Tech Session VII: Nanomedicine and Nanoscale Delivery (Focus: Bioengineering)

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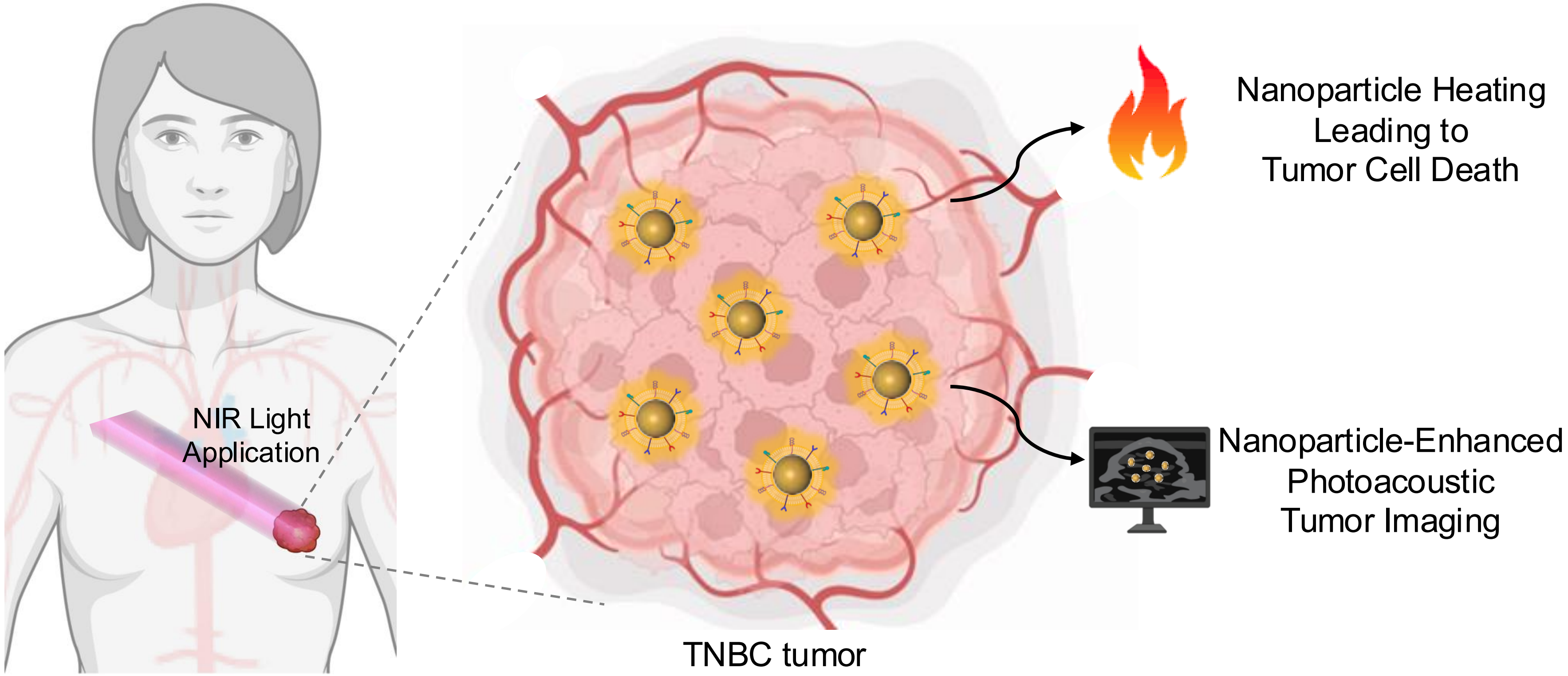
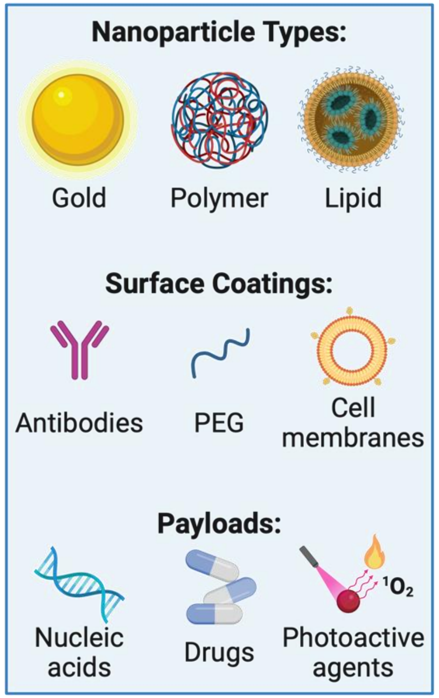
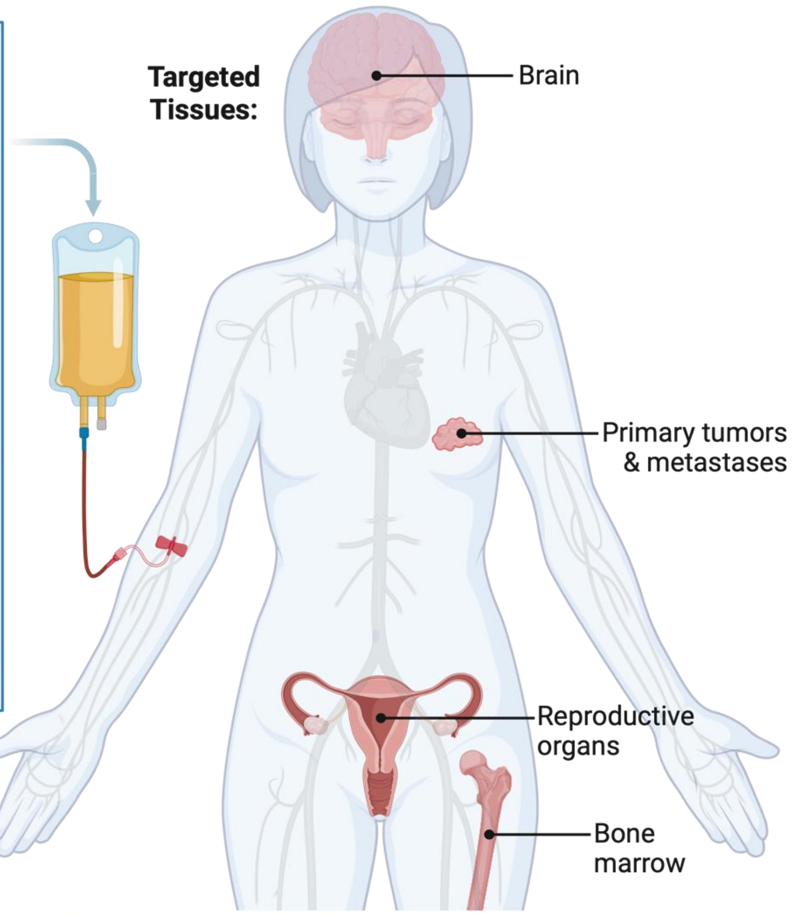
University of Delaware

Membrane-Wrapped Nanoparticles for Photoacoustic Imaging and Photothermal Therapy of Triple-Negative Breast Cancer



Day Lab: Advancing Health with Precision Nanomedicines





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Triple-Negative Breast Cancer Requires New Treatment Strategies

Accounts for 15-20% of diagnosed breast cancers

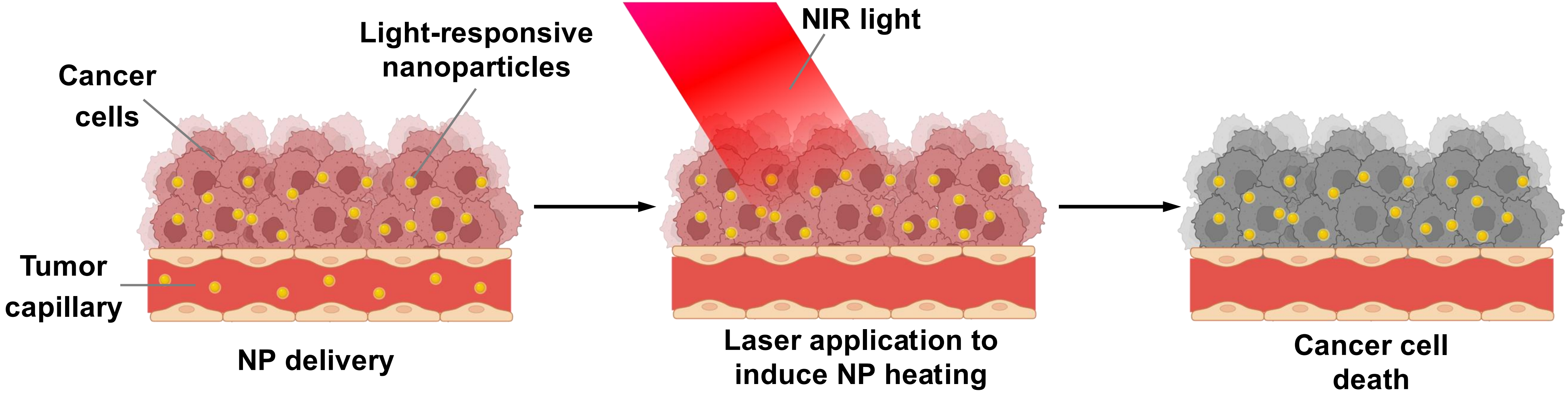
High risk of metastasis to vital organs

Unsusceptible to existing targeted or hormonal therapies

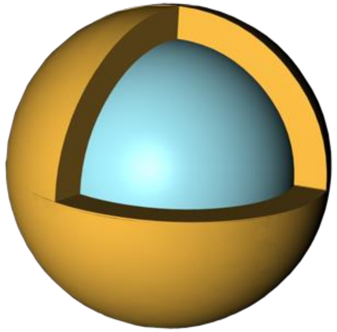
2X higher risk of death than other types of breast cancer

