



Bio-Responsive DNA Nanostructure Conjugates for Neutrophil-Driven Targeted Therapy of Bone Diseases

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MULTISECTOR
INNOVATION
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DELIVERY SCIENCE
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Bone marrow lesions are dysregulated therapeutic niches

Therapeutic challenges in bone diseases:

1. Bone marrow-blood barrier limits drug entry
2. Systemic drugs show insufficient lesion exposure
3. Diseased bone marrow requires microenvironmental control

Key need:

Active delivery

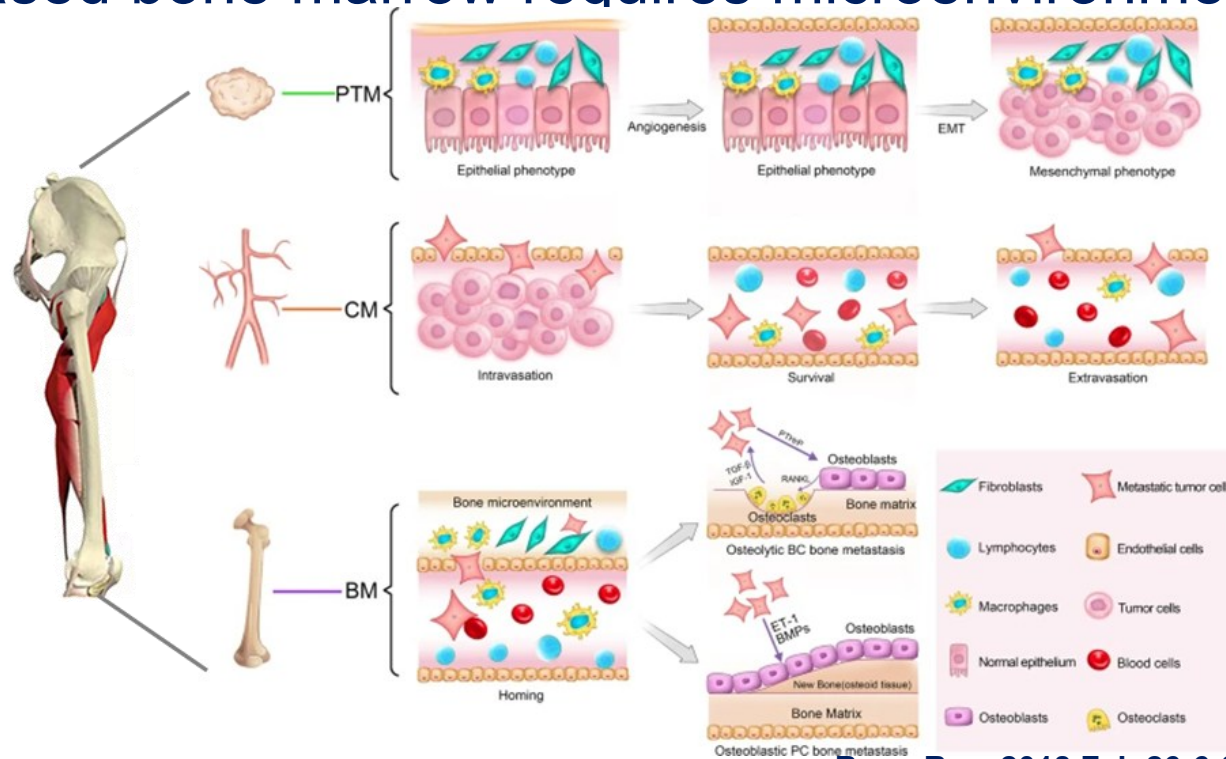
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Local functional regulation

Poor access ❌

Low local concentration ❌

Immune dysregulation ❌

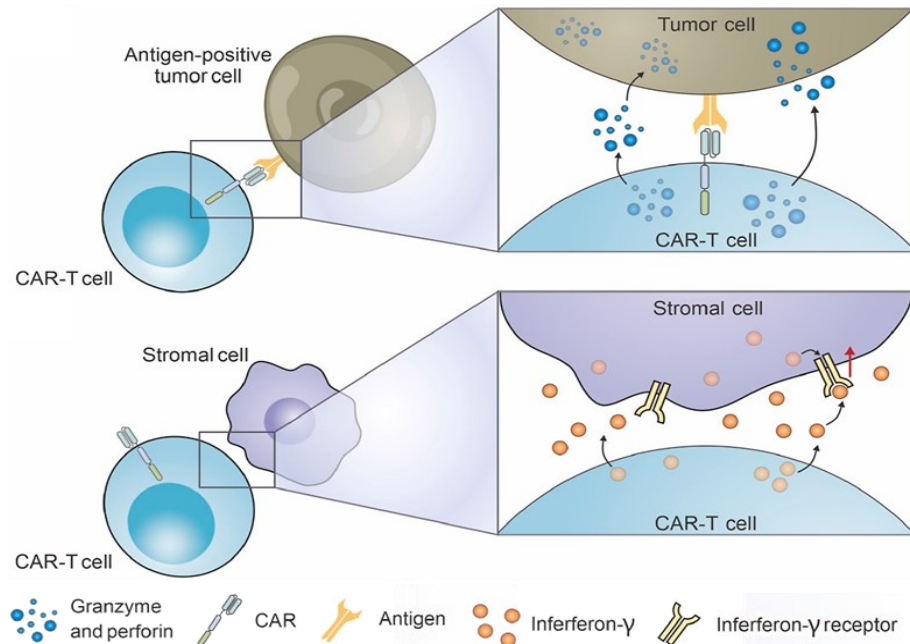


Bone Res. 2018 Feb 26;6:3.



Cell-drug conjugates integrate cellular functions with drugs

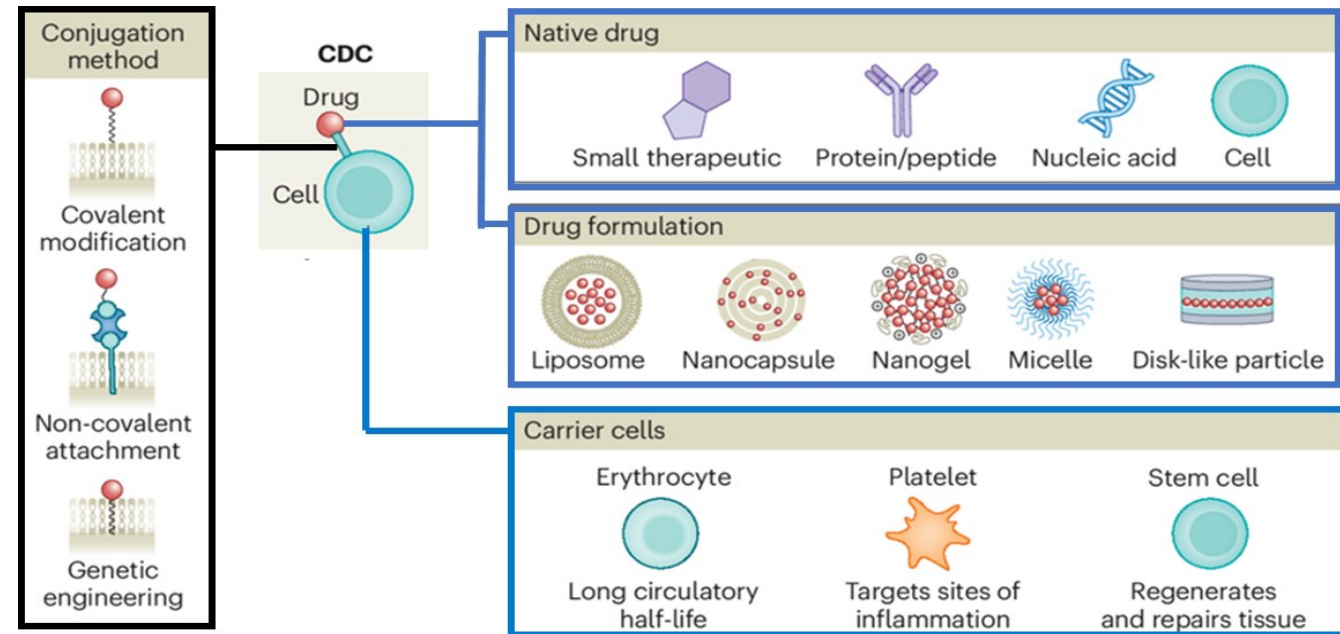
Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T)



Mol Ther. 2023 Nov 1;31(11):3146-3162.

- Limited efficacy in solid tumor
- Systemic toxicity / off-target effects

Cell-drug conjugate strategy (CDC)



Nat Biomed Eng. 2024 Jul 1.

