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Overview of Nanoparticle-Based Targeted Drug Delivery

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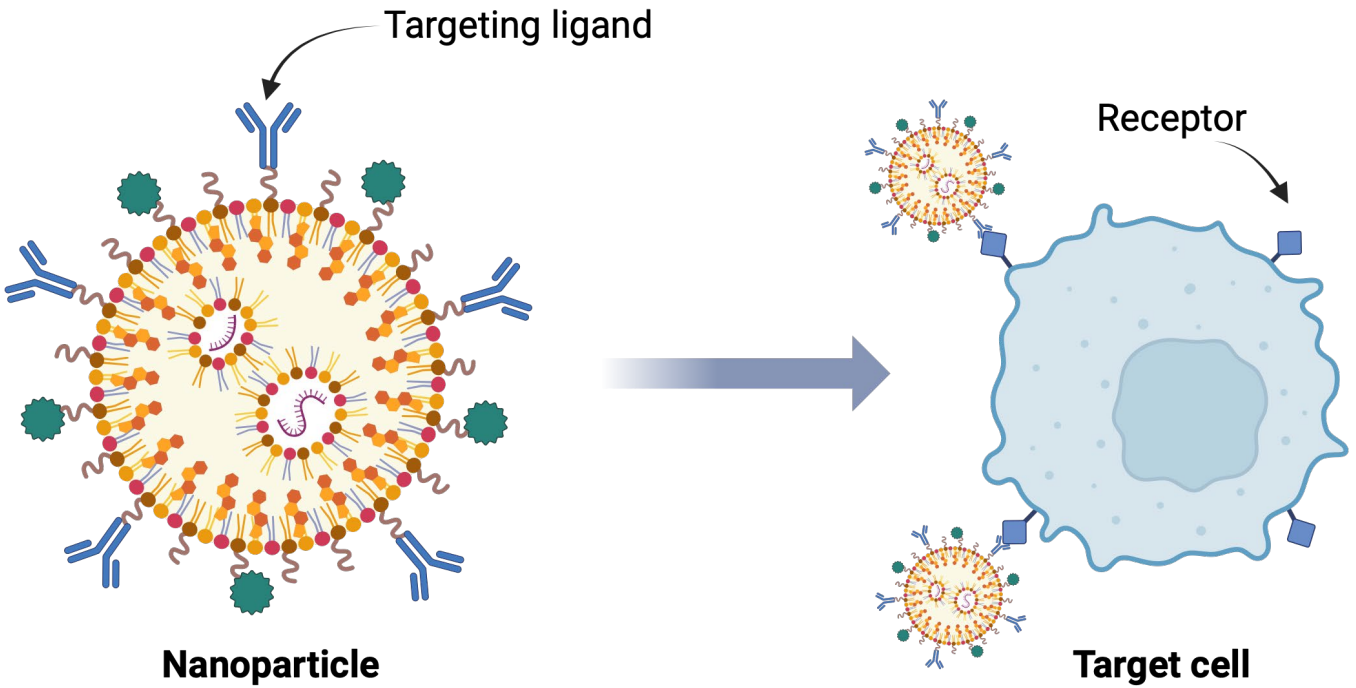
What is “Active Targeting”?

Definition - **nanocarrier surface is functionalized with ligands that enhance its affinity for a specific cell type or biological substrate.**



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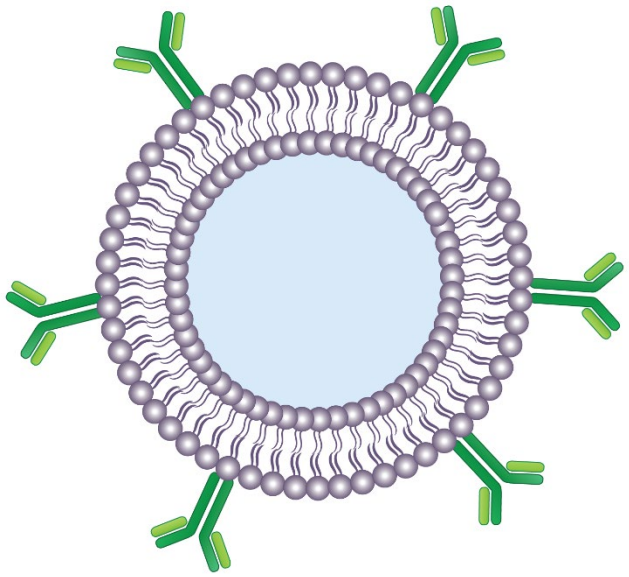
Origins of Targeted Nanodelivery



- Antibodies show exceptional affinity for their targets
- Antibody-functionalized liposomes (immunoliposomes) is the first type of actively targeted nanocarrier

› Biochem Biophys Res Commun. 1979 Aug 28;89(4):1114-9. doi: 10.1016/0006-291x(79)92123-5.

Preservation of antimyosin antibody activity after covalent coupling to liposomes

V P Torchilin, B A Khaw, V N Smirnov, E Haber

PMID: 496941 DOI: 10.1016/0006-291x(79)92123-5

› Science. 1980 Oct 31;210(4469):539-41. doi: 10.1126/science.7423203.

Antibody targeting of liposomes: cell specificity obtained by conjugation of F(ab')2 to vesicle surface

T D Heath, R T Fraley, D Papahdjopoulos

PMID: 7423203 DOI: 10.1126/science.7423203

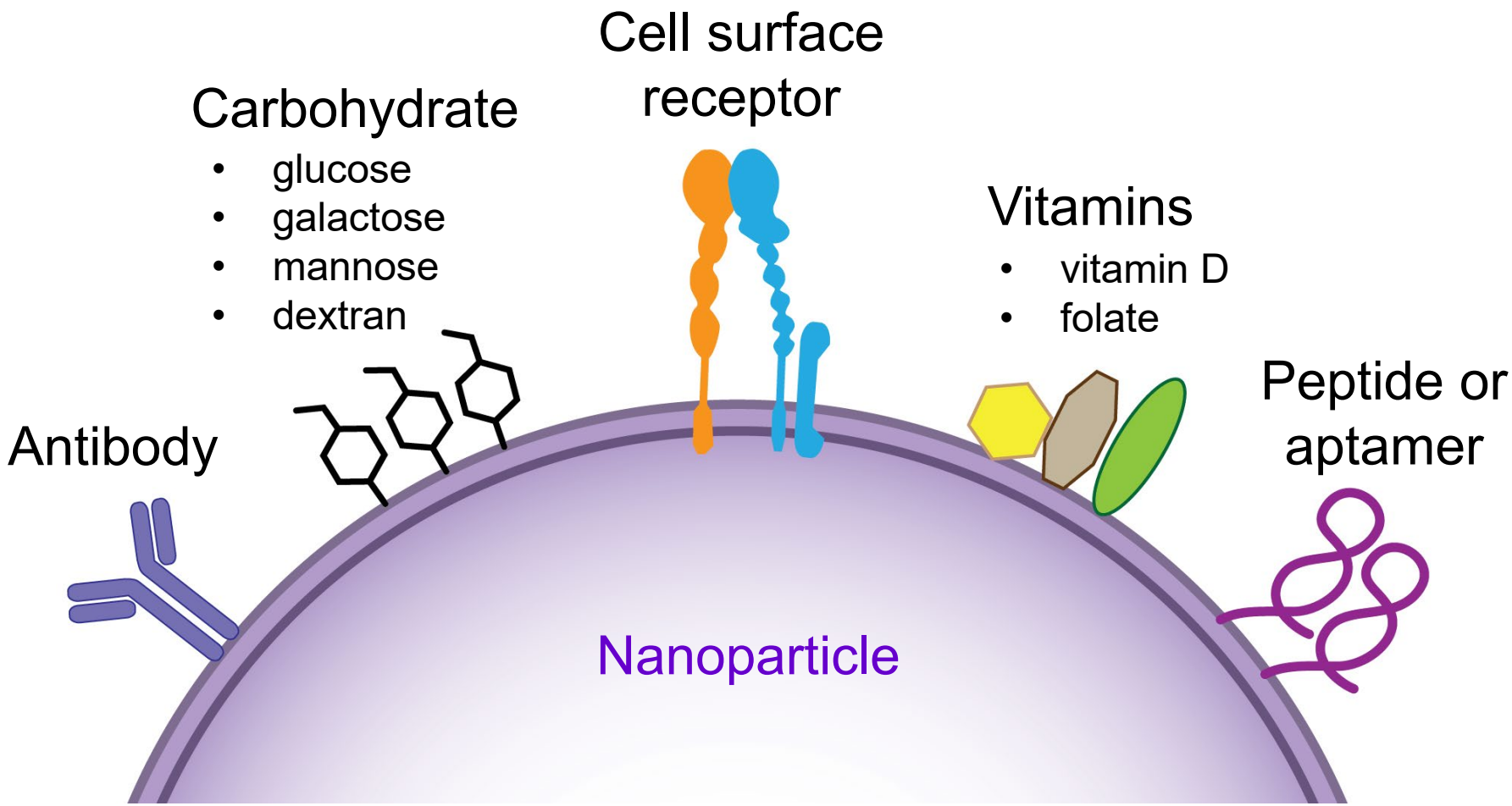
› Nature. 1980 Dec 11;288(5791):602-4. doi: 10.1038/288602a0.

