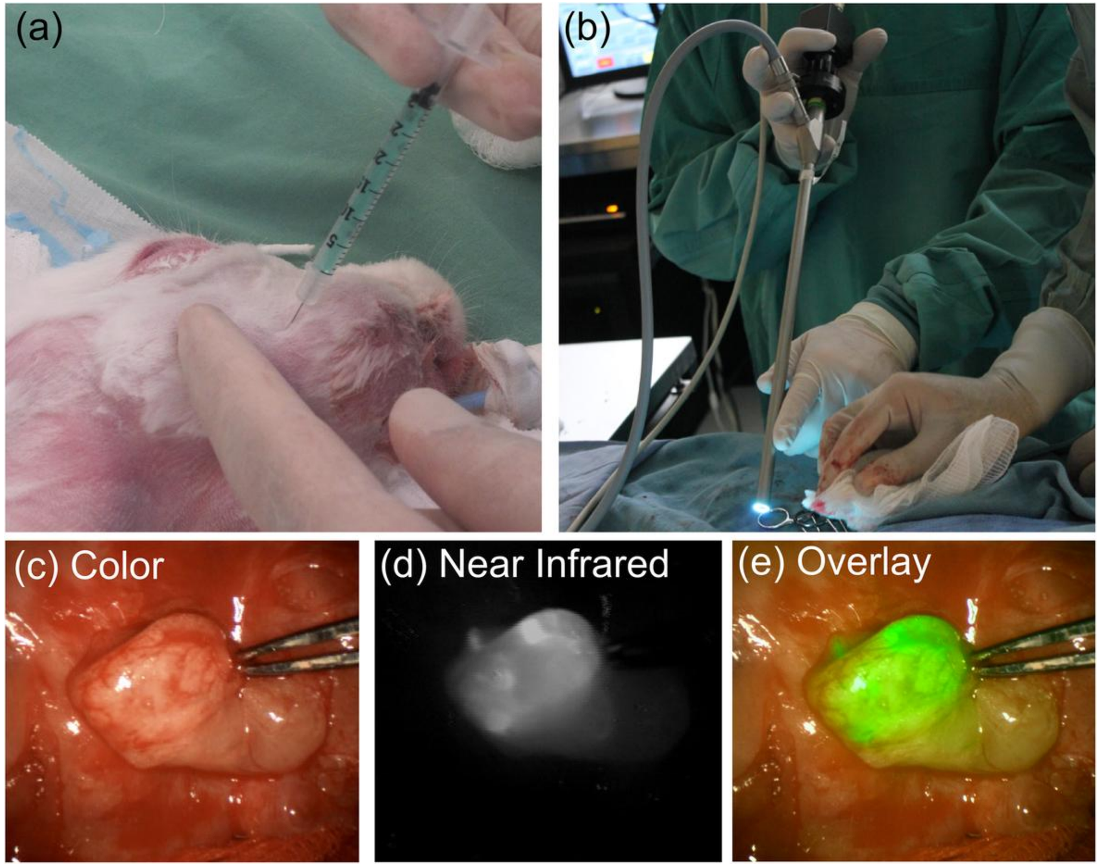
Tumor penetrating NPs

ex vivo NIRF imaging at 8 h post injection



Rectal cancer

Fluorescence image-guided surgery (FGS)