- Cell physiological functions
 - Therapeutic payloads
- } Active targeted delivery



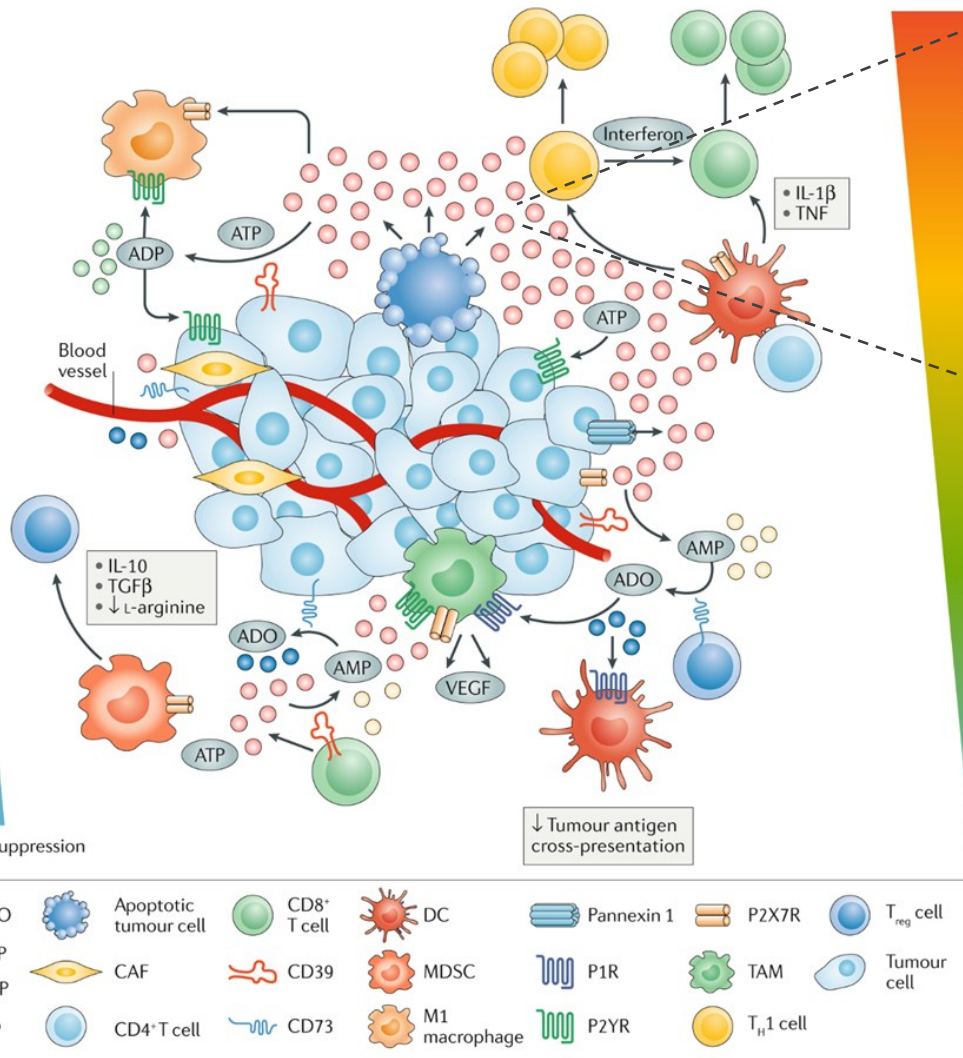
ATP as an endogenous trigger in pathological bone marrow

Adenosine Triphosphate (ATP):

- Normal physiological ATP: 10–100 nM
- Pathological ATP: 100–500 μ M
- Difference: 10^3 – 10^4 fold

ATP aptamer:

- Short DNA/RNA sequence
- Easy to synthesize and modify
- High affinity to ATP
- Enables ATP-triggered structural switching

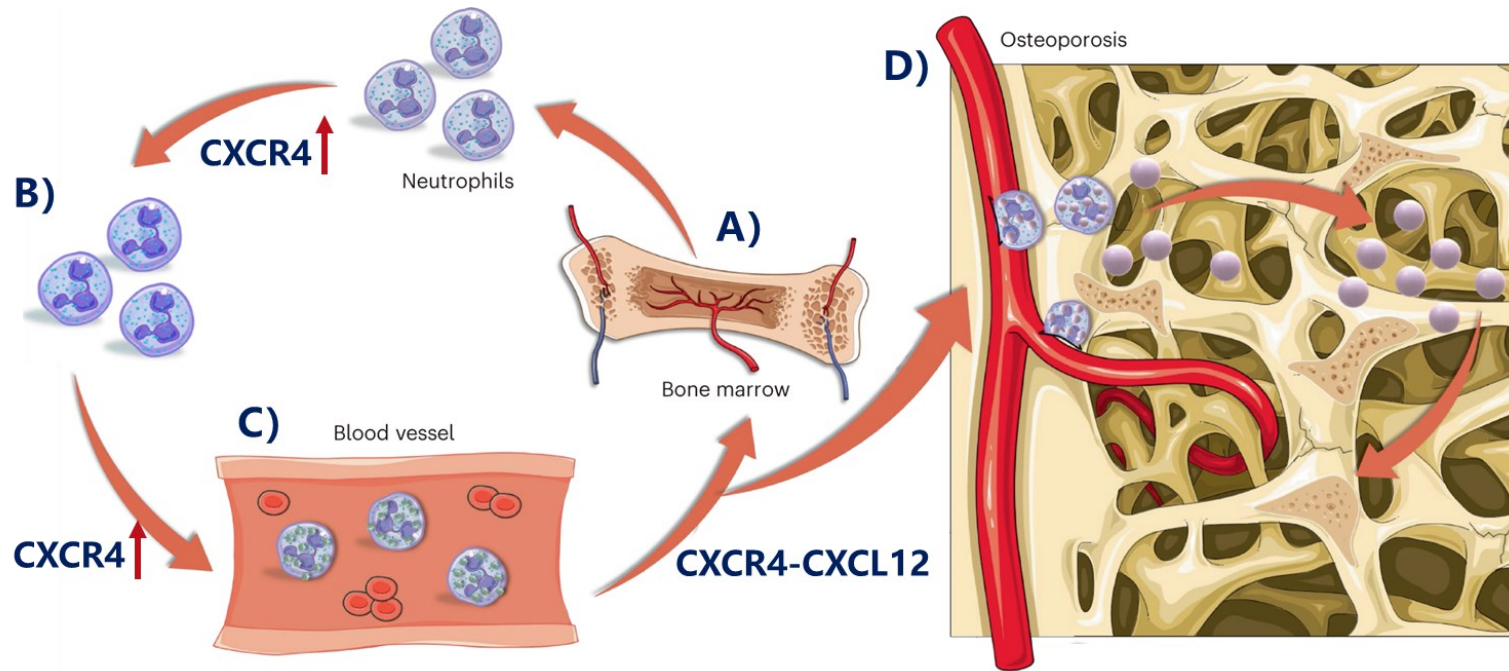


Nat Rev Cancer. 2018 Oct;18(10):601-618.

Neutrophil carriers need controlled interfaces and release

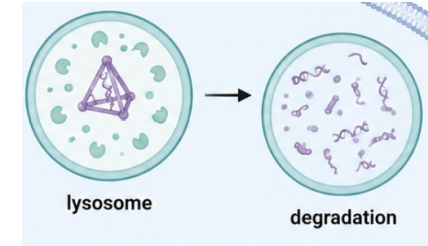
Neutrophils (NE) offer natural bone lesion trafficking

- ✓ Inflammatory chemotaxis
- ✓ Endothelial adhesion and transmigration
- ✓ Bone marrow homing

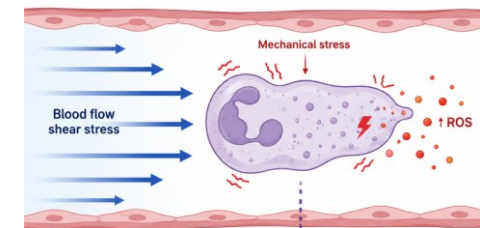


Nat Nanotechnology. 2023 Jun;18(6):647-656.