Targeting to cells of fluorescent liposomes covalently coupled with monoclonal antibody or protein A

L D Leserman, J Barbet, F Kourilsky, J N Weinstein

PMID: 7442804 DOI: 10.1038/288602a0

Development Over the Past Several Decades

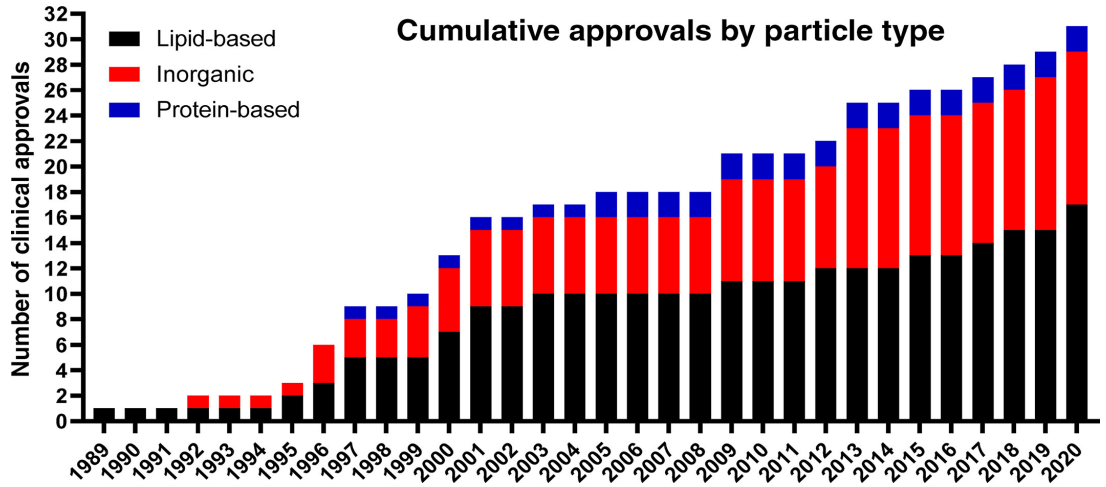


- Researchers have utilized various ligands for targeted nanodelivery, including antibodies (+ derivatives), oligonucleotides, peptides, and small molecules, among others.

Nat Rev Drug Discov. 2021, 20(2): 101-124.

From Bench to Bedside

- **Nanoparticle approvals are increasing rapidly**



Source:
Bioeng. Transl. Med. 2021, *6*, e10246.

- **However, actively targeted formulations remain scarce**

2016: Liposome with anti-transferrin receptor antibody
PSMA-targeted PEG-PLGA or PEG-PLA nanoparticle
HER2-targeted PEGylated liposome

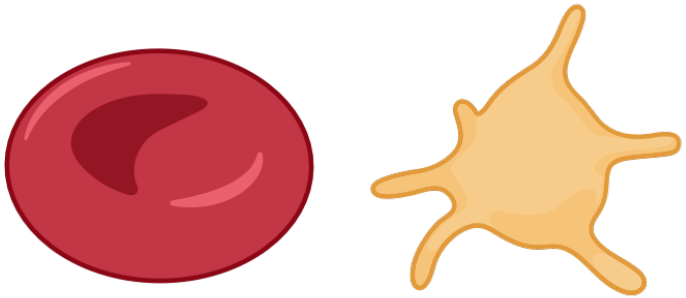
2019: Anti-EGFR conjugated liposome
Liposome with anti-EphA2 antibody

Key Challenges for Targeted Nanodelivery

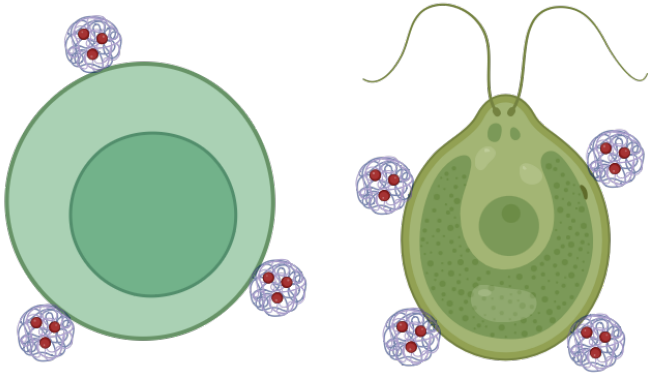
- **Manufacturing**
  - Added complexity associated with chemical conjugation
  - Per nanoparticle ligand density is hard to control
  - Incorporating >1 ligand for multifunctionality is difficult
- **Disease heterogeneity**
  - Single marker may lead to resistance to treatment
- **Endosomal uptake**
  - Receptor-mediated uptake leads to endosomal degradation
- **Immunogenicity**
  - Many ligands are not naturally occurring, which can lead to anti-carrier immunity that facilitates premature clearance

Emerging Natural and Biomimetic Platforms for Targeted Delivery

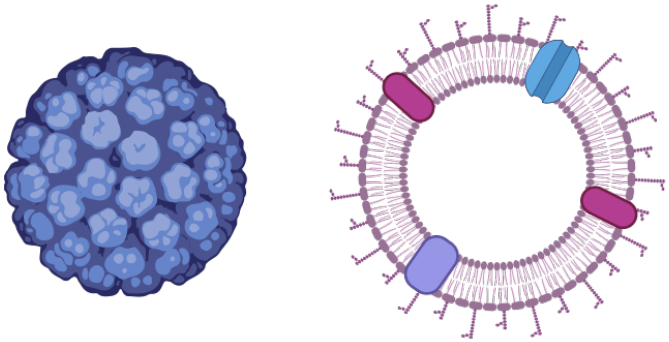
Cellular carriers



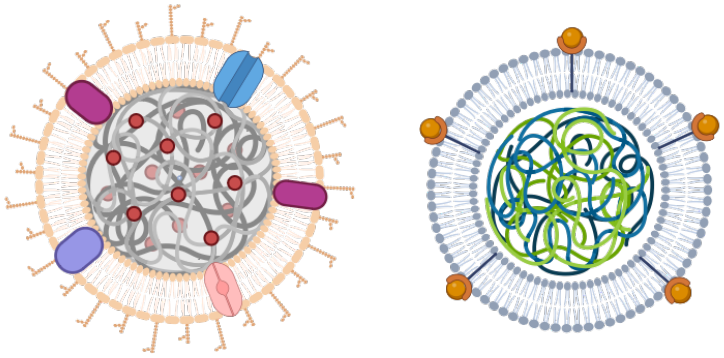
Biohybrids



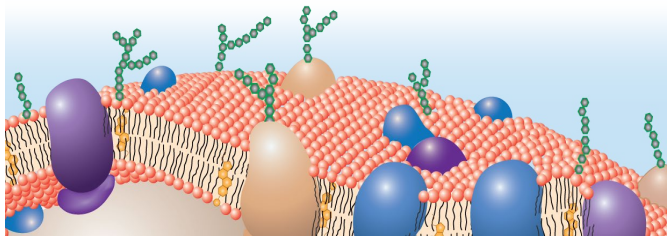
Natural particulates



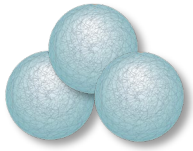
Membrane-coated nanoparticles



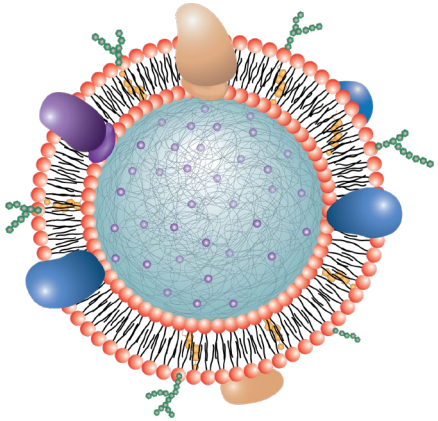
Cell Membrane Coating Nanotechnology



Coating



Nanoparticle core



Cell membrane-coated nanoparticle

"Cellular Nanoparticle (CNP™)"