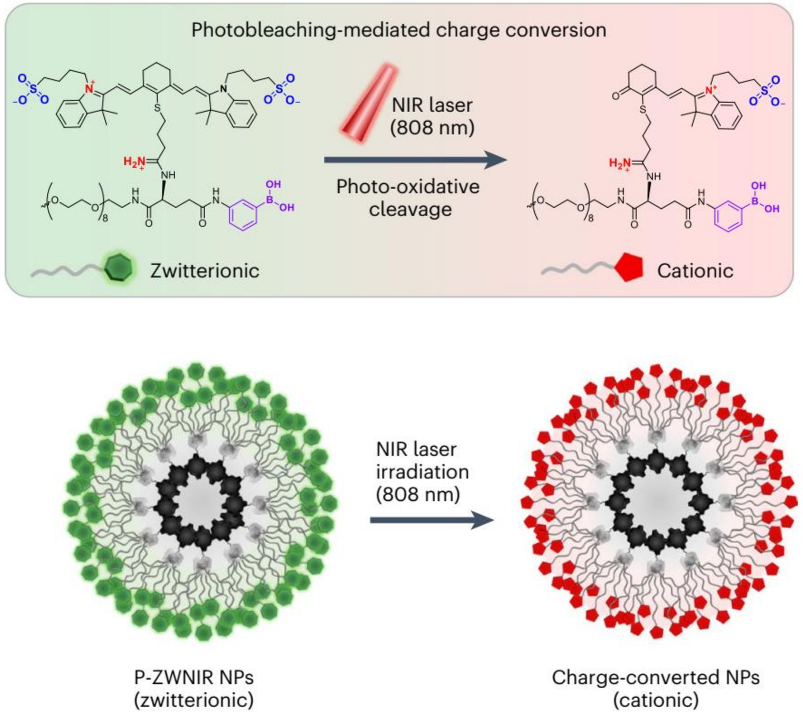


Surgical guidance using intraoperative NIR fluoresence im
aging in head and neck surgery with VX2 carcinoma beari
ng New Zealand White rabbit in buccal area

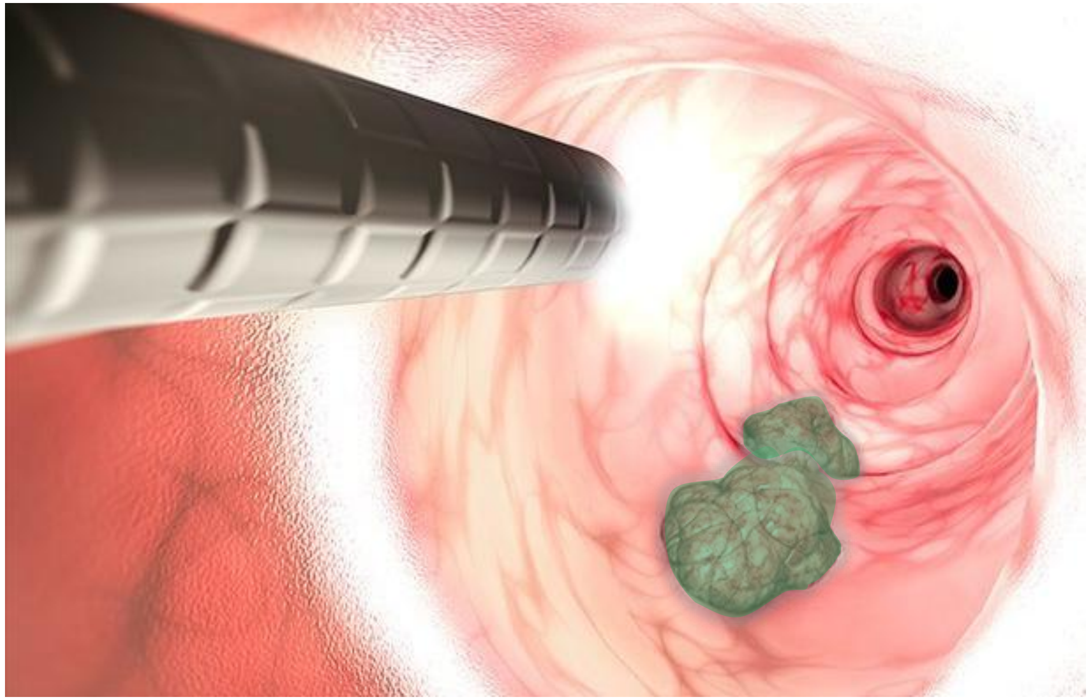
BMC Medical Imaging **20**, 106 (2020)

High tumor selectivity makes image-guided therapy

Fine tuning of chemical structures
*Nanocarrier + Fluorophore



Fluorescence image-guided phototherapy



One-shot laser therapy → Complete remission

Current research and interests

Research fields

Small chemical drug delivery

Chemical engineering of nanomaterials
- Renal or hepatobiliary clearable materials
- Photobleaching materials

Chemical engineering of organic fluorophores
- Photobleaching materials
- Anti-photobleaching materials

Potential fields for collaboration

Biopharmaceutical delivery
- RNA therapeutics
- Prime editors: base edit

Developing delivery technique
- Light (NIR-I or NIR-II)
- Ultrasound

Current research and interests

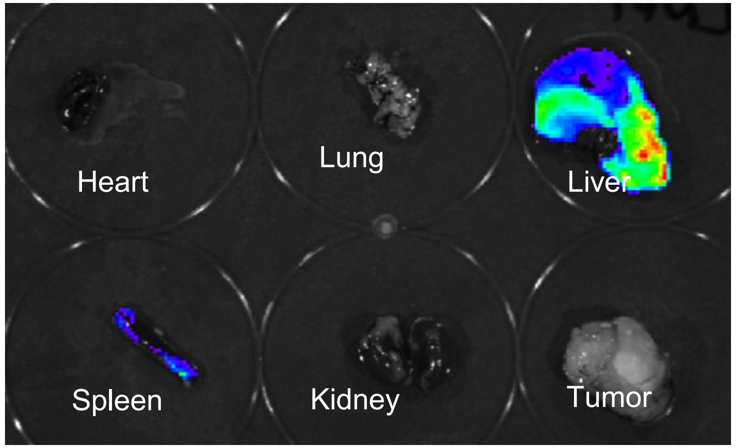
❖ Utilizing cyclodextrin derivatives to modulate biodistribution of mRNA LNPs