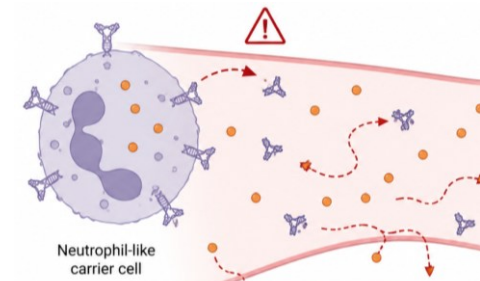
Remaining challenges



Nanostructure degradation



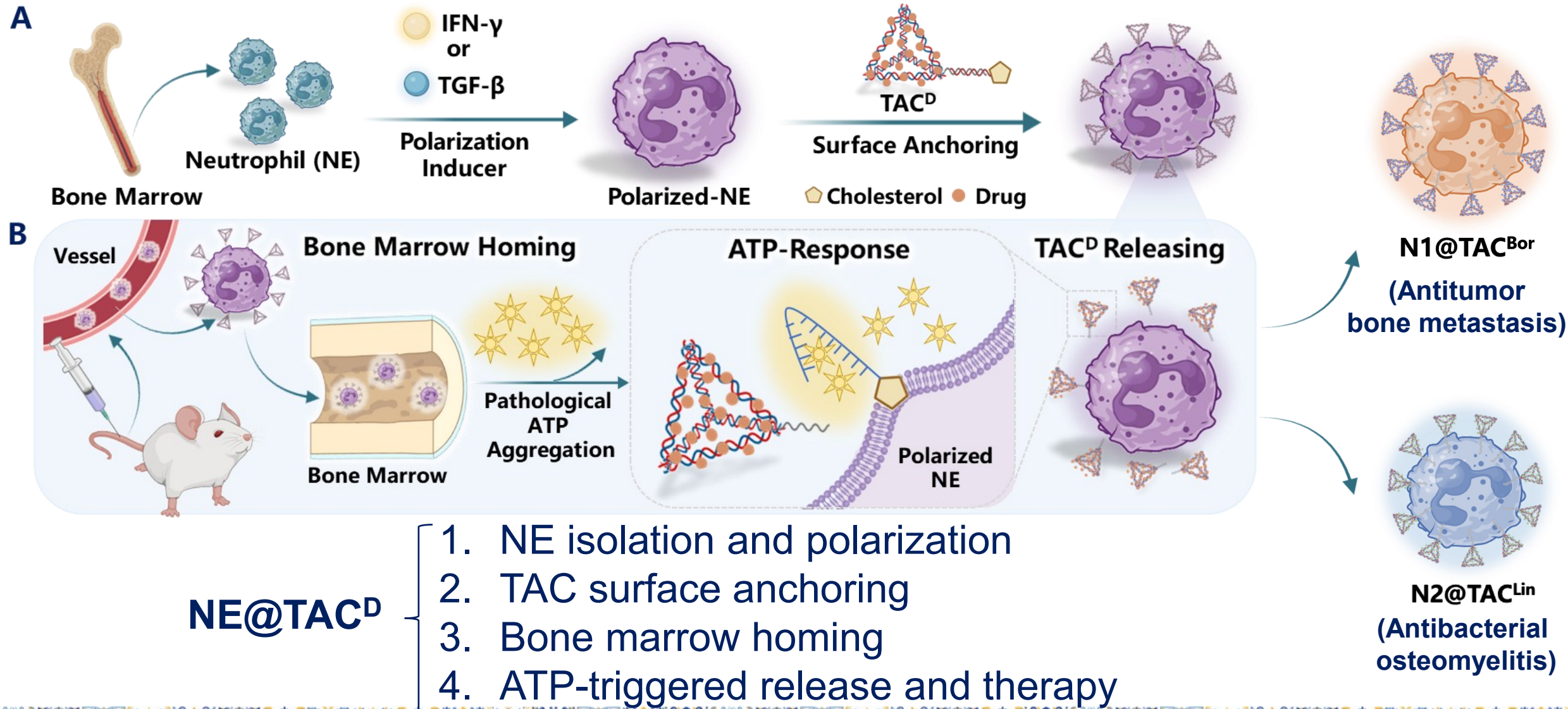
Shear stress damaging NE



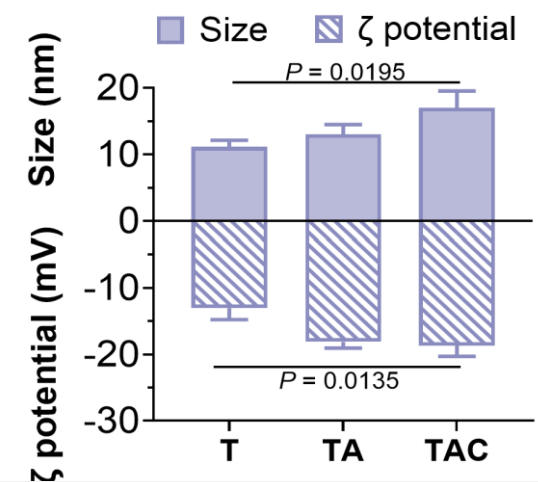
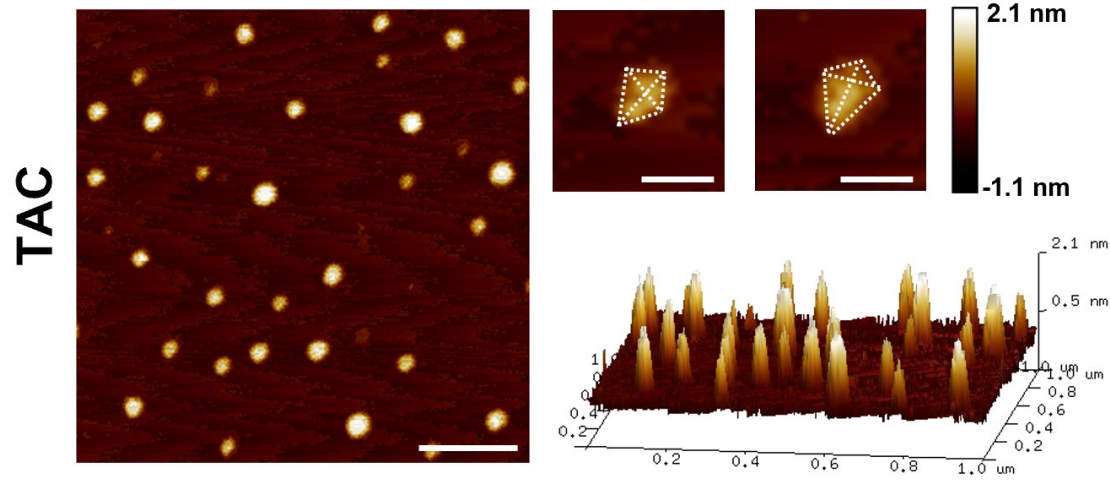
Uncontrolled cargo release



ATP-gated TAC converts NE into lesion-responsive carriers

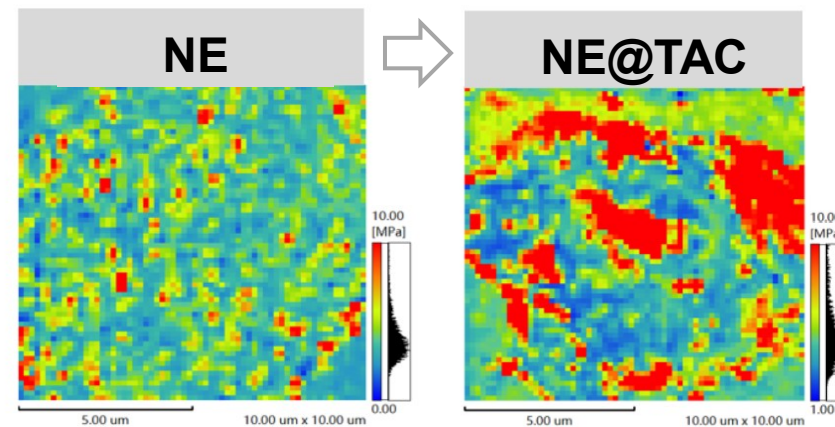
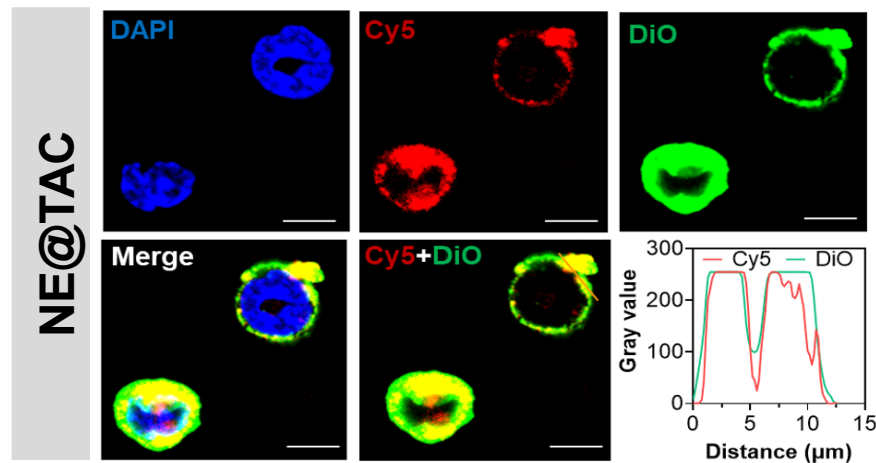