2011 First **paper** on cell membrane coated nanoparticle technology (*PNAS* **2011**, *108*, 10980)

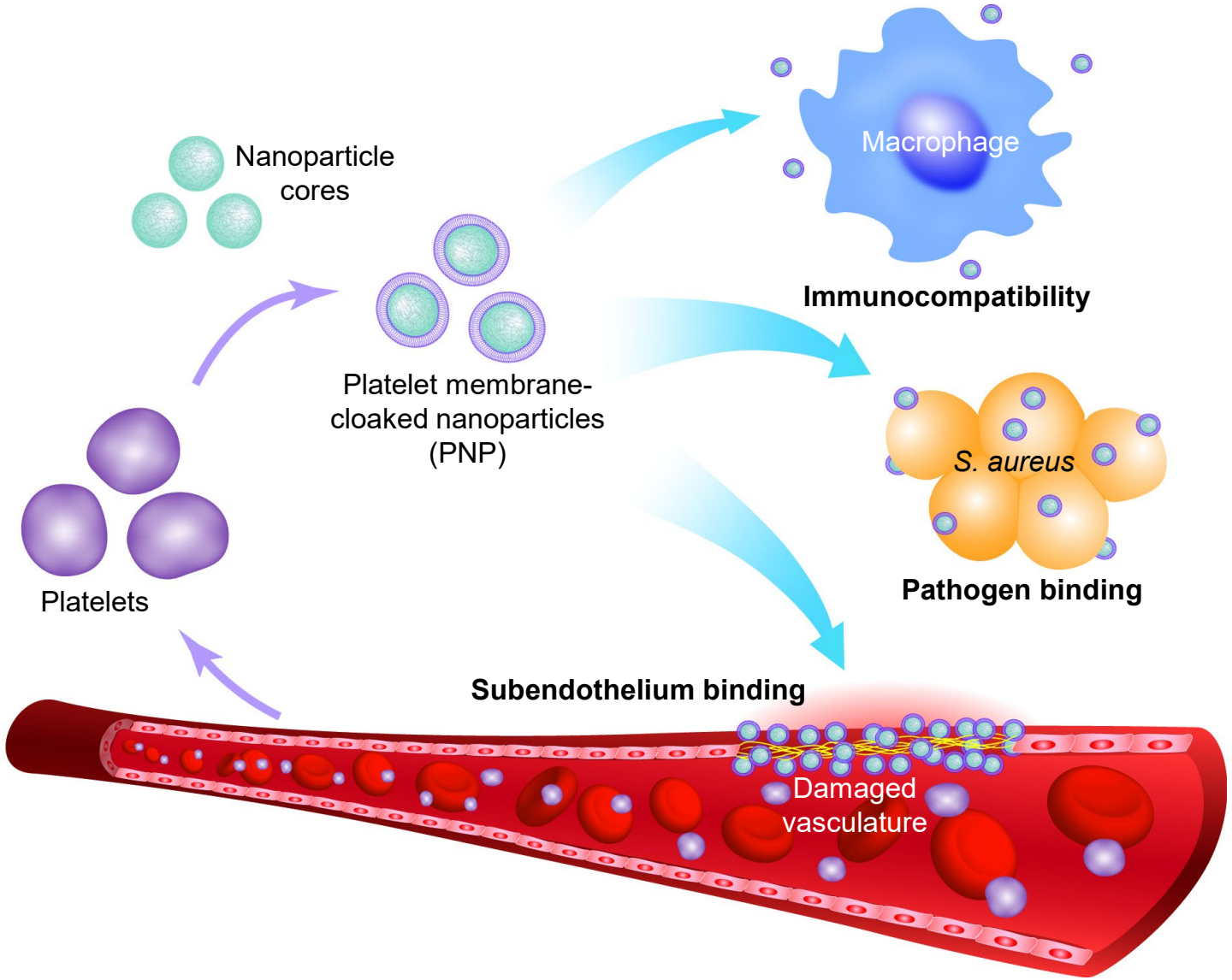
2017 First **patent** on cell membrane coated nanoparticle technology was issued in **2017**.

2022 First **trademark** on CNP and Cellular Nanoparticle (CNP) was approved in **2022**.

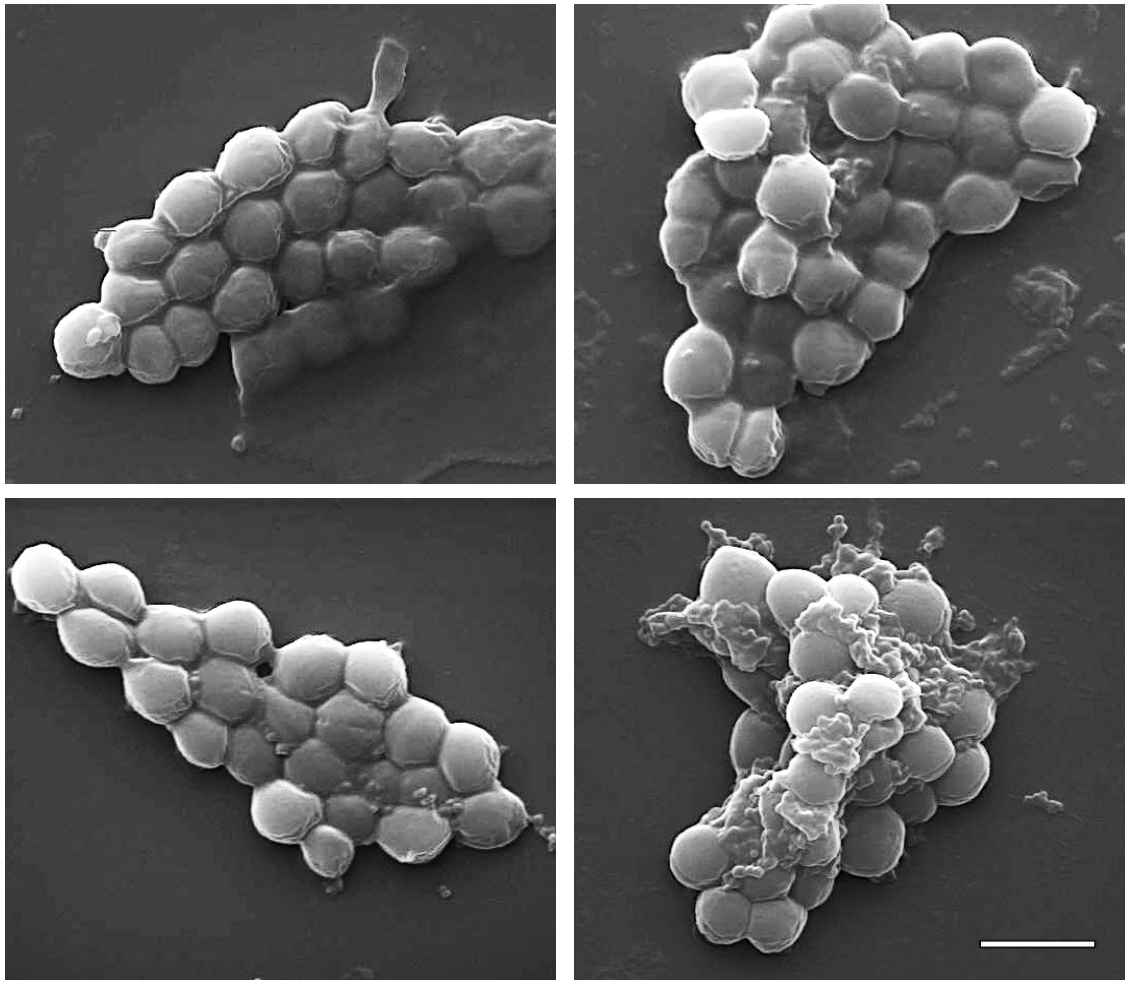
First **IND** of RBC-NPs for the treatment of MRSA pneumonia was approved by FDA in **2022**.