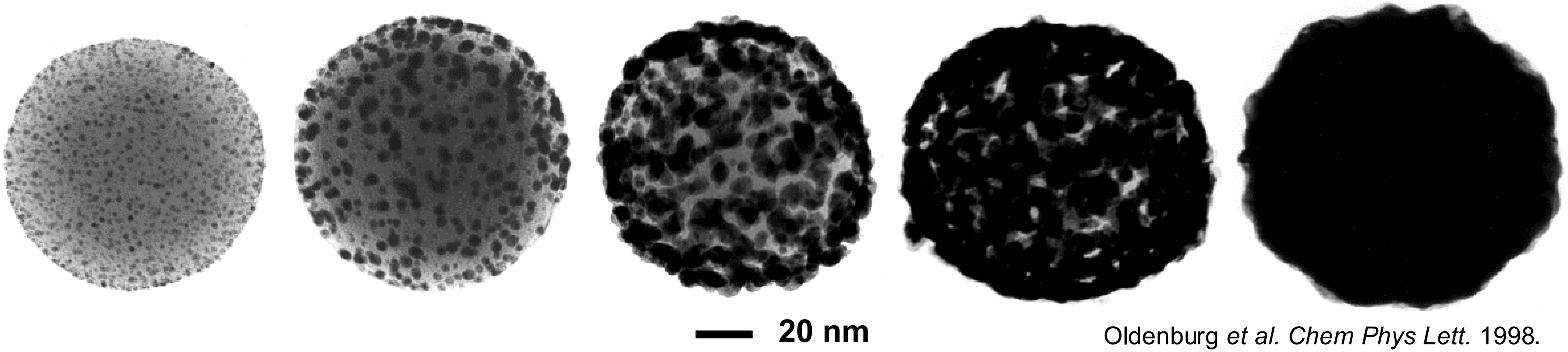
Nanoparticle-based therapies have substantial potential to improve patient outcomes

Nanoparticle-Mediated Photothermal Therapy Enables High Precision Tumor Ablation



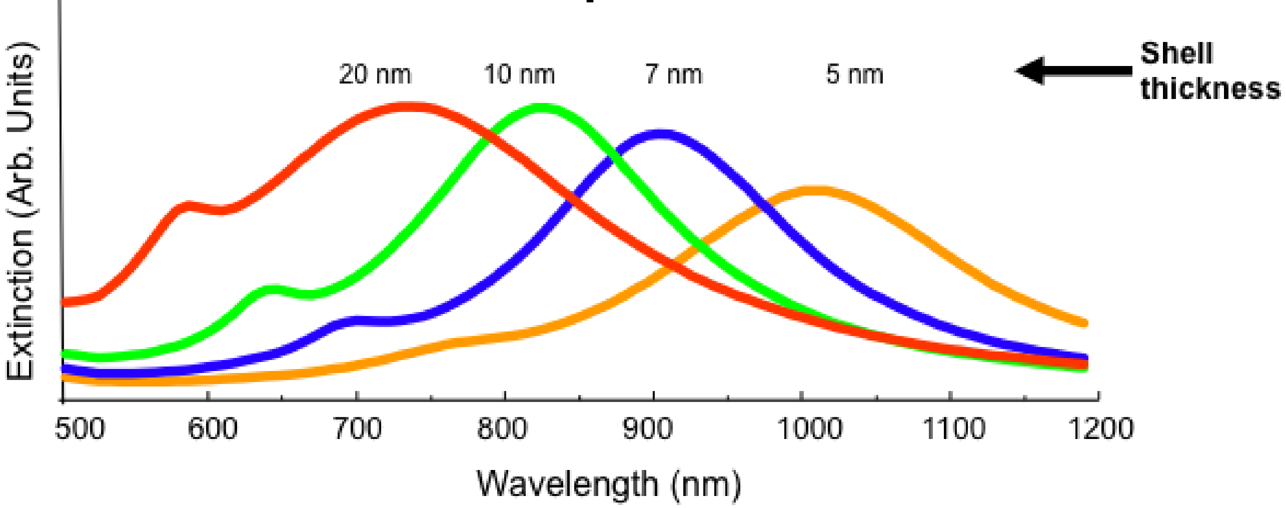
Nanoshells as Phototherapeutic Agents





Oldenburg *et al. Chem Phys Lett.* 1998.

NS structure dictates plasmon resonance



Reflected Light **Transmitted Light**

Nanoshells Have Proven Clinical Safety and Efficacy

Abstract

To evaluate the clinical safety profile for the use of gold nanoshells in patients with human prostate cancer. This follows on the nonclinical safety assessment of the AuroShell particles reported previously. Twenty-two patients, with biopsy diagnosed prostate cancer, underwent nanoshell infusion and subsequent radical prostatectomy (RRP). Fifteen of these patients had prostates that were additionally irradiated by a single-fiber laser ablation in each prostate hemisphere prior to RRP. Patients in the study were assessed at 9 time points through 6 months postinfusion. Adverse events were recorded as reported by the patients and from clinical observation. Blood and urine samples were collected at each patient visit and subjected to chemical (16 tests), hematological (23 tests), immunological (3 tests, including total PSA), and urinalysis (8 tests) evaluation. Temperature of the anterior rectal wall at the level of the prostate was measured. The study, recorded 2 adverse events that were judged attributable to the nanoparticle infusion: (1) an allergic reaction resulting in itching, which resolved with intravenous antihistamines, and (2) in a separate patient, a transient burning sensation in the epigastrium. blood/hematology/urinalysis assays indicated no device-related changes. No change in temperature of the anterior rectal wall was recorded in any of the patients. The clinical safety profile of AuroShell particles is excellent, matching nonclinical findings. A recent consensus statement suggested that the published literature does not support a preference for any ablation technique over another.[1] Now that clinical safety has been confirmed, treatment efficacy of the combined infusion plus laser ablation in prostate will be evaluated in future studies using imaging modalities directing the laser against identified prostate tumors.

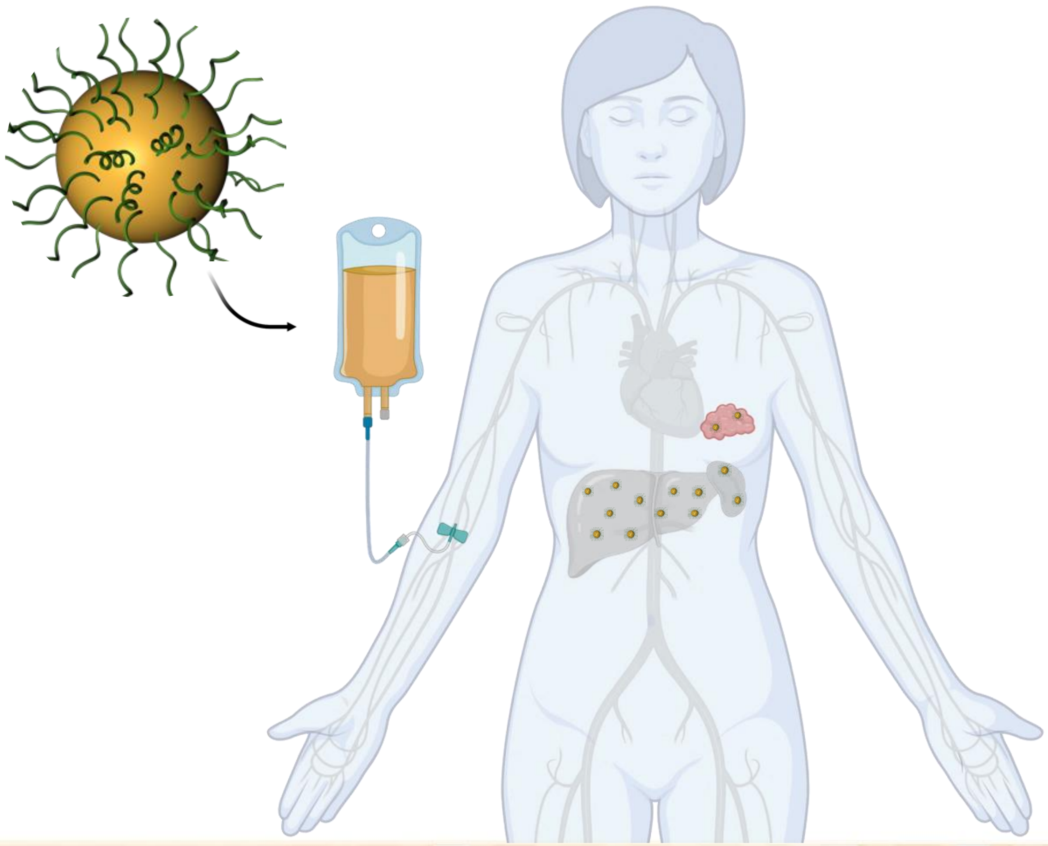
Stern *et al. Int J Toxicology.* 2015.