TAC is efficiently anchored and retained on NE



TAC retained a sharp-edged tetrahedral morphology

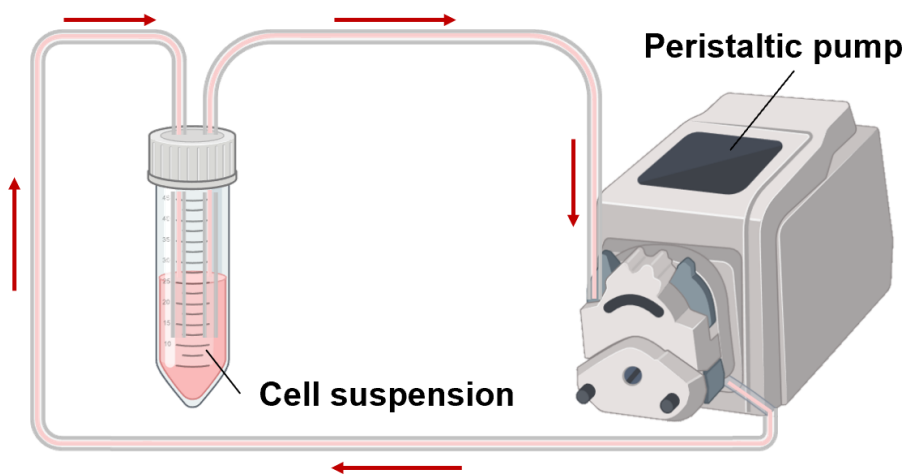
TAC with a diameter of ~17 nm



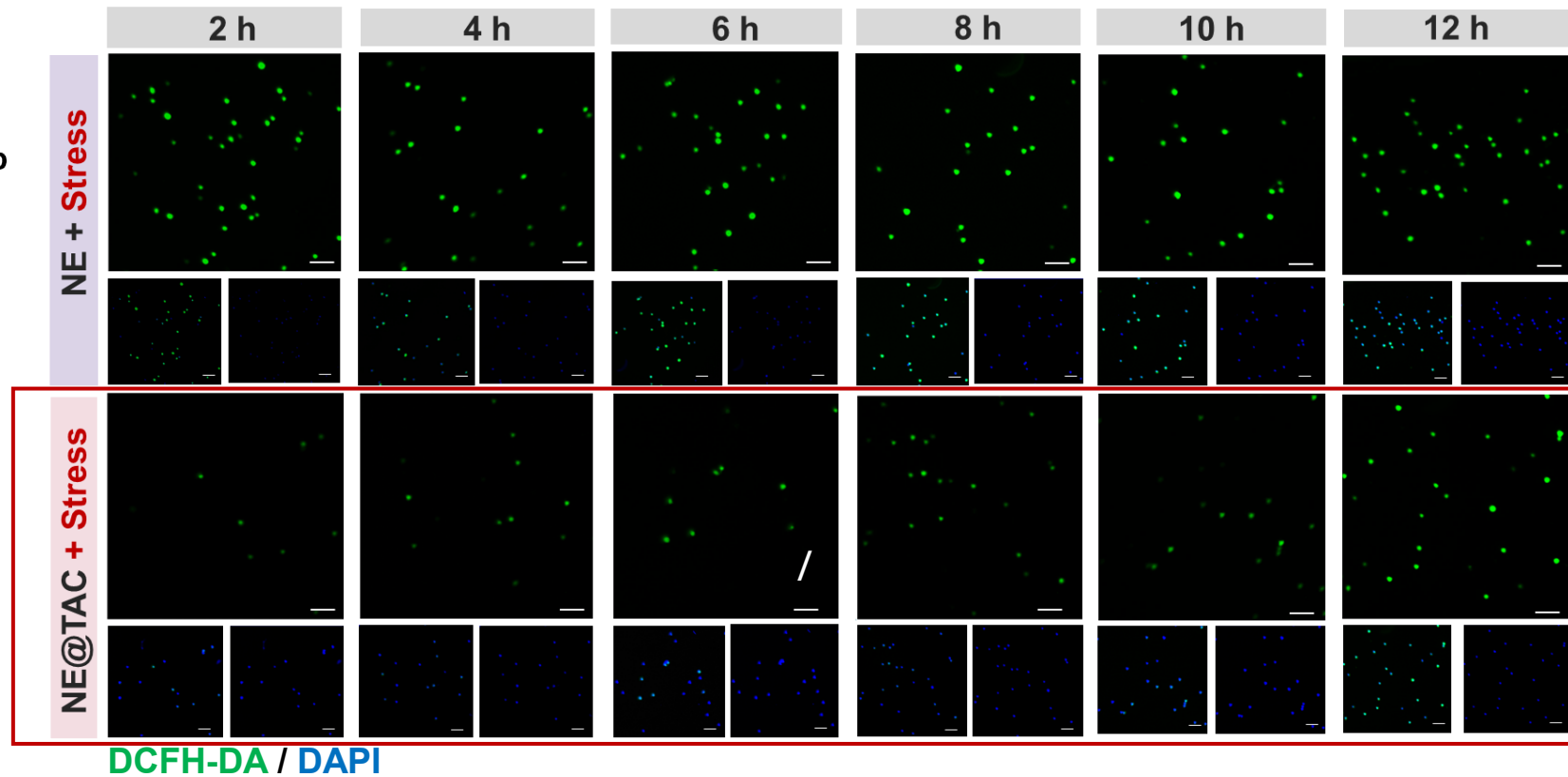
Membrane
localization



TAC protects NE from shear stress



Schematic illustration of the
in vitro fluid shear stress (FSS)
simulation system

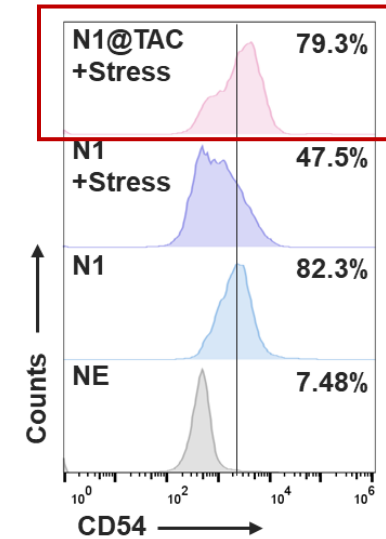
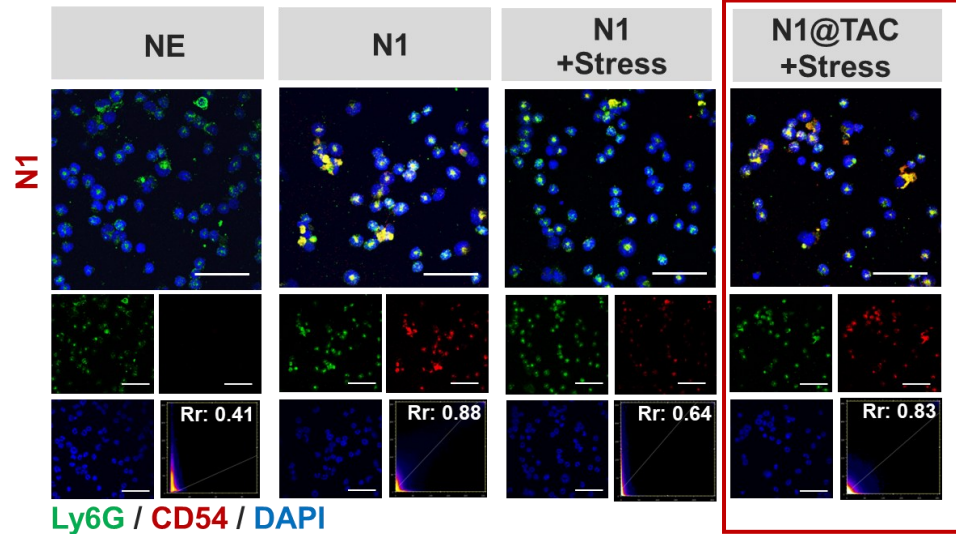


TAC modification could protect NE
against circulation-induced damage



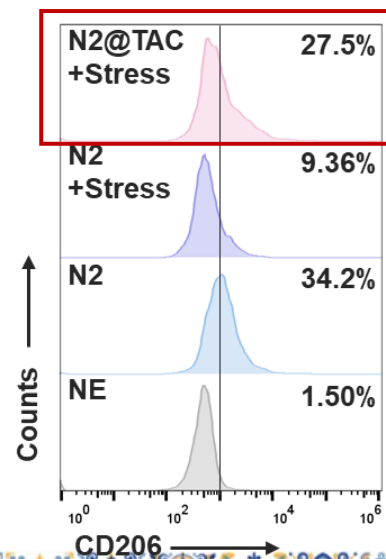
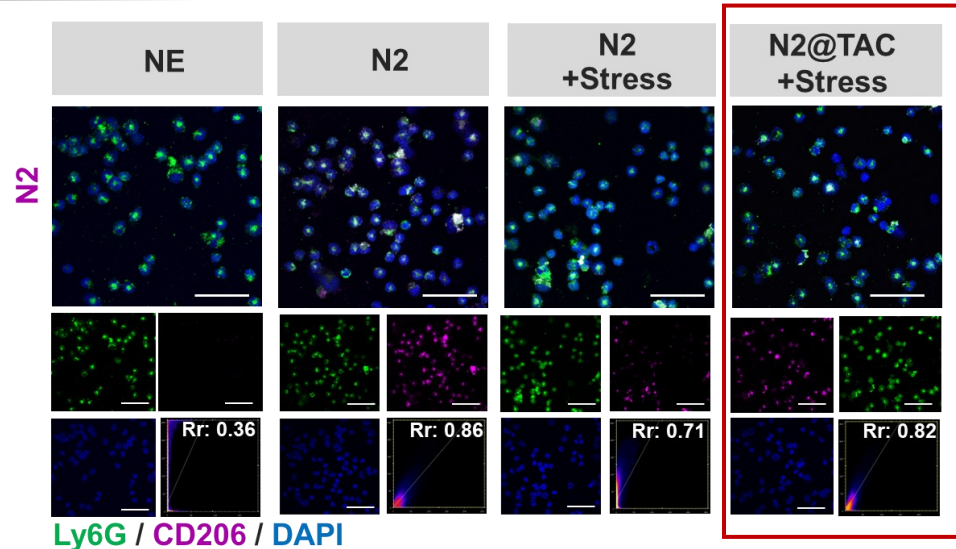
TAC stabilize NE phenotypes under simulated circulation

N1 Type



N1@TAC more effectively maintained N1-associated markers (CD54) than unmodified N1 cells