Basic research continues
More translation is to come

I. Wild-Type Platelet CNP for Targeted Delivery



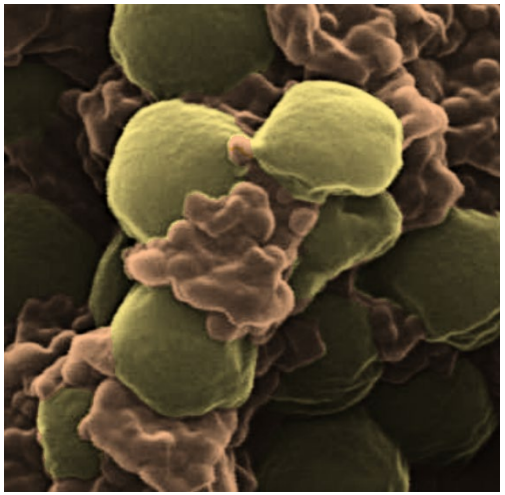
In Vitro Bacterial Targeting of PNP



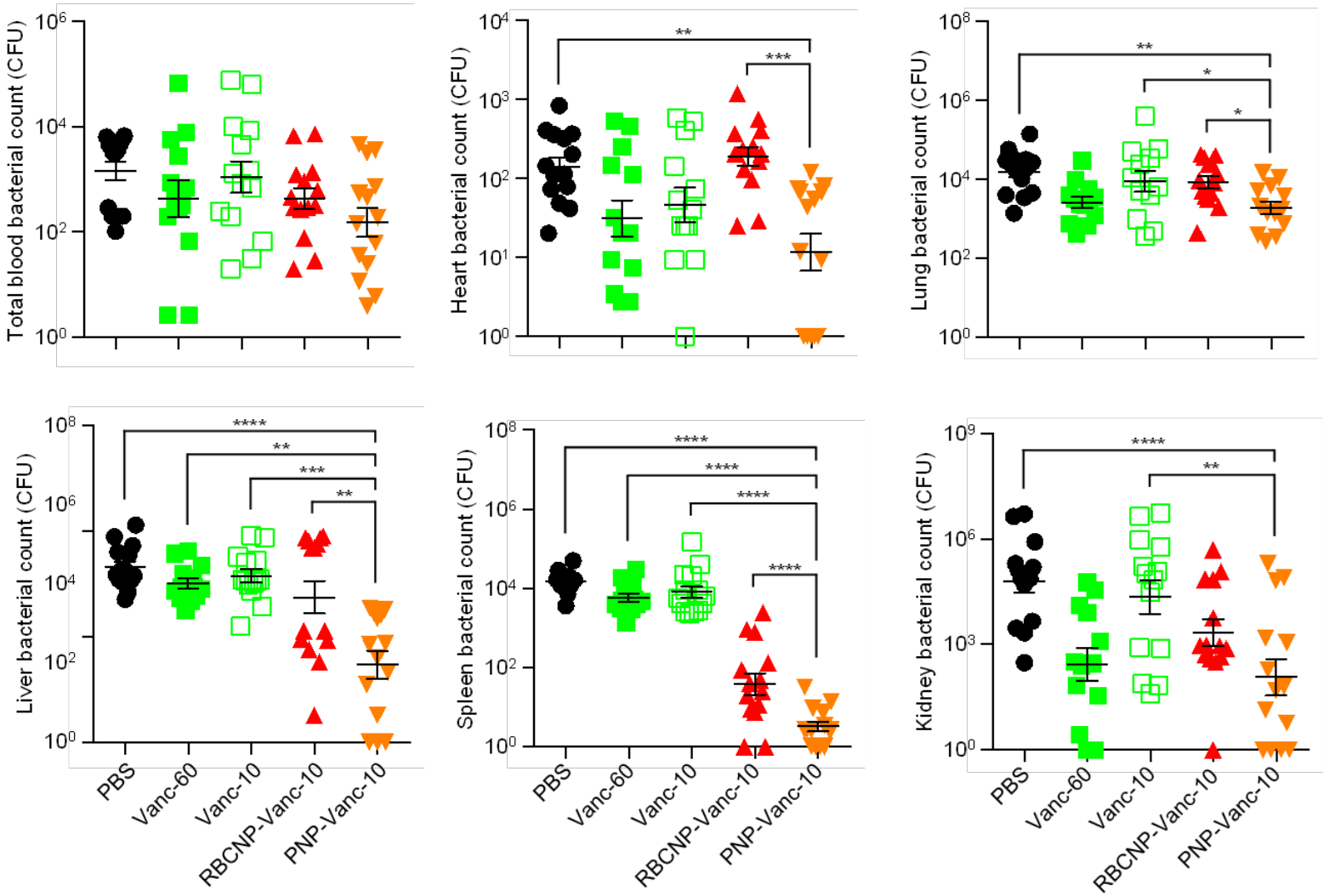
Bacteria: MRSA252

Top left: PBS
Top right: Bare NP
Bottom left: RBCNP
Bottom right: PNP

Pseudocolored SEM Image



In Vivo Antimicrobial Efficacy of PNP(antibiotics)