Biocompatible gold nanoparticles designed to absorb light at wavelengths of high tissue transparency have been of particular interest for biomedical applications. The ability of such nanoparticles to convert absorbed near-infrared light to heat and induce highly localized hyperthermia has been shown to be highly effective for photothermal cancer therapy, resulting in cell death and tumor remission in a multitude of preclinical animal models. Here we report the initial results of a clinical trial in which laser-excited gold-silica nanoshells (GSNs) were used in combination with magnetic resonance–ultrasound fusion imaging to focally ablate low-intermediate-grade tumors within the prostate. The overall goal is to provide highly localized regional control of prostate cancer that also results in greatly reduced patient morbidity and improved functional outcomes. This pilot device study reports feasibility and safety data from 16 cases of patients diagnosed with low- or intermediate-risk localized prostate cancer. After GSN infusion and high-precision laser ablation, patients underwent multiparametric MRI of the prostate at 48 to 72 h, followed by postprocedure mpMRI/ultrasound targeted fusion biopsies at 3 and 12 mo, as well as a standard 12-core systematic biopsy at 12 mo. GSN-mediated focal laser ablation was successfully achieved in 94% (15/16) of patients, with no significant difference in International Prostate Symptom Score or Sexual Health Inventory for Men observed after treatment. This treatment protocol appears to be feasible and safe in men with low- or intermediate-risk localized prostate cancer without serious complications or deleterious changes in genitourinary function.

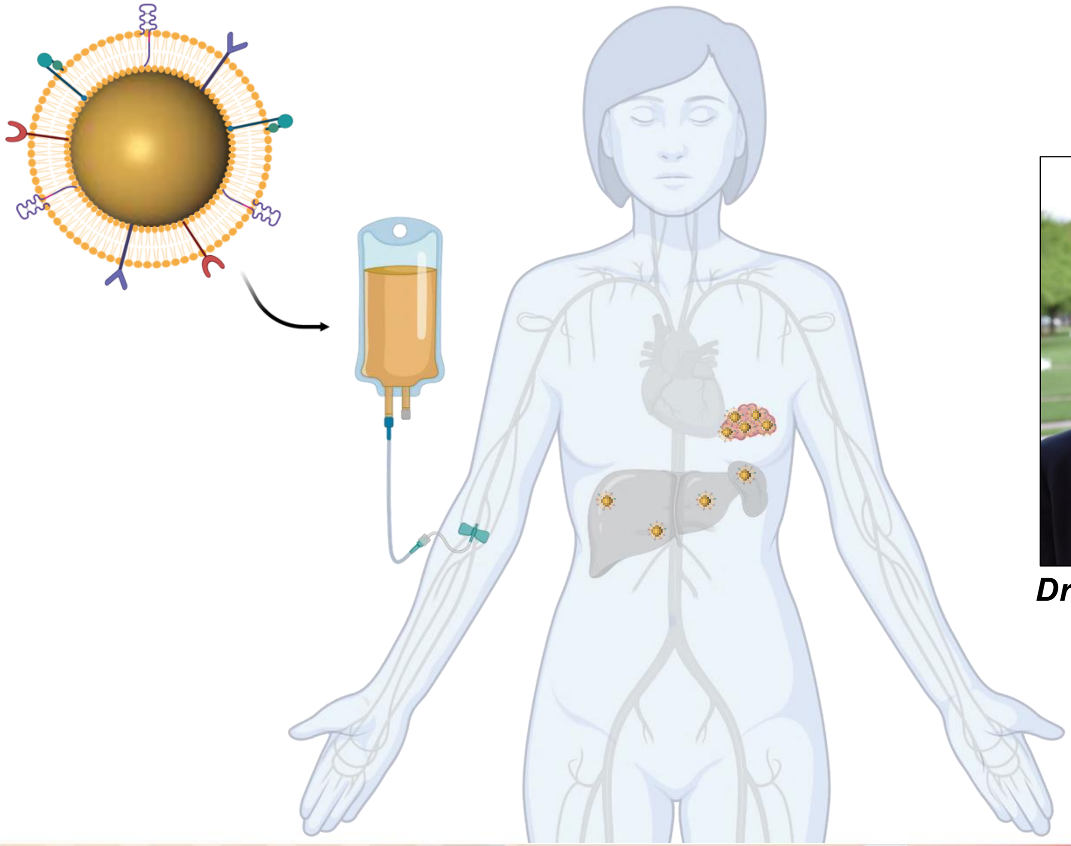
Rastinehad *et al. PNAS.* 2019.