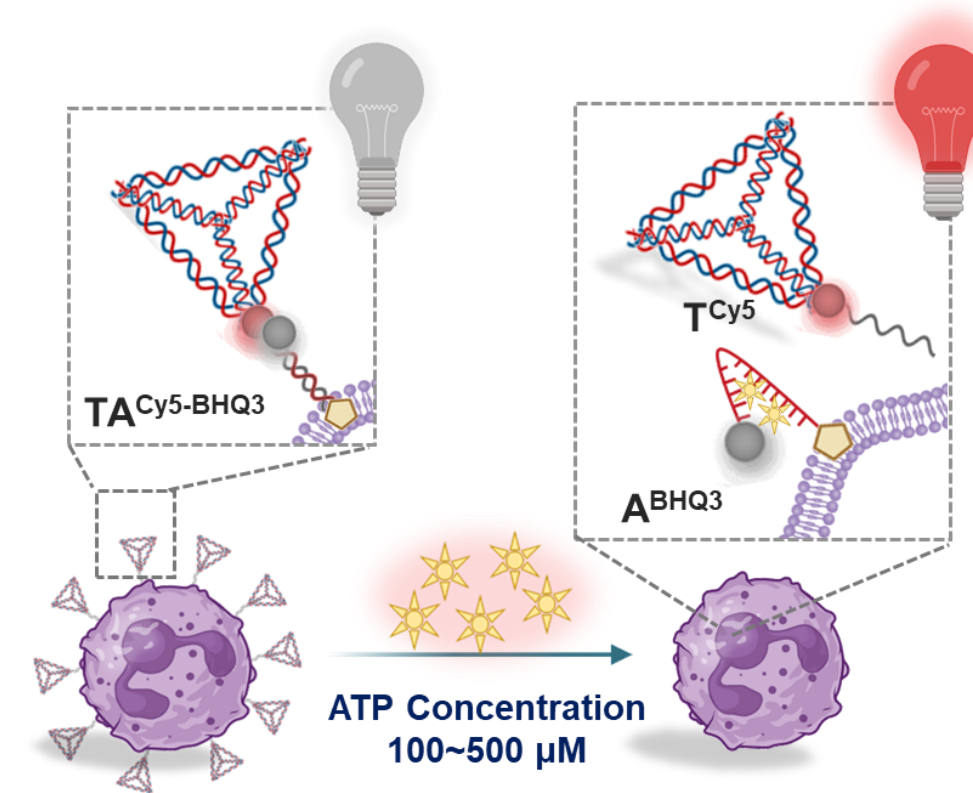
N2 Type



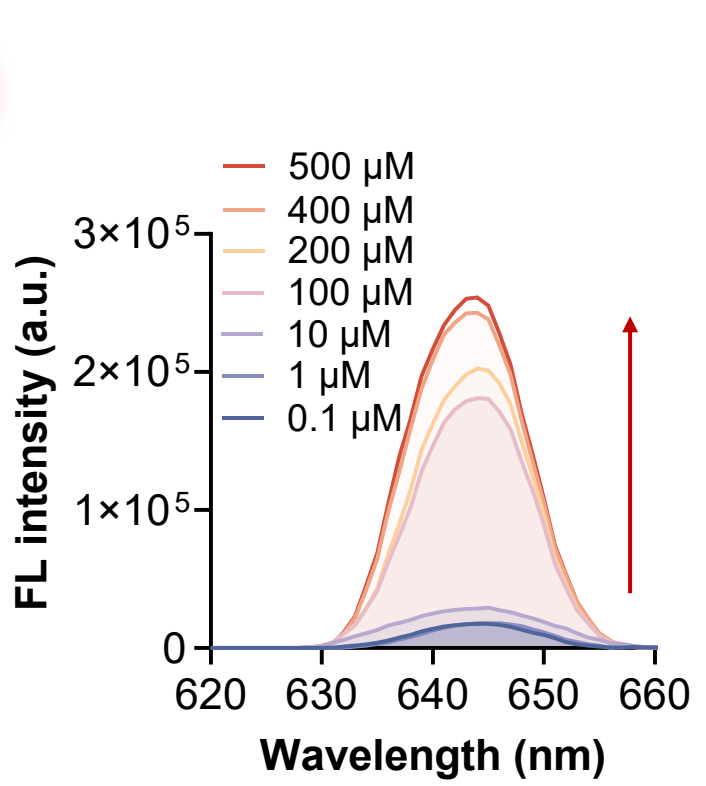
N2@TAC more effectively maintained N2-associated markers (CD206) than unmodified N2 cells



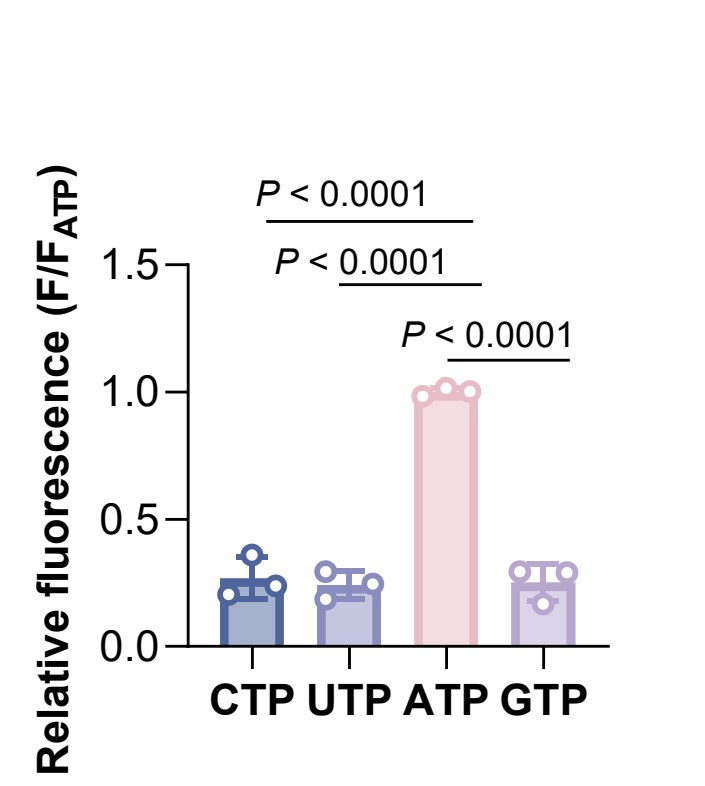
ATP triggered TAC release from NE@TAC



Schematic illustration of the fluorescence quenching assay



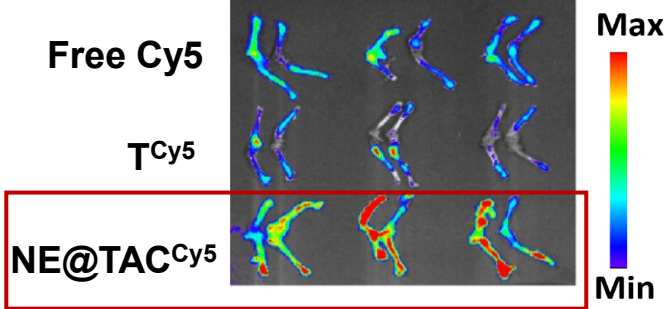
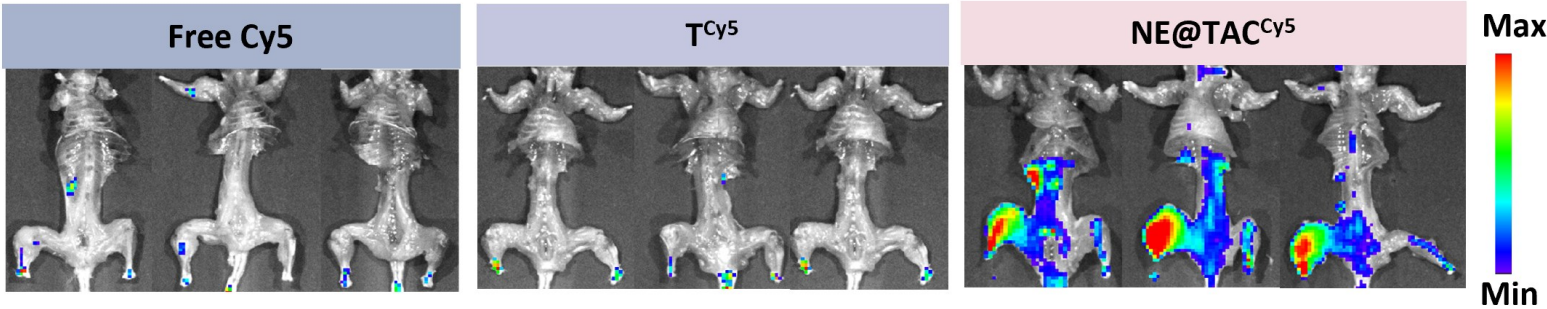
ATP gradient fluorescence recovery