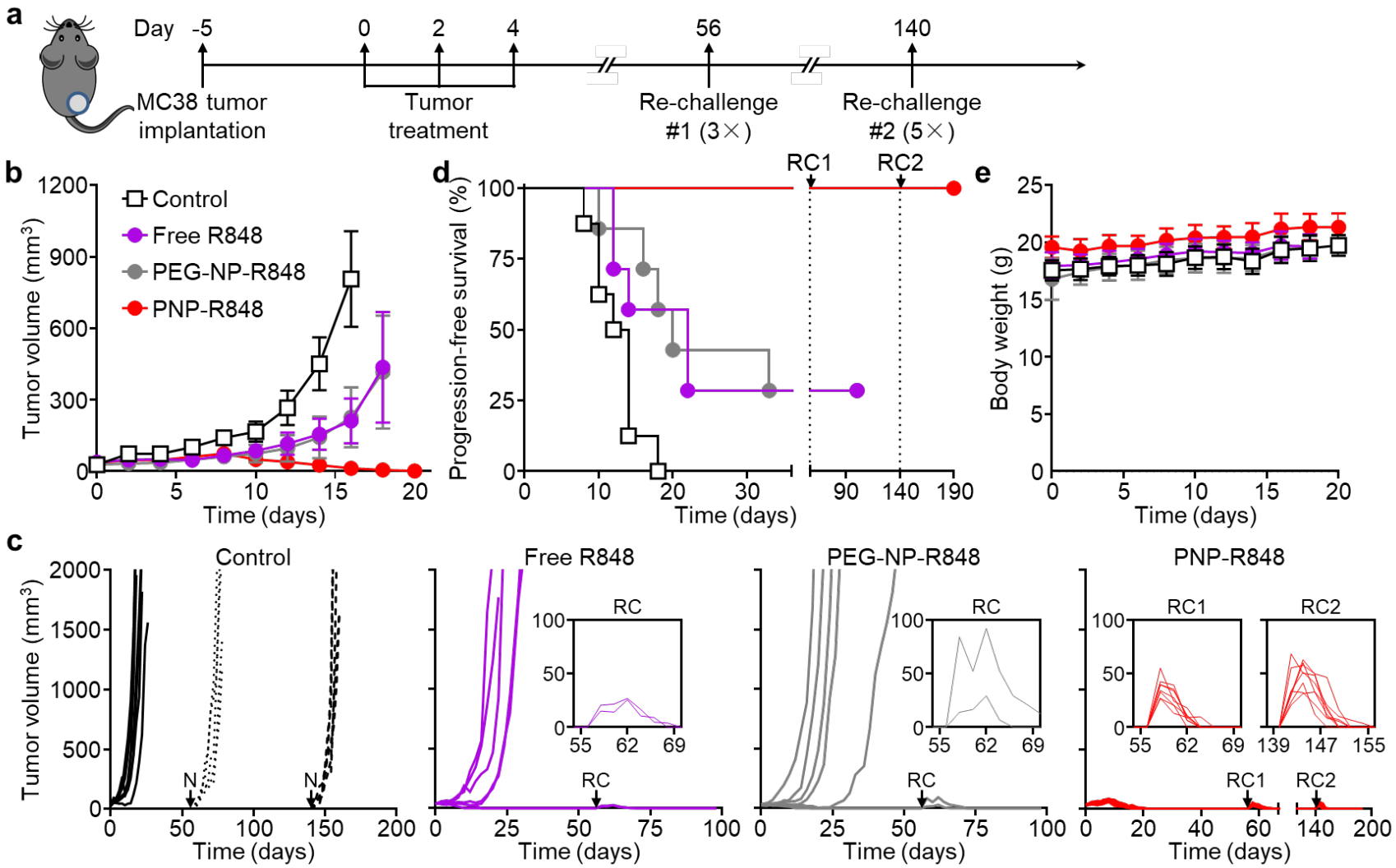


I.V. challenge of 6x10^6 CFU of MRSA252
Once daily I.V. treatment for 3 days
Bacterial enumeration 24 h post last treatment

1/6th of clinical antibiotic dosage
1000 times more reduction of bacterial count

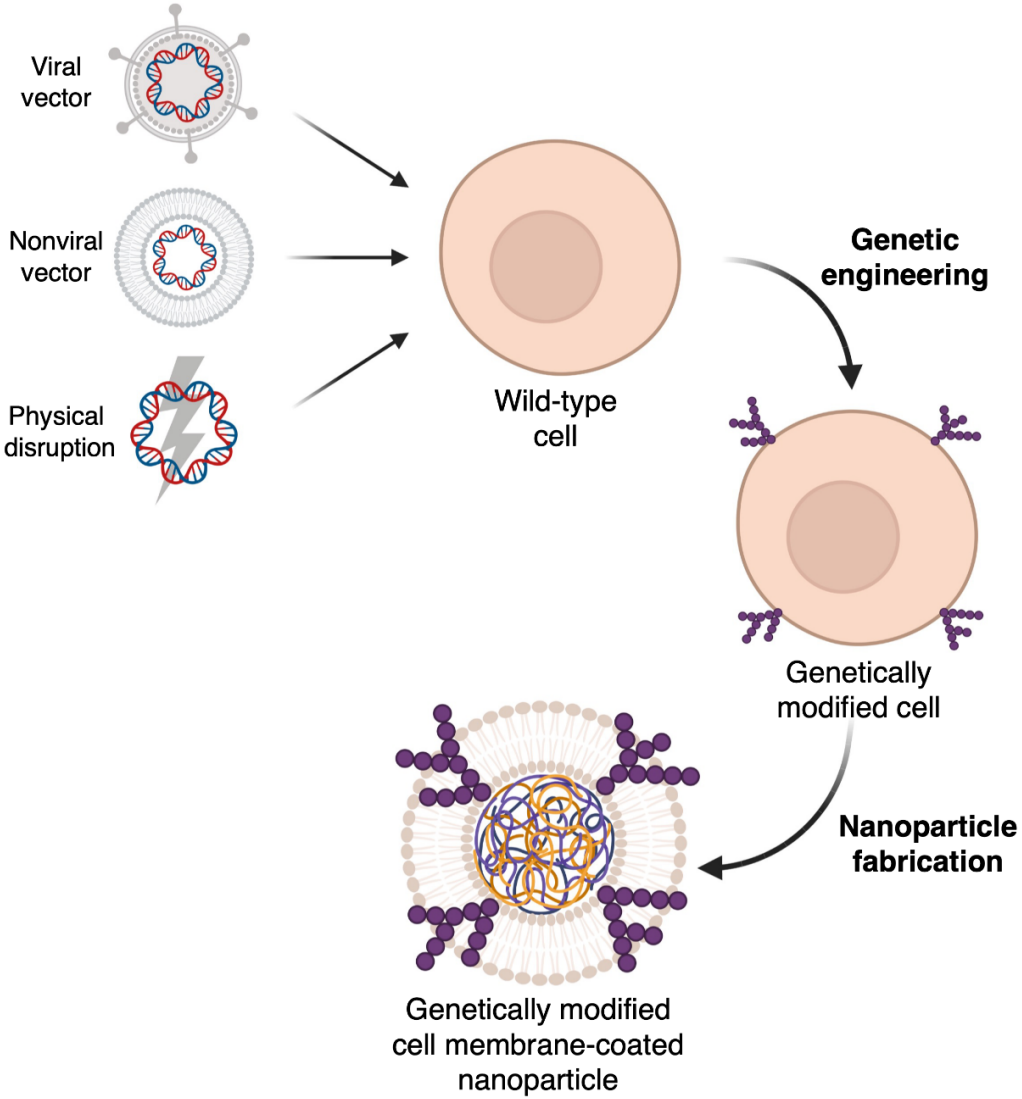
Nature 2015, *526*, 118-121

Therapeutic Antitumor Efficacy of PNP(R848)



Nature Communications 2021, *12*, 1999

II. Genetically Engineered CNP for Targeted Delivery



- Wild-type cells are genetically engineered through a viral vector, nonviral vector, or physical disruption.
- Engineered cell membrane is then harvested to fabricate cellular nanoparticles for enhanced functionalities.

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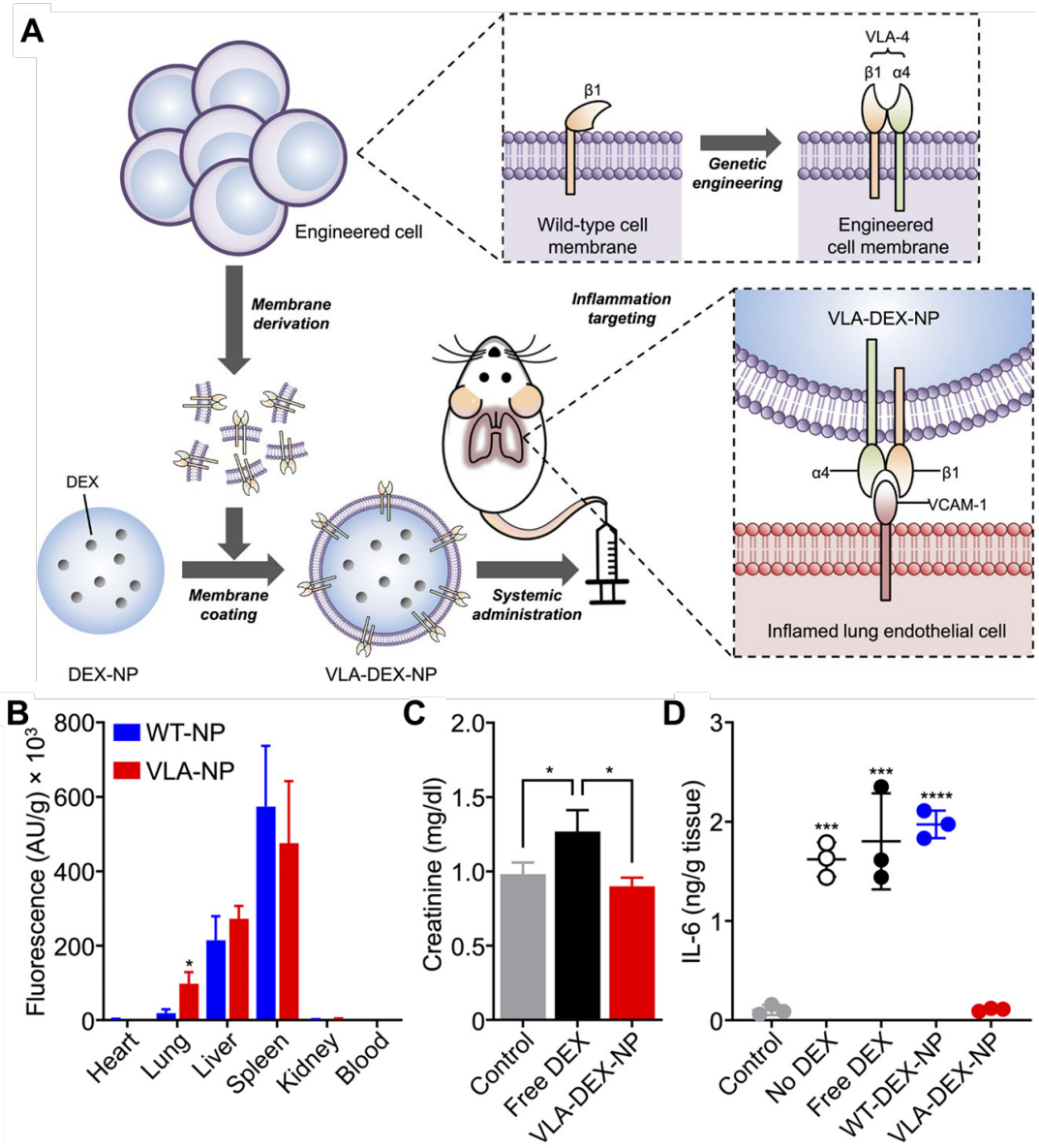
Targeted Delivery to Inflamed Lungs