Membrane-Wrapped Nanoshells (MWNS) for Enhanced Tumor Delivery

Traditional NS Exhibit Off-Target Delivery

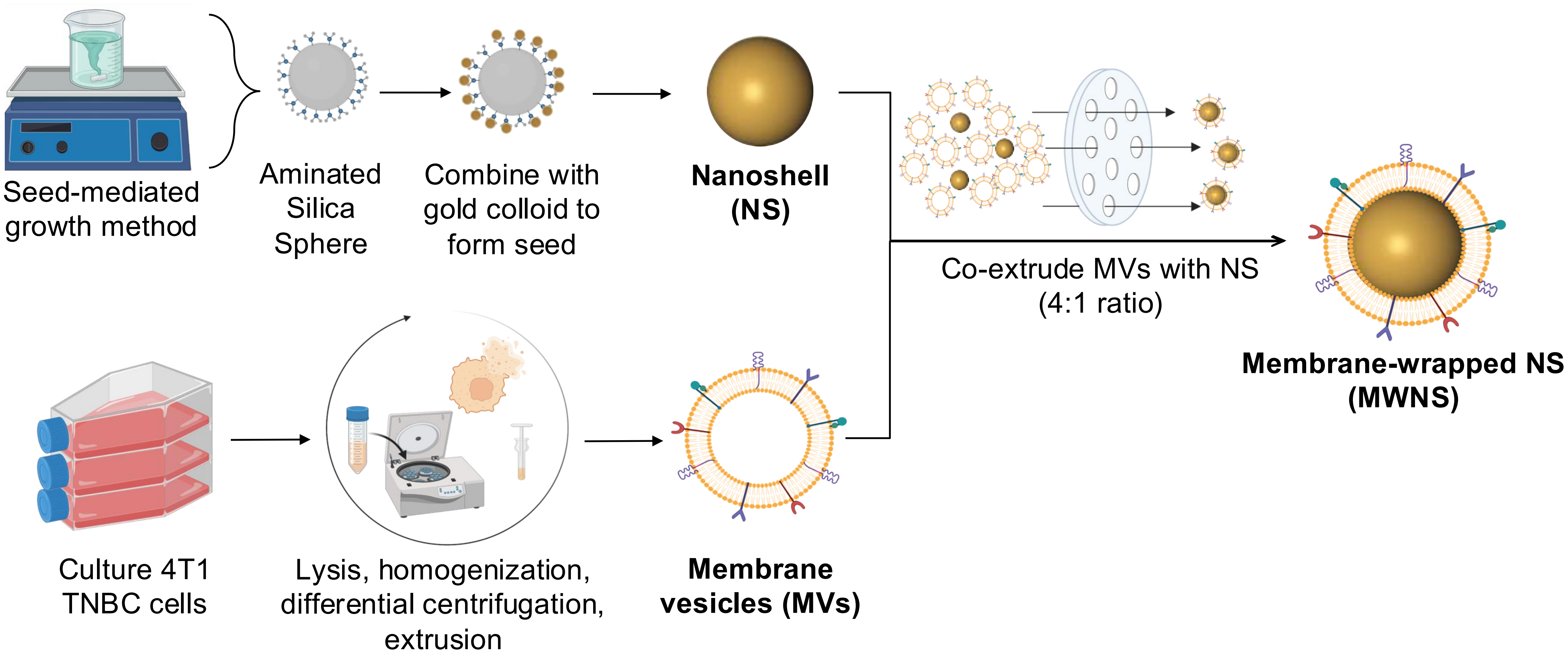


MWNS Improve Tumor Delivery Efficiency

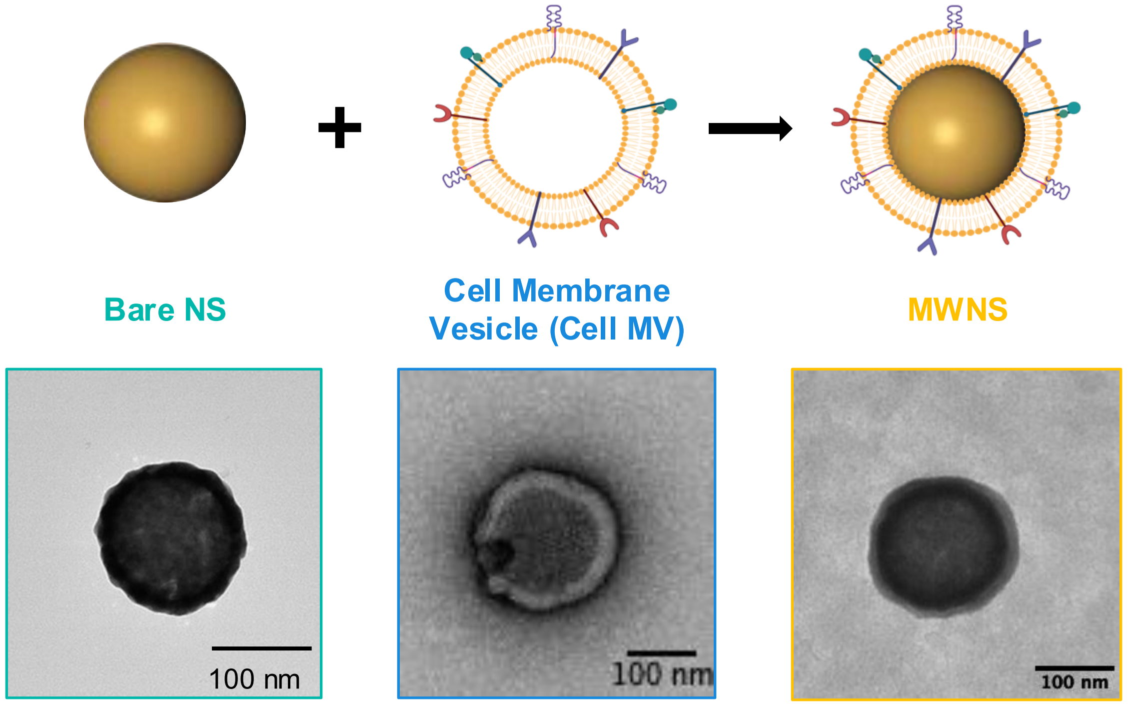


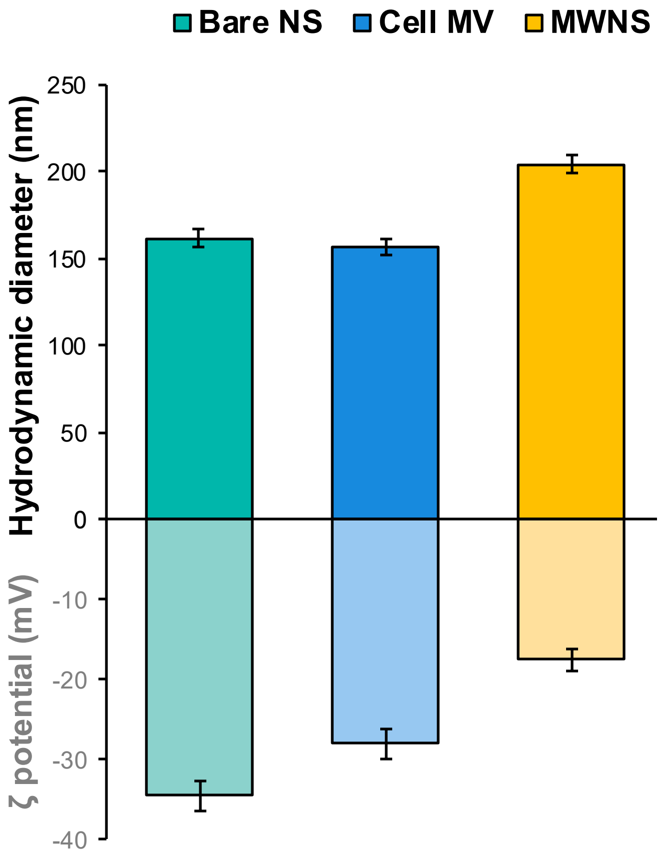
Dr. Sara Aboeleneen

Synthesis of Membrane-Wrapped Nanoshells

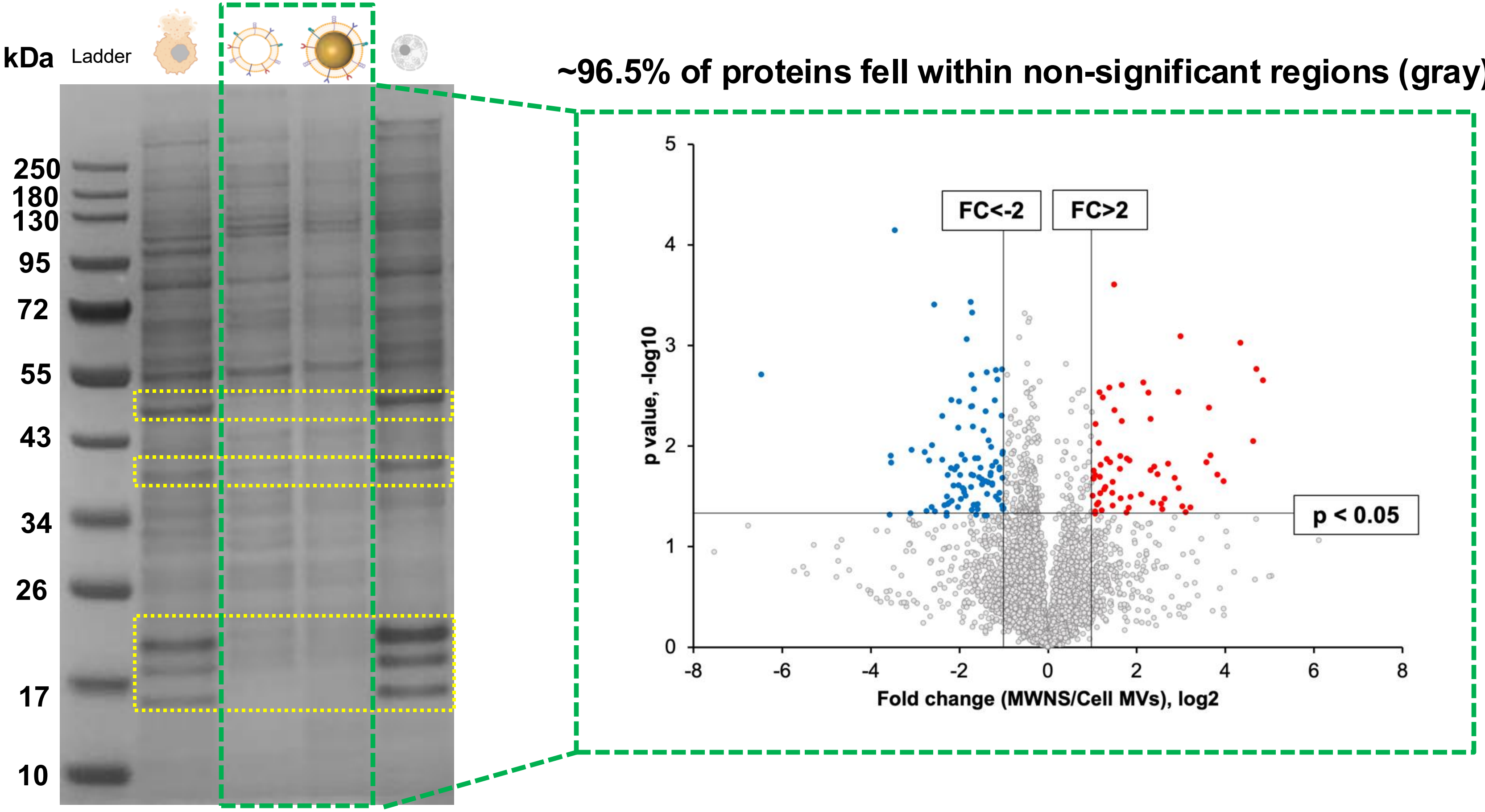


Physicochemical Characterization of MWNS

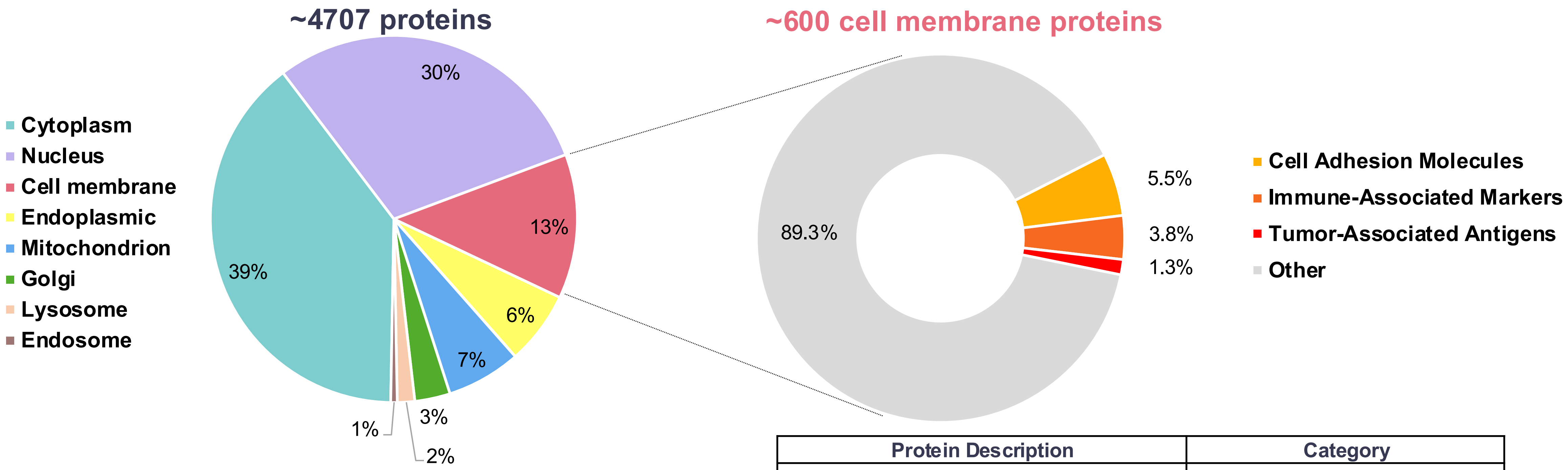




MWNS Closely Mimic the Proteomic Landscape of their Source Cell Plasma Membrane