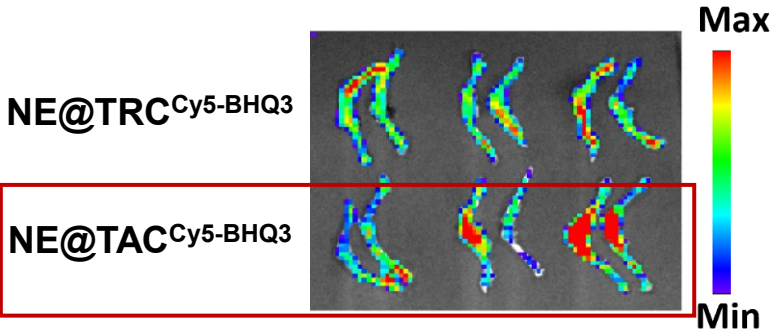
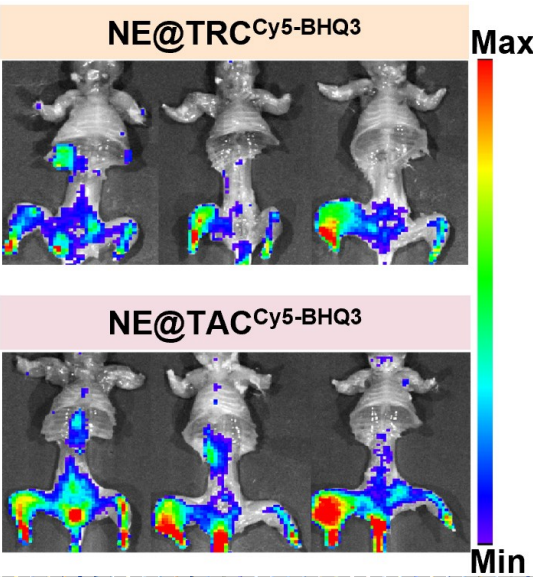
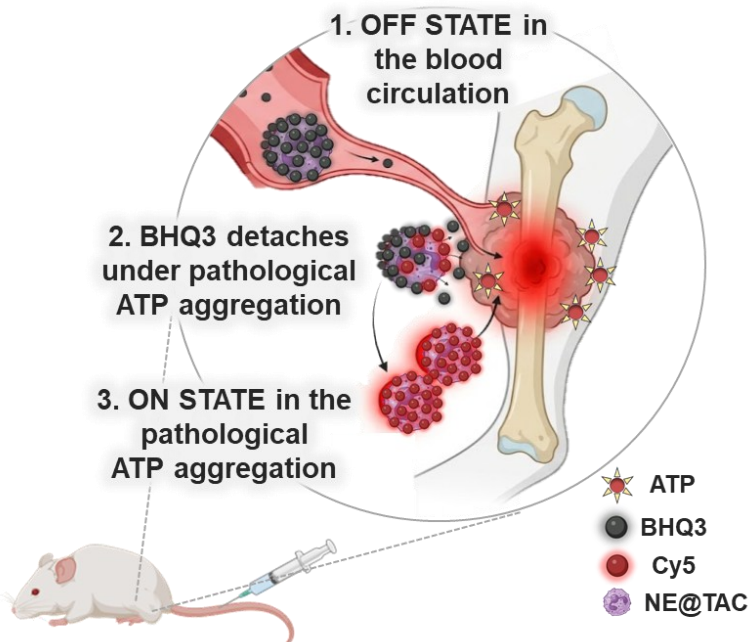
Negligible responses to CTP, UTP or GTP