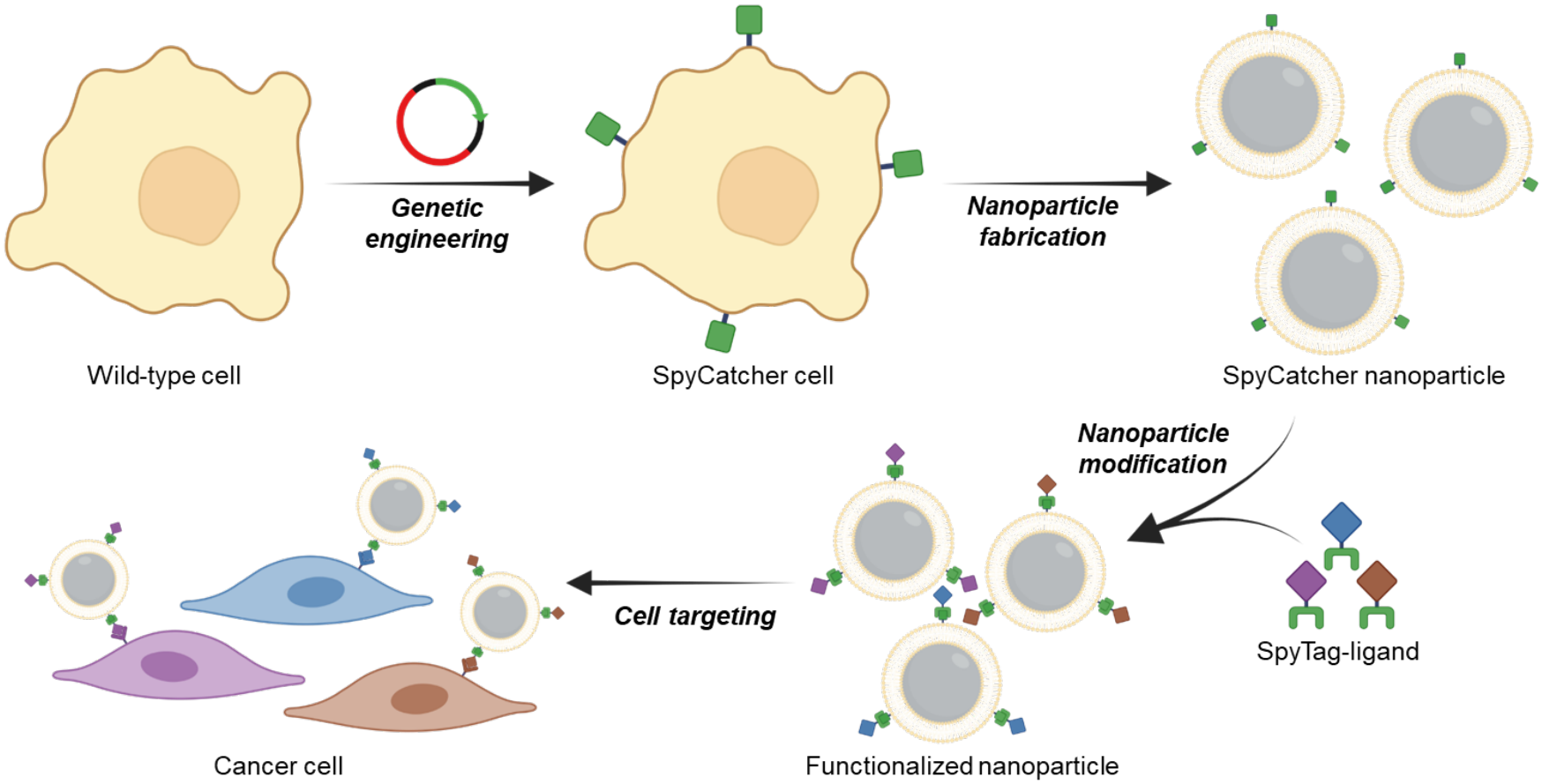


Wild-type cells were genetically engineered to express VLA-4 (very late antigen-4), which is comprised of integrins α4 and β1.

VLA-4 can target VCAM-1 (vascular cell adhesion molecule-1) on inflamed lung endothelial cells for enhanced drug delivery.

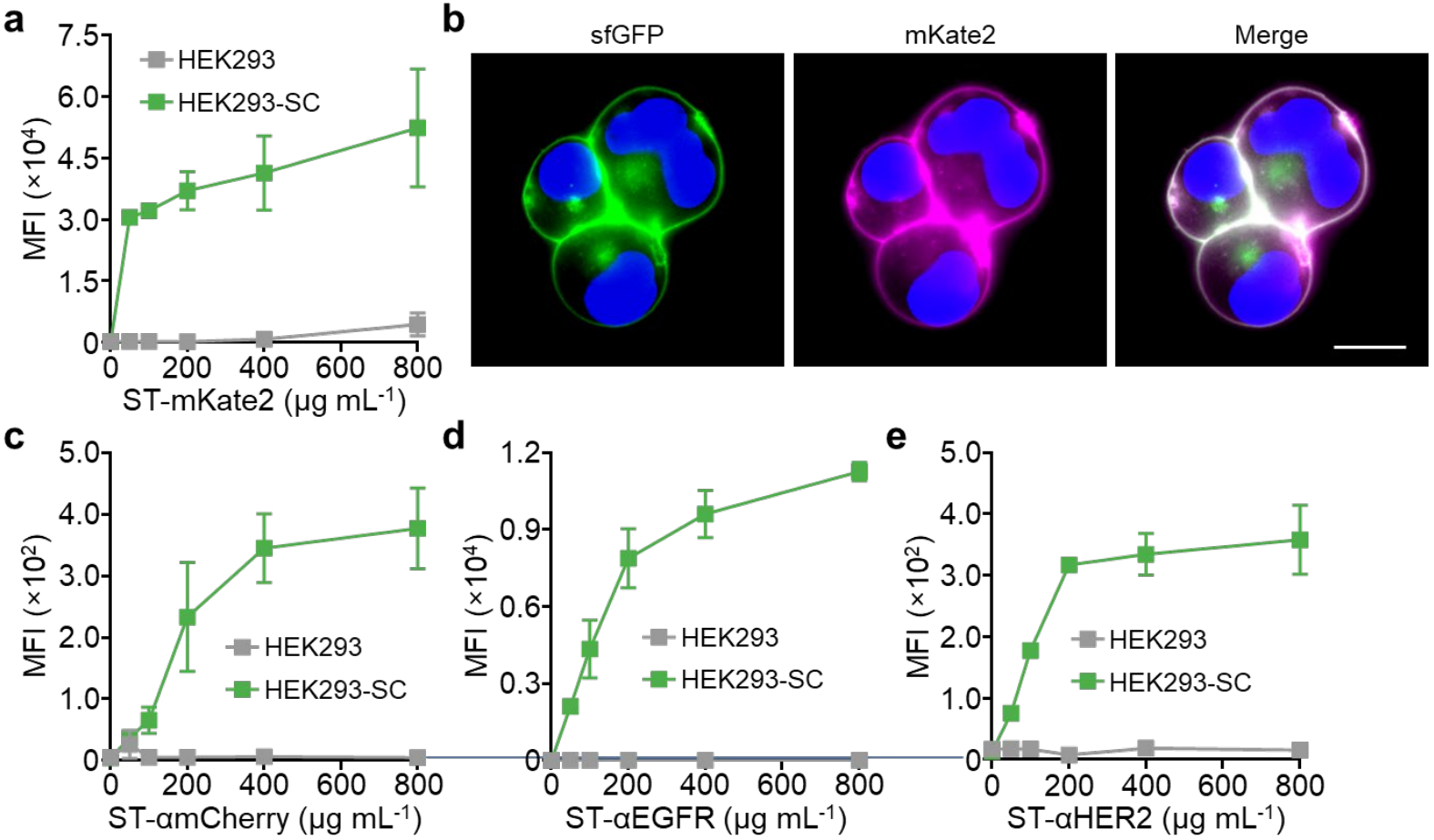
Science Advances 2021, 7, eabf7820.