Lipid nanoparticles (LNPs) + CD derivatives

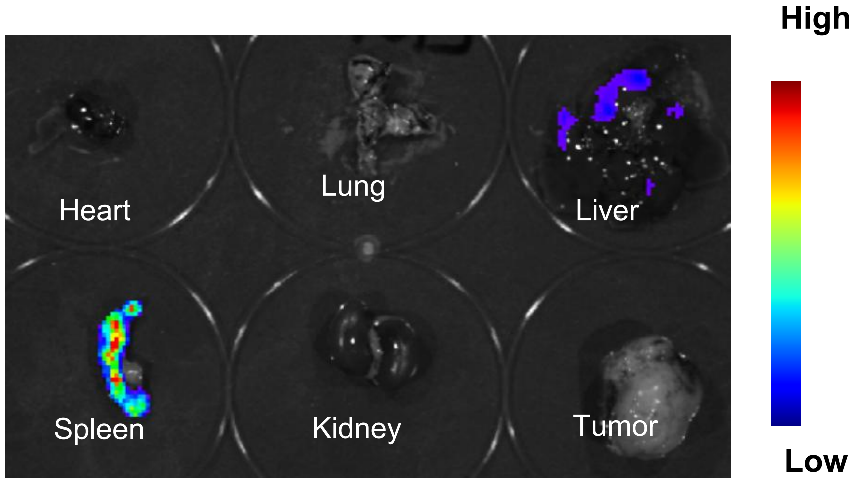
➔ **Hybrid LNP**

Conventional mRNA-LNP
MC3LNP

Spleen-targeted Hybrid LNP
Candidate#B12



vs

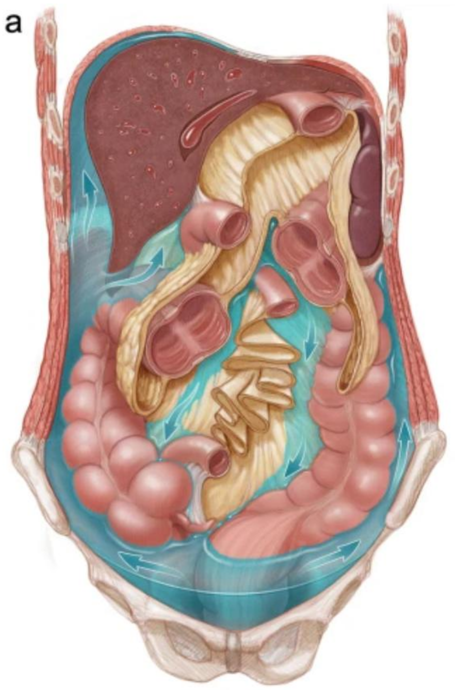


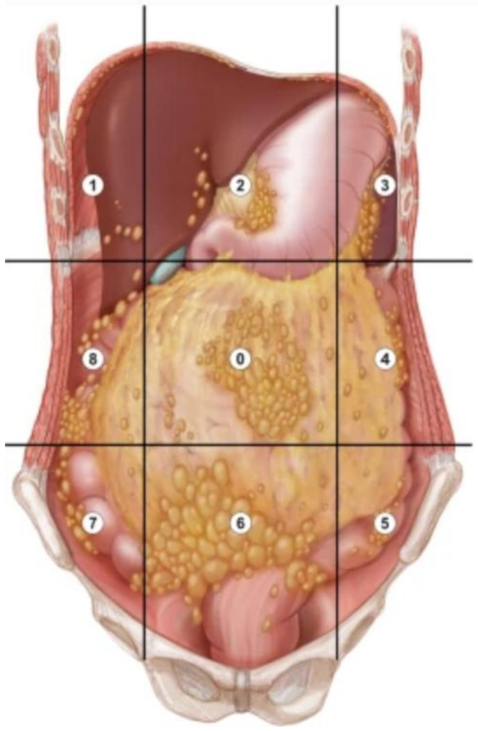
Unpublished data

Current research and interests

❖ Expanding the application of the **phototheranostics** to Intractable cancer such as **peritoneal metastasis** and **pancreatic cancer**.

a





Q&A

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- Piljae Song

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- Dr. So-Yeol Yoo
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