NE@TAC homes to bone marrow lesions

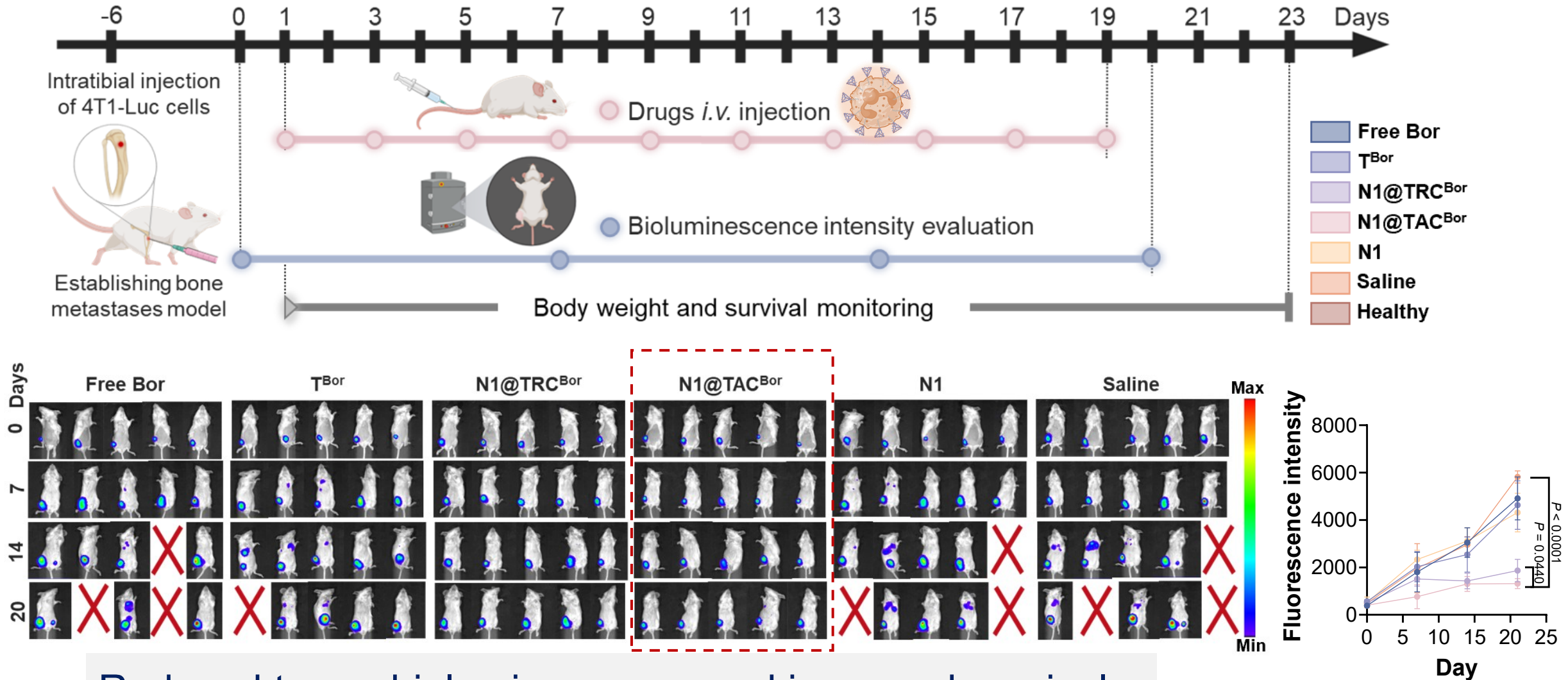
Bone marrow homing



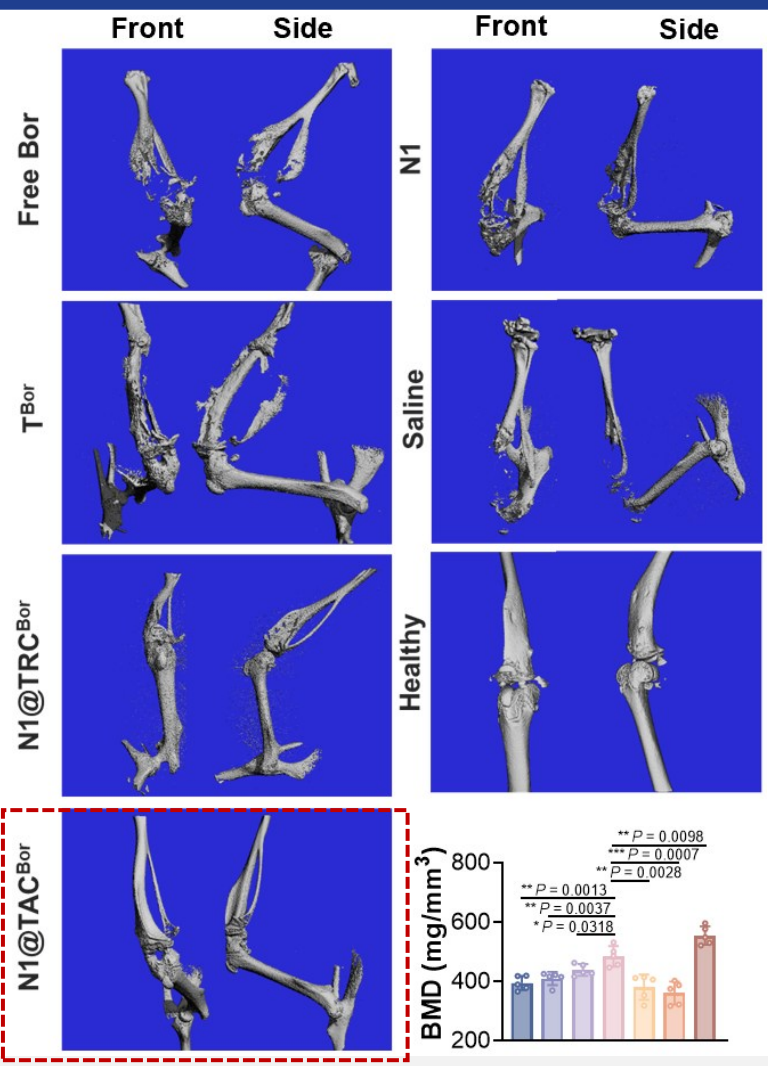
ATP-triggered release



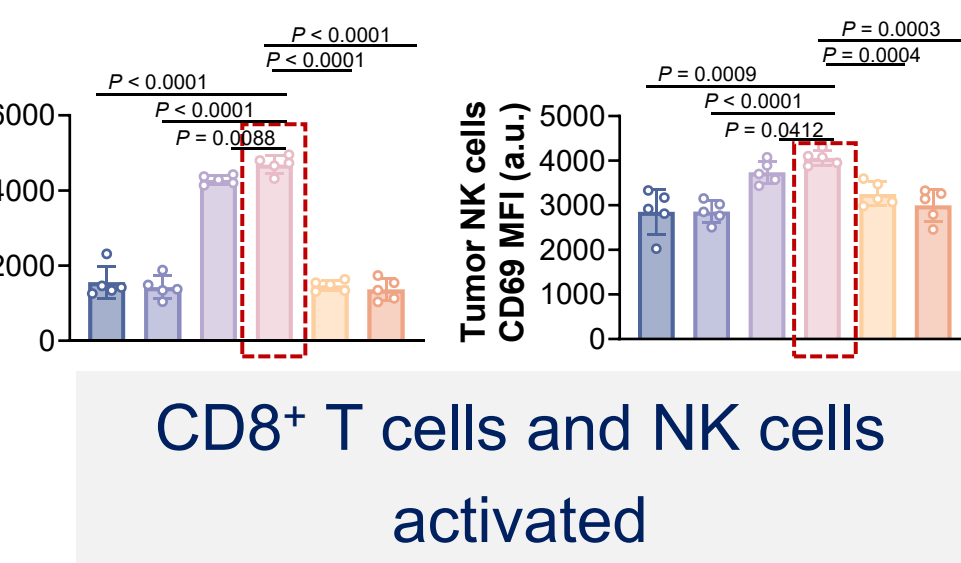
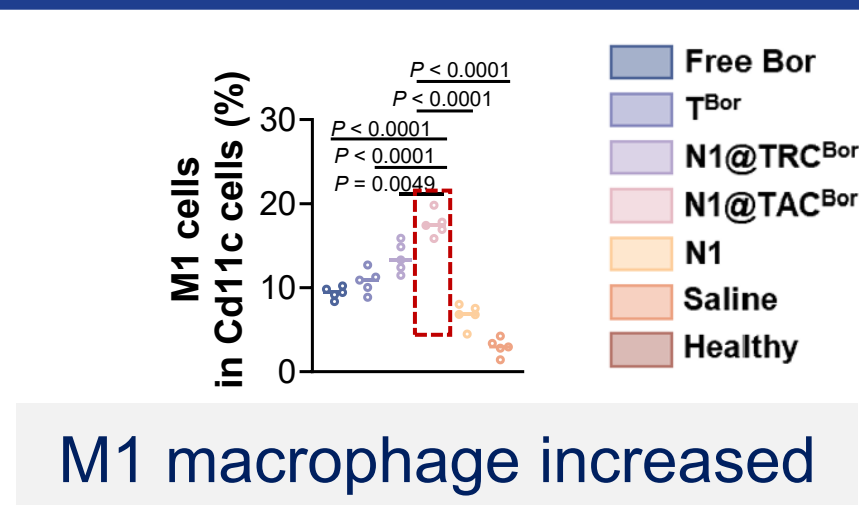
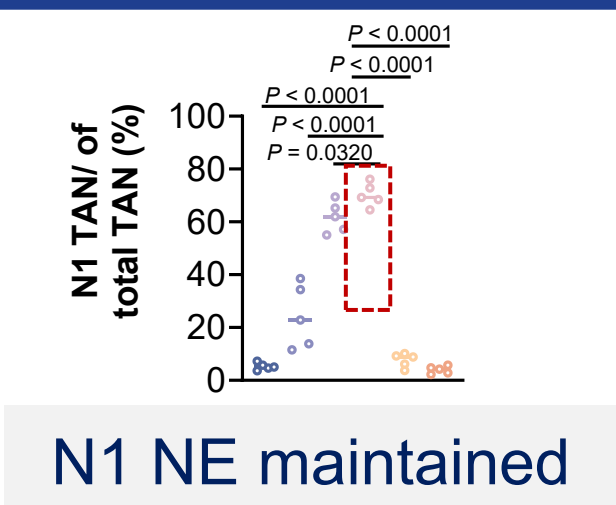
Therapeutic application I: breast cancer bone metastasis



N1@TAC^{Bor} activates antitumor immunity

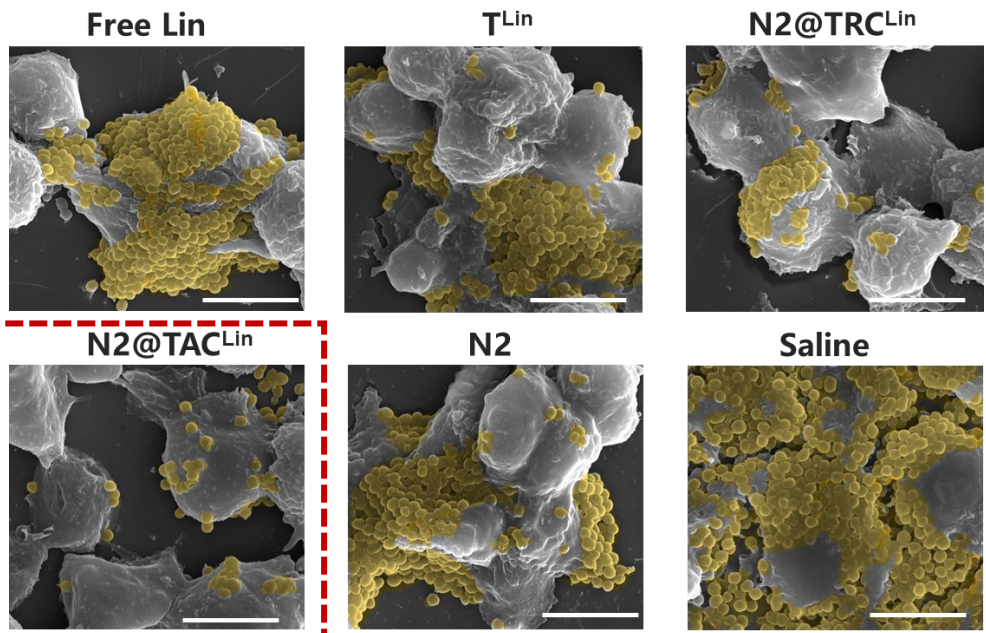
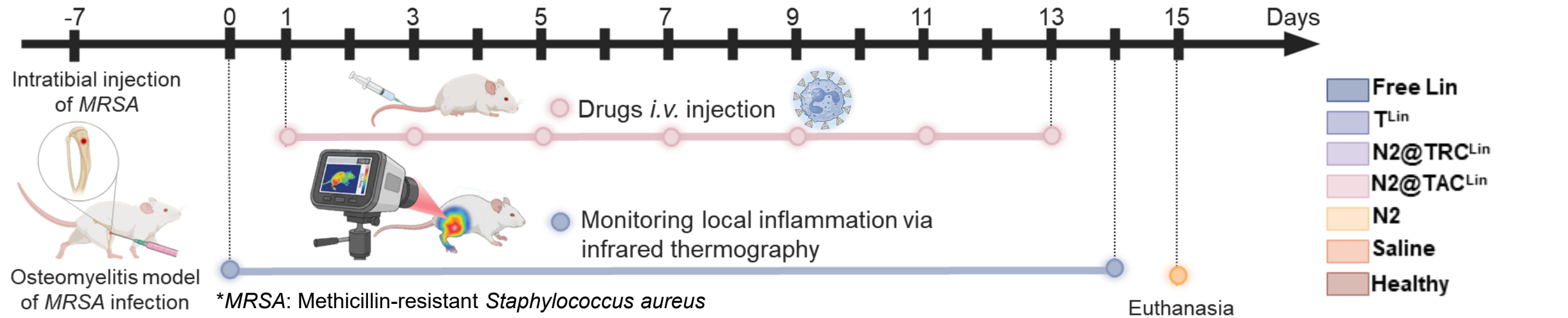