A Modular Approach to Functionalizing CNPs



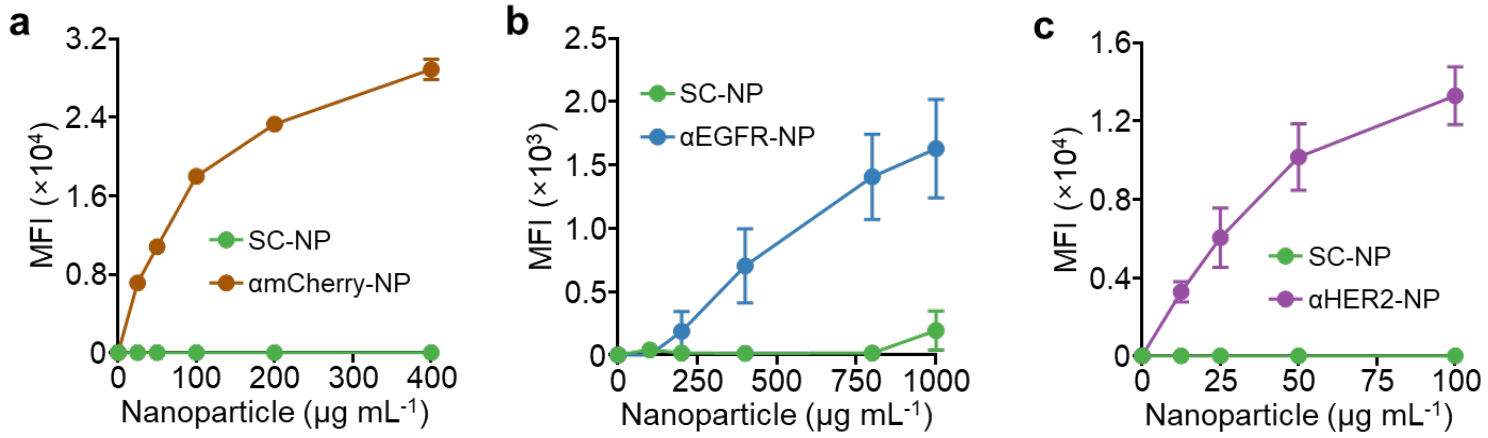
The cell membrane coating is engineered to express a SpyCatcher anchor that can readily form a covalent bond with any moiety modified with SpyTag. Three unique targeted CNP formulations are generated using a designed ankyrin repeat protein, an affibody, and a single-chain variable fragment.

Functional Characterization of SpyTag-Ligands

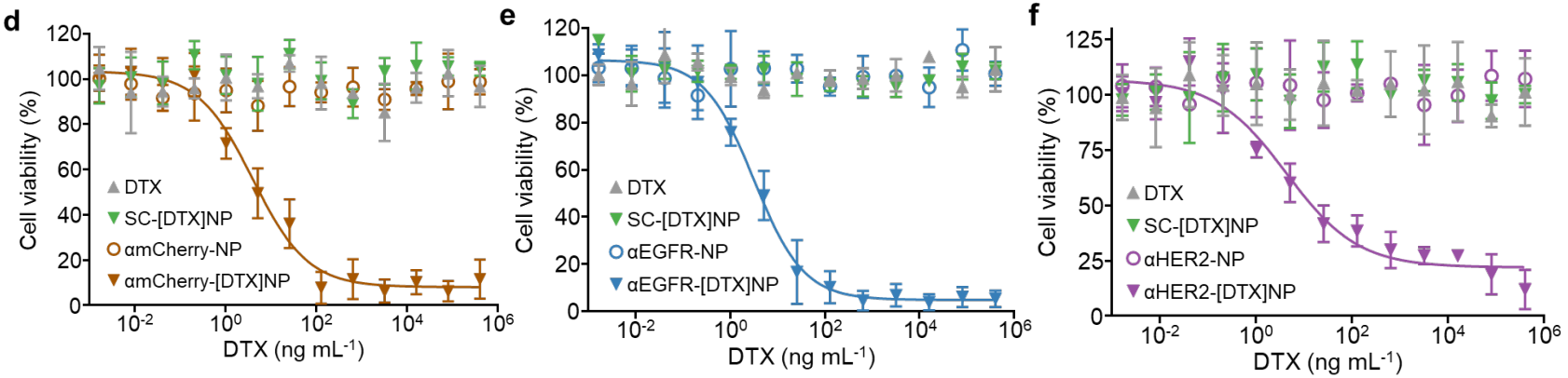


a, Dose-dependent binding of ST-mKate2 with wild-type HEK293 or HEK293-SC cells. **b,** Live cell fluorescent visualization of ST-mKate2 after binding with HEK293-SC cells. Blue: nuclei (DAPI), green: SpyCatcher (sfGFP), magenta: mKate2; scale bar: 10 μm. **c-e,** Dose-dependent binding of ST-αmCherry (c), ST-αEGFR (d), and ST-αHER2 (e) with wild-type HEK293 or HEK293-SC cells .