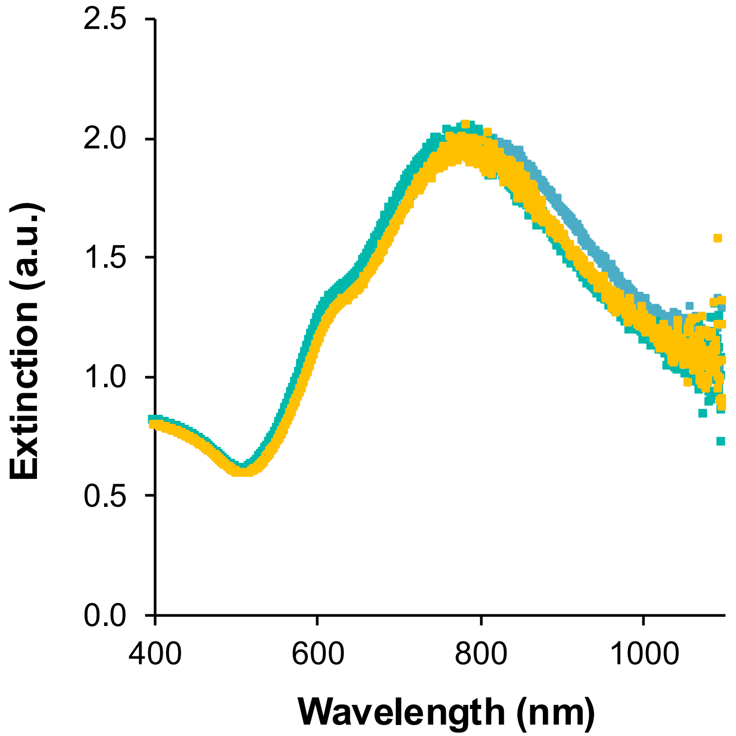


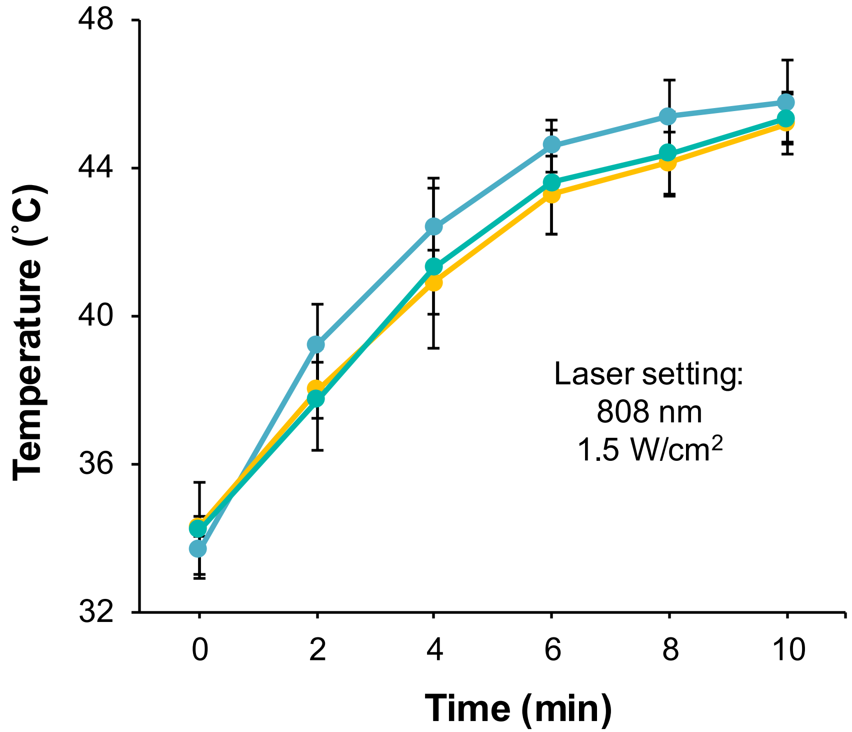
Understanding the Protein Composition of MWNS



Protein Description	Category
Epithelial cell adhesion molecule (EpCAM)	Cell Adhesion Molecule
Cadherin-1 (E-Cadherin)	Cell Adhesion Molecule
Vascular cell adhesion protein 1 (VCAM-1)	Cell Adhesion Molecule
CD44 antigen	Cell Adhesion Molecule
Galectin-3	Cell Adhesion Molecule
Leukocyte surface antigen CD47	Immune-Associated Marker

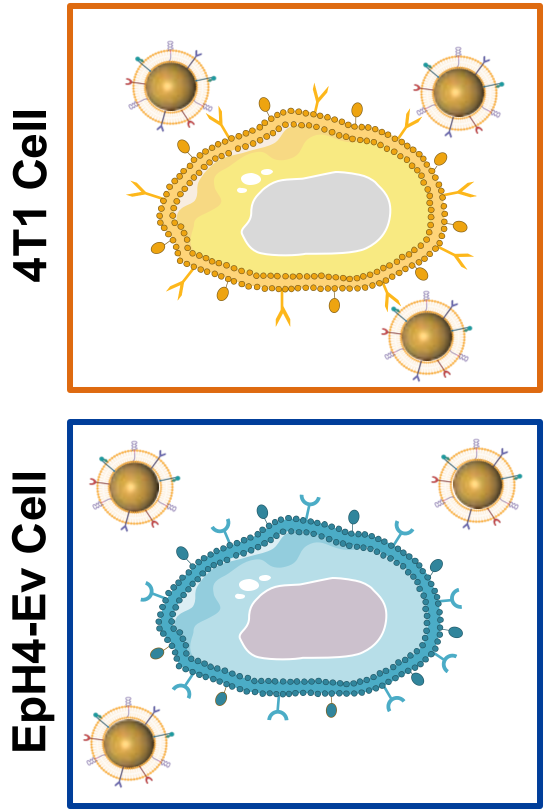
MWNS Maintain NIR Absorbance and Heating Ability



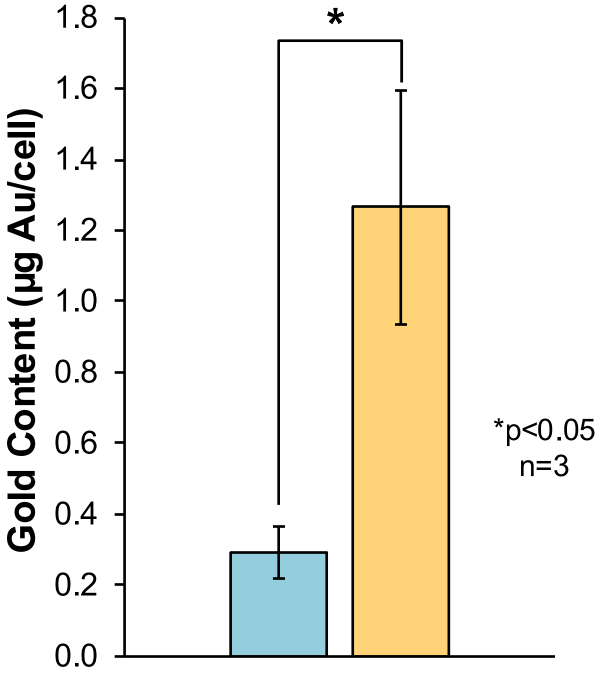


Bare NS MWNS PEG-NS

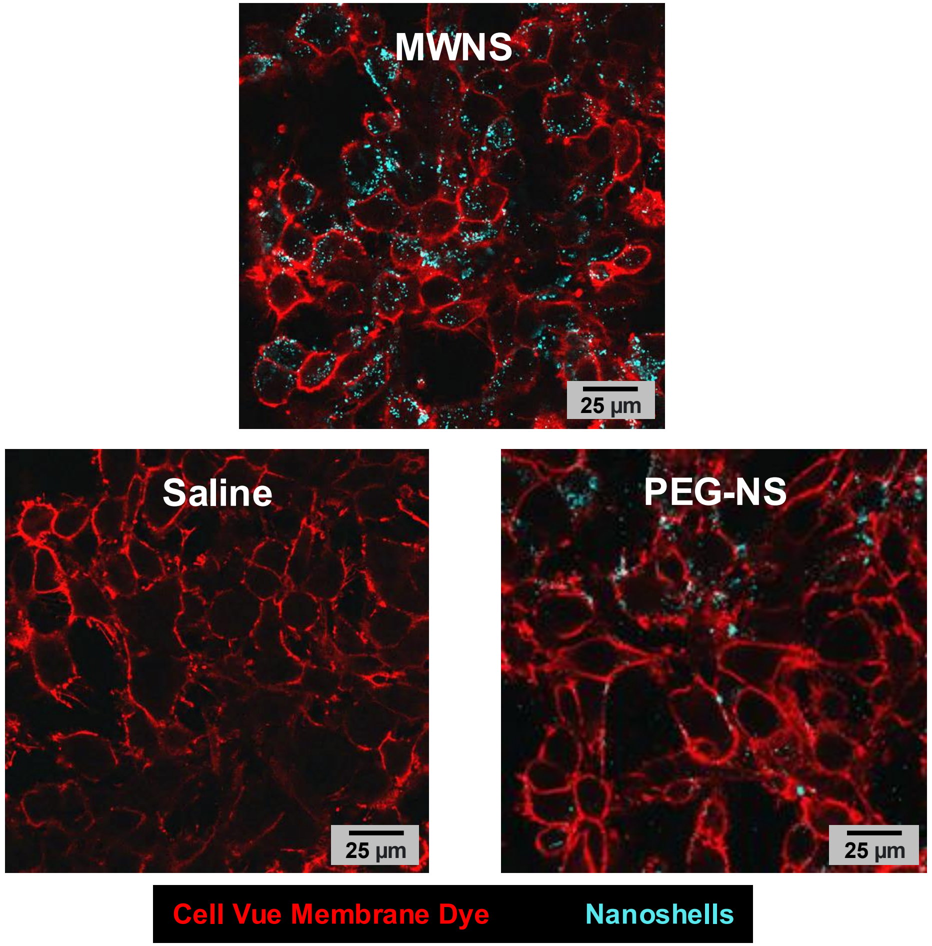
MWNS Preferentially Bind Targeted 4T1 TNBC Cells versus Non-Targeted Breast Epithelial Cells

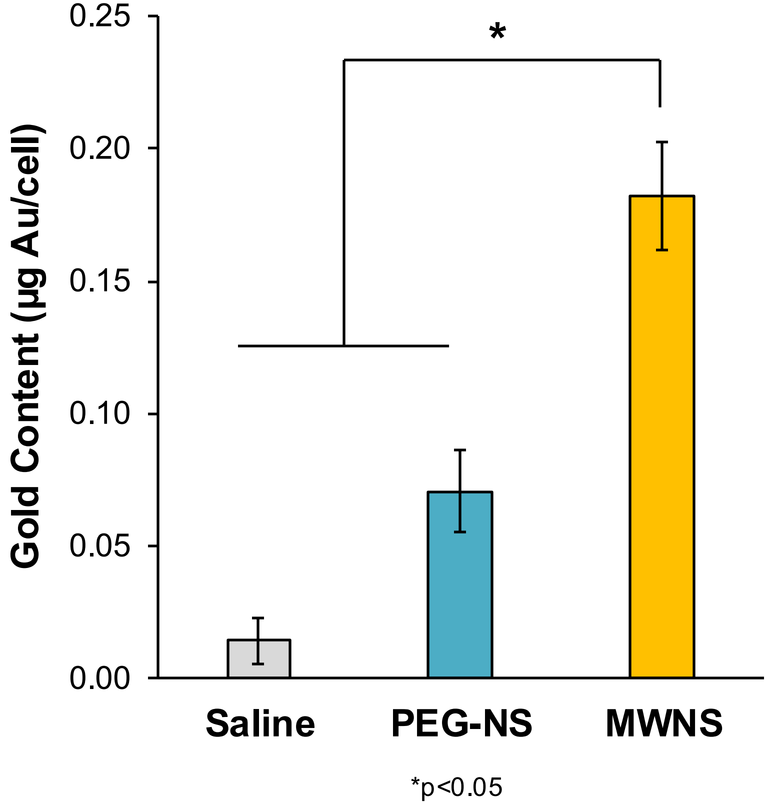


Measure gold in cells with ICP-MS



TNBC Cells Internalize More MWNS than PEG-NS



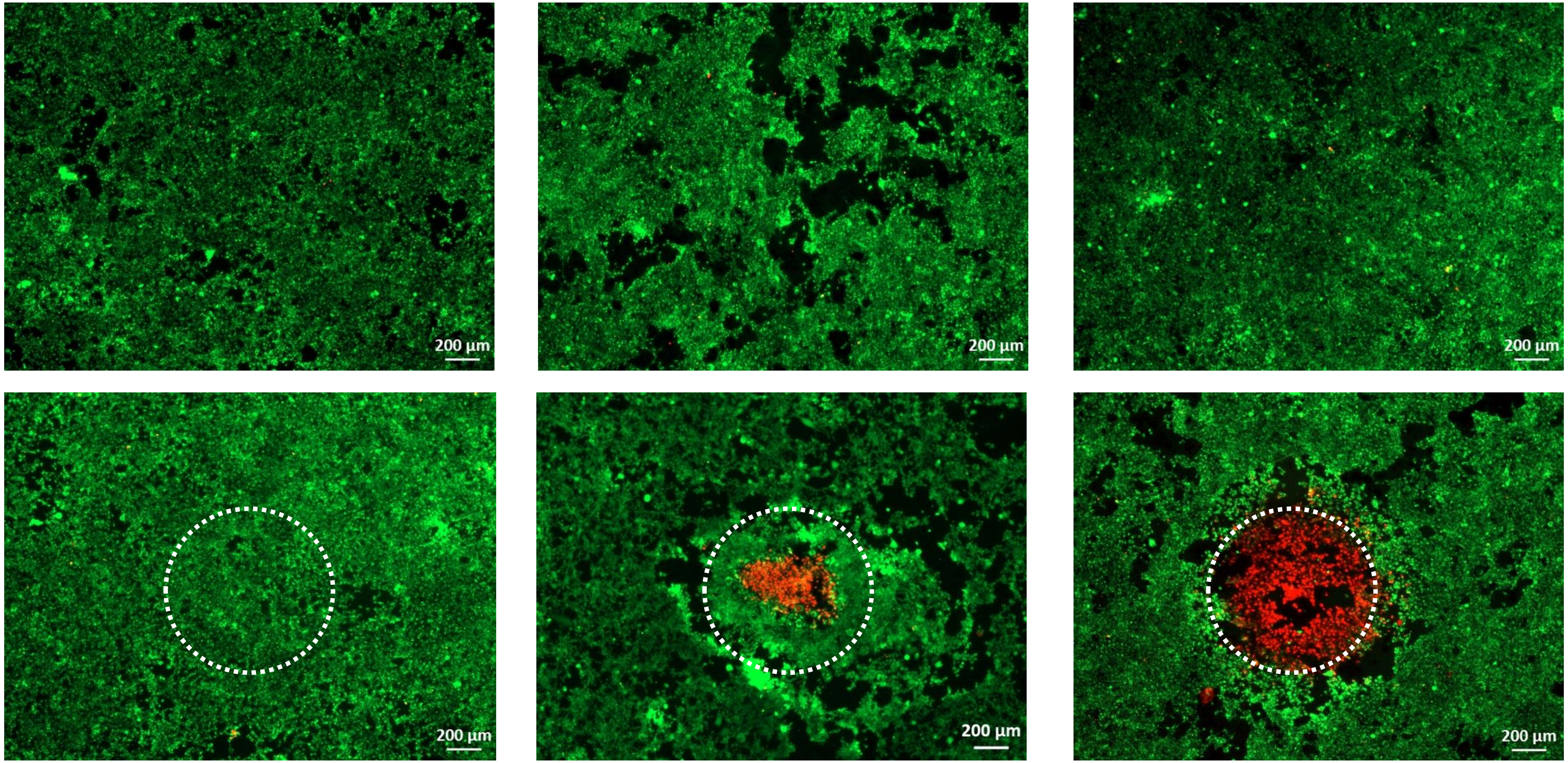


MWNS Enhance Photothermal Therapy *In Vitro*

Saline | PEG-NS | MWNS

-Laser

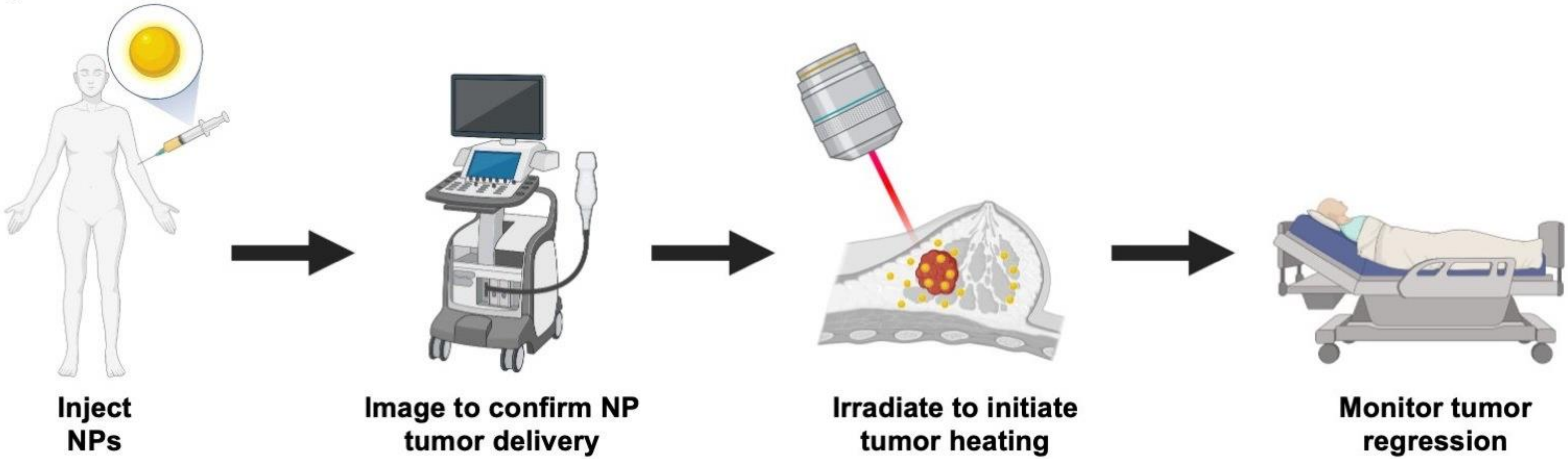
+Laser



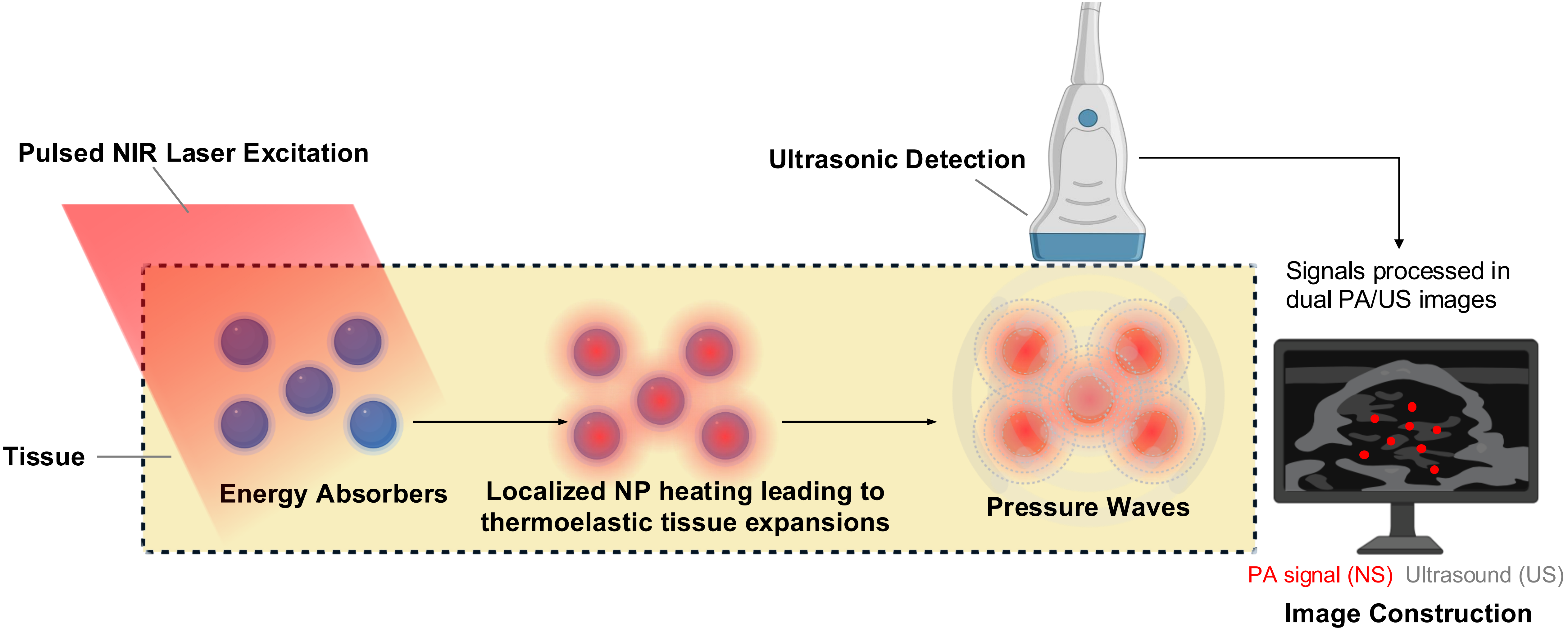
Live cells (Calcein AM) Dead cells (EthD-1)

Irradiation: 60 W/cm^2, 2 min
Nanoparticle OD: 1.5

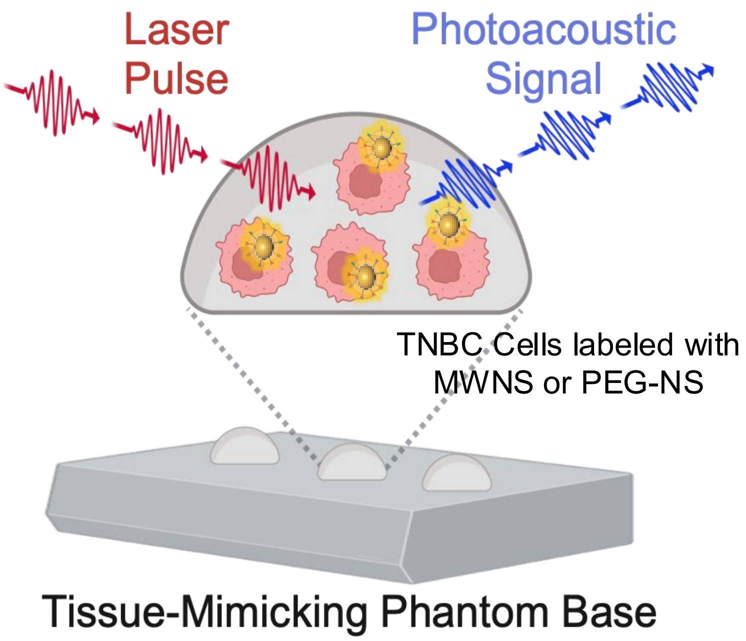
Combining Imaging with Therapy to Maximize Treatment Success

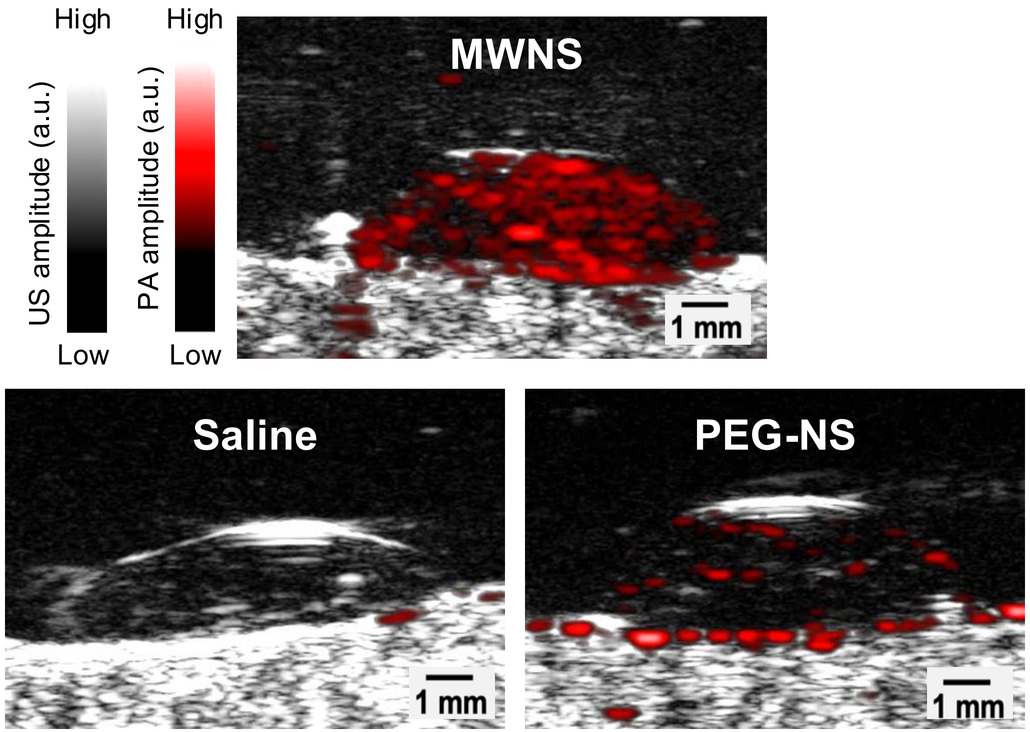


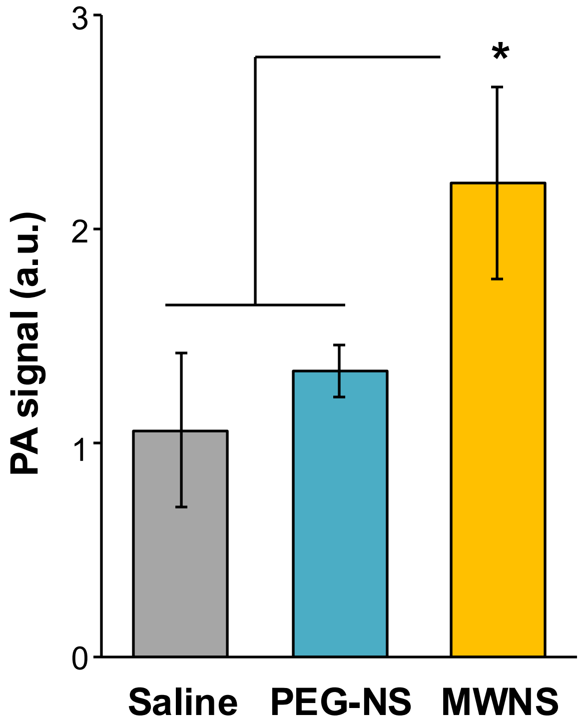
Mechanism of Photoacoustic (PA) Imaging: From Light Application to Image Construction



MWNS Enhance Photoacoustic Imaging of TNBC Cells *In Vitro*

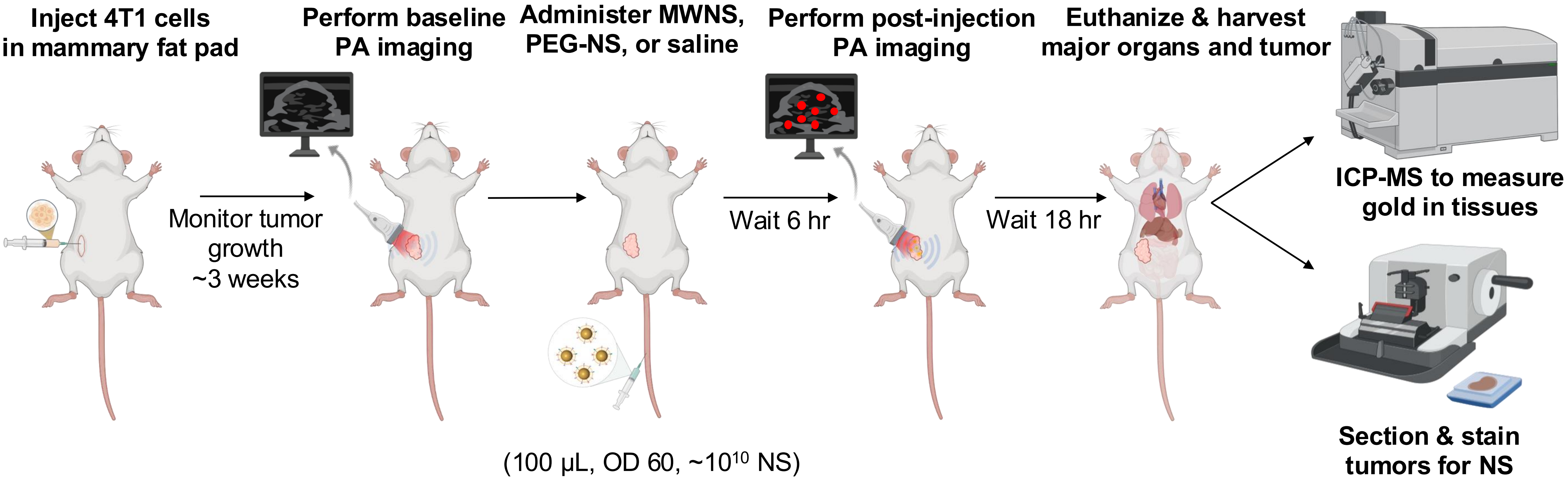




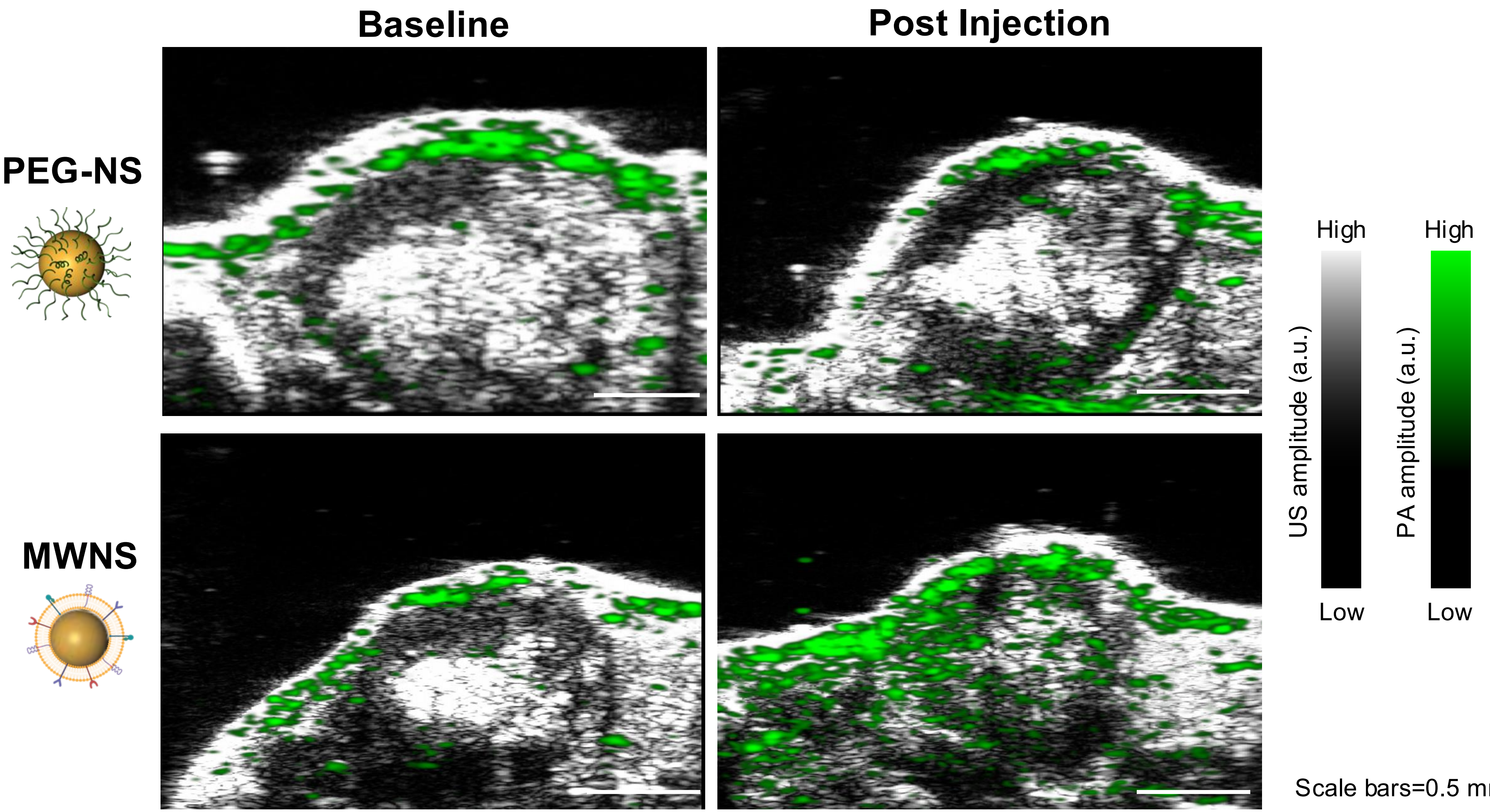


*p<0.05, n=3

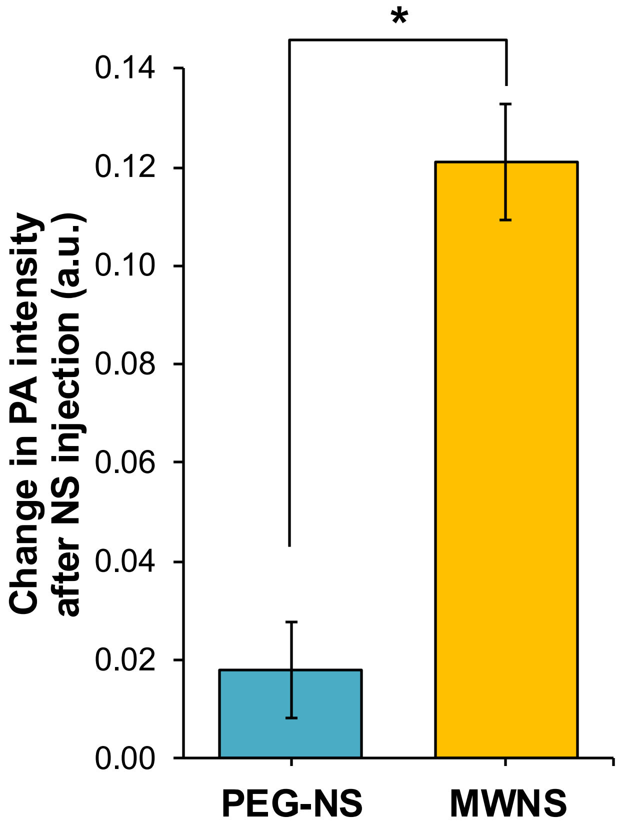
Evaluation of MWNS Biodistribution *In Vivo*



MWNS Exhibit Greater Tumor Accumulation than PEG-NS Based on Photoacoustic Imaging Contrast