Alleviated osteolytic destruction

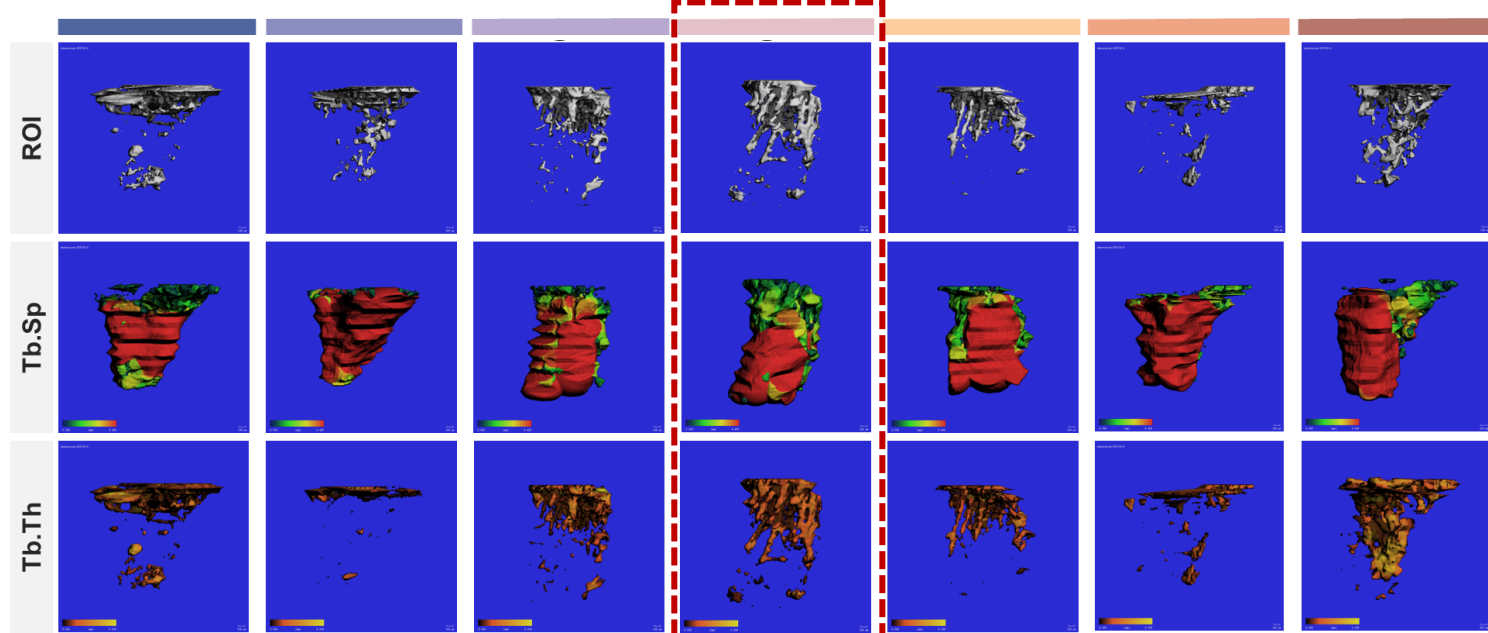


Effector memory enhanced

Therapeutic application II: *S. aureus* -induced osteomyelitis

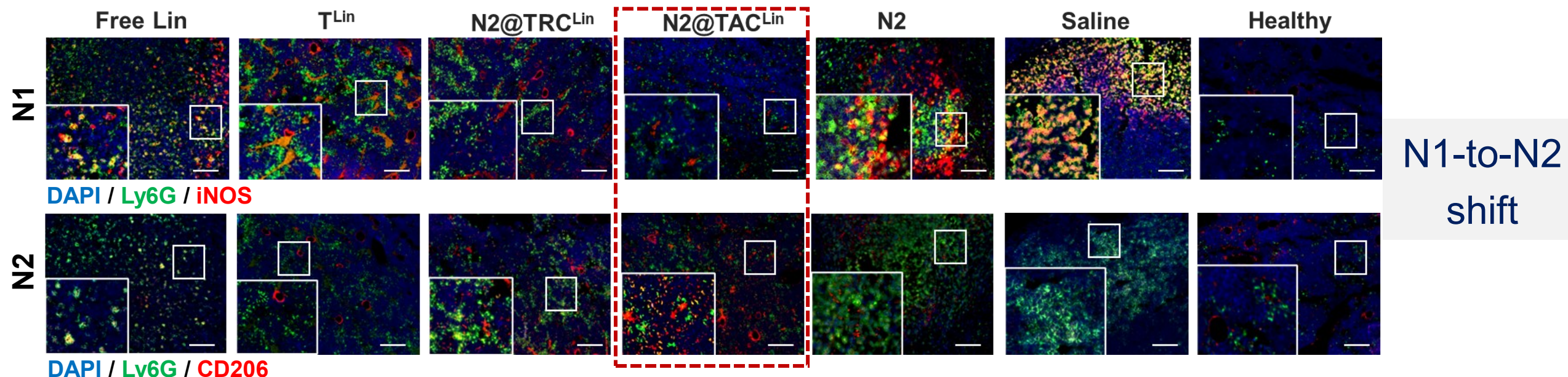


Biofilm reduction on infected implants

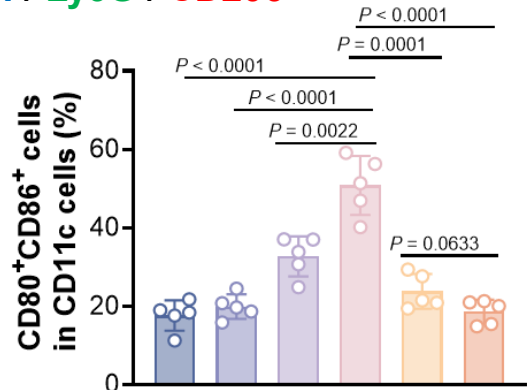


Biofilm reduction on infected implants

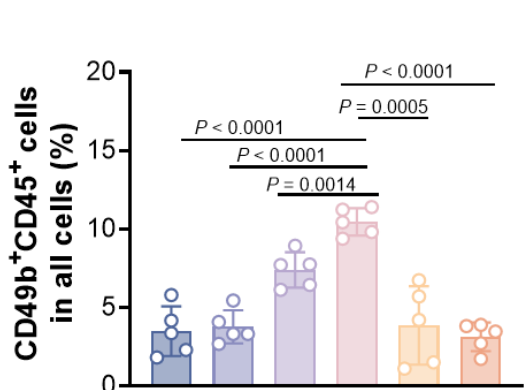
N2@TAC^{Lin} restored antibacterial immune activation



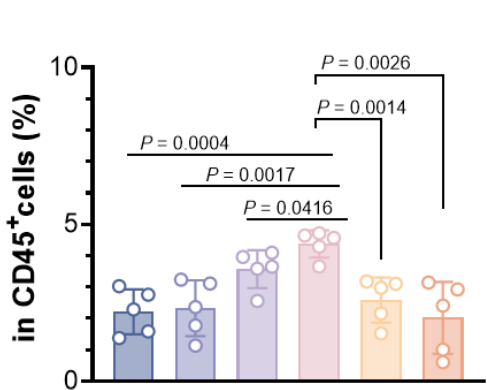
N1-to-N2
shift



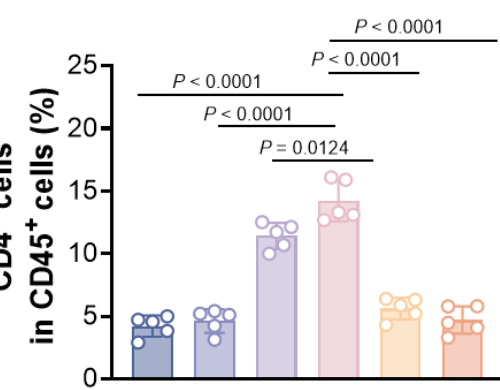
DC maturation



NK activation



CD4⁺ /CD8⁺ T cells infiltration



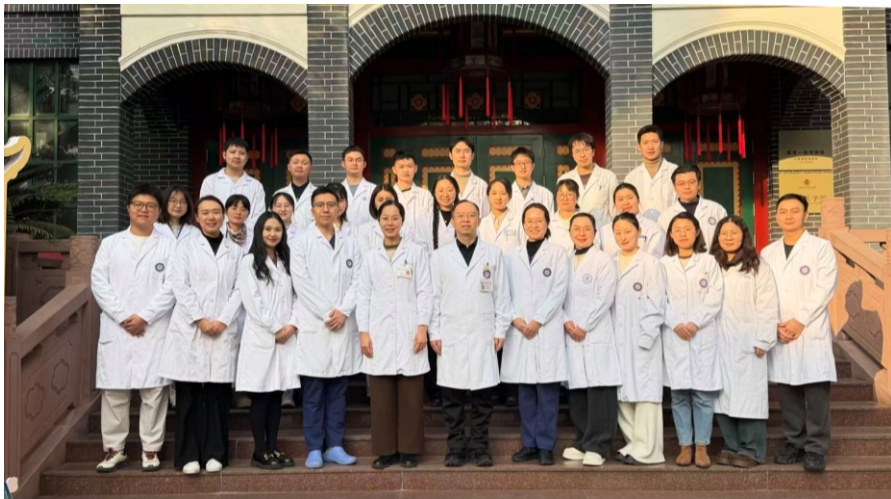
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State Key Laboratory of Oral Diseases
Laboratory for Nucleic Acid Nanomaterials



International Joint Lab

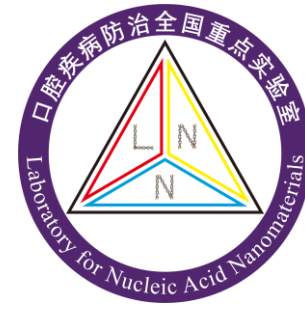
Laboratory for Nano-bio-imaging and Devices
UCSD

Laboratory for Nucleic Acid Nanomaterials
SKLOD

West China Hospital of Stomatology, Sichuan University
State Key Laboratory of Oral Diseases

Lin Lab





Thank you for your attention!

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Lisbon, Portugal