Characterization of Modularly Functionalized CNPs

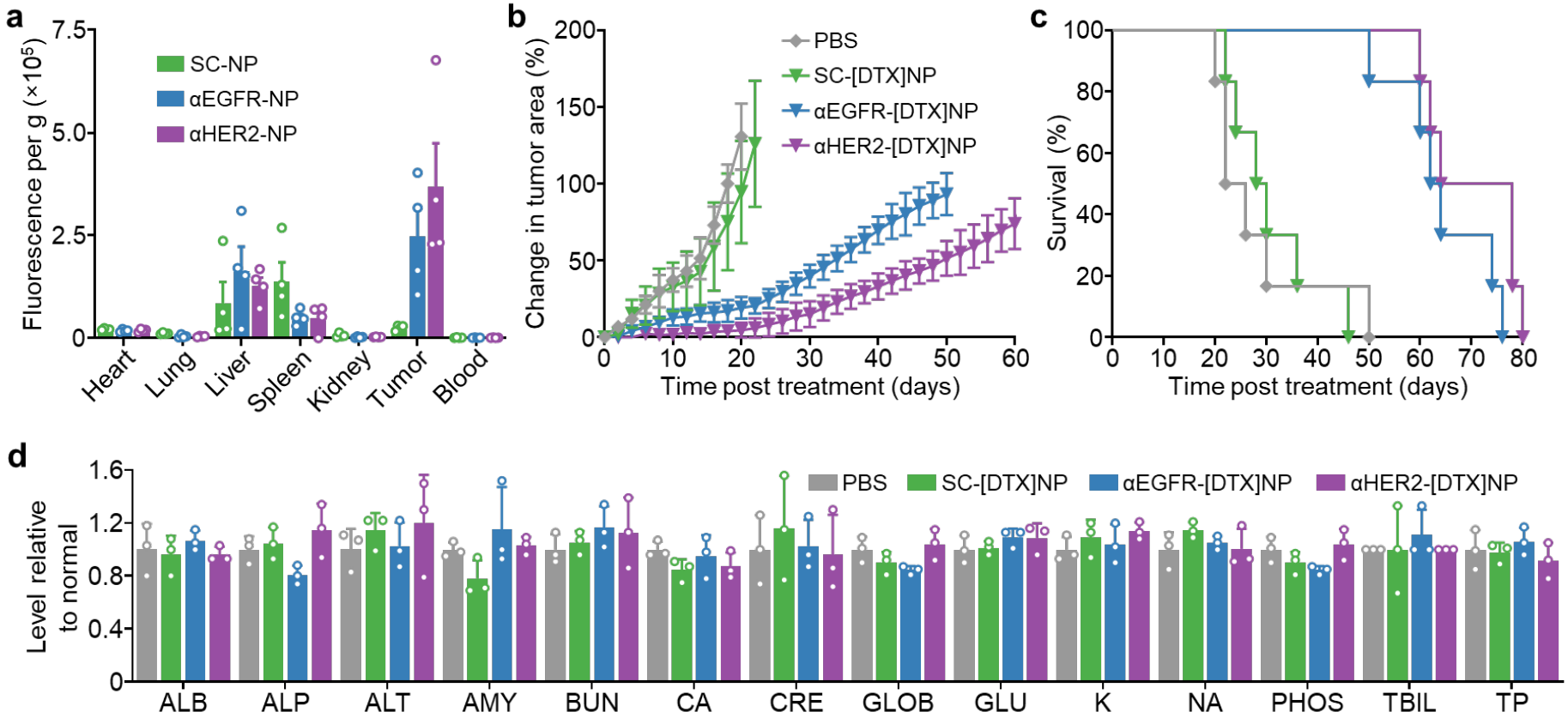


- Dose-dependent binding of αmCherry-NPs to HEK293T-mCherry cells (a), αEGFR-NPs to SKOV3 cells (b), and αHER2-NPs to SKOV3 cells (c). non-targeted SC-NPs were used as controls.



- Dose-dependent cytotoxicity of αmCherry-[DTX]NPs against HEK293T-mCherry cells (d), αEGFR-[DTX]NPs against SKOV3 cells (e), and αHER2-[DTX]NPs against SKOV3 cells (f) measured at 72 h after 15 min of co-incubation.

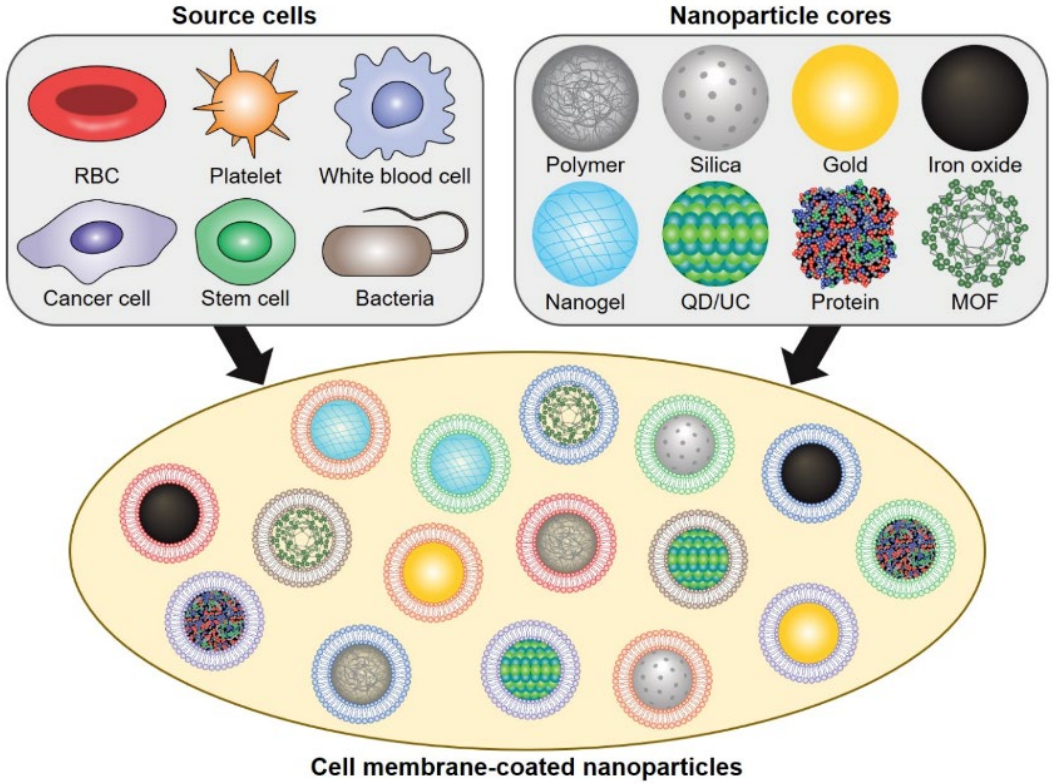
In Vivo Tumor Targeting, Therapeutic Efficacy and Safety

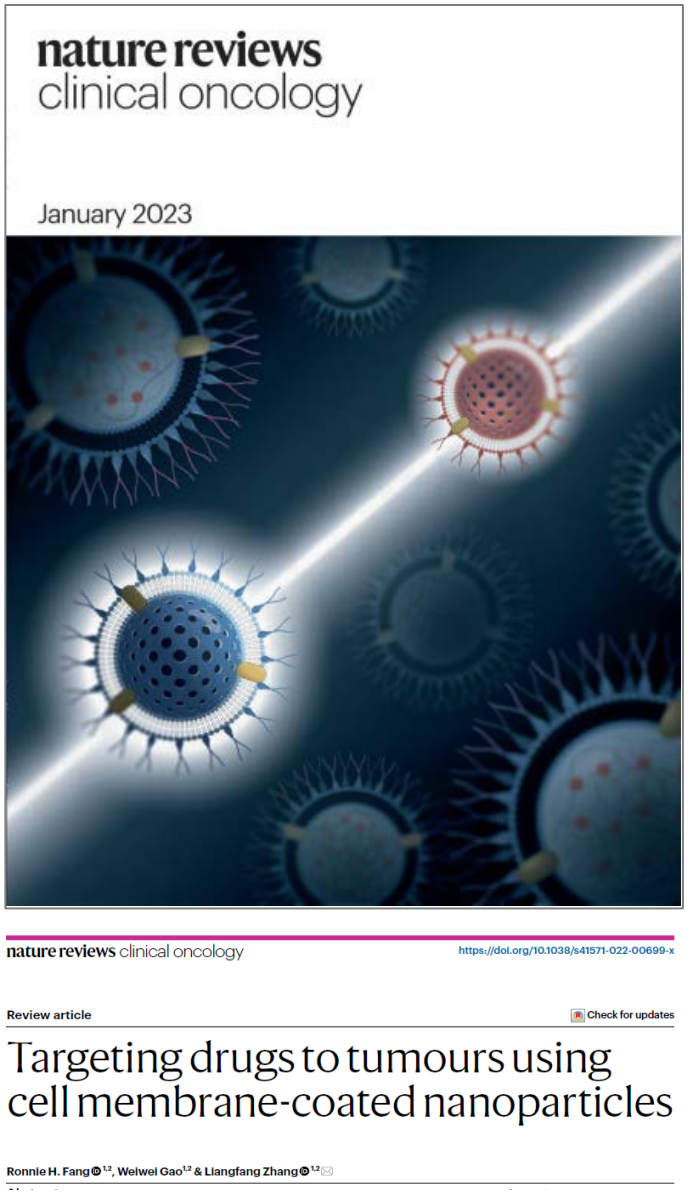


a, Weight-normalized fluorescence of tumors and major organs collected 24 h after intravenous administration. **b,** Growth kinetics of SKOV3 tumors treated intravenously with different groups. **c,** Survival of mice in (d) over time. **d,** Serum biochemistry of immunocompetent mice on day 10 after intravenous administration of different groups; injections were performed on days 0, 3, 6, and 9.

Nature Nanotechnology 2023, *in press* (DOI: 10.1038/s41565-023-01533-w).

CNP as a Versatile Platform for Broad Applications





Nature Reviews Clinical Oncology 2023, *20,* 33-48.

Summary & Outlook

- **Nanoparticle-based targeted delivery continues to be a dynamic and thrilling research field, yet certain challenges persist without resolution.**

- **Natural and bioinspired delivery systems exhibit significant potential in overcoming translational barriers encountered by traditional delivery platforms.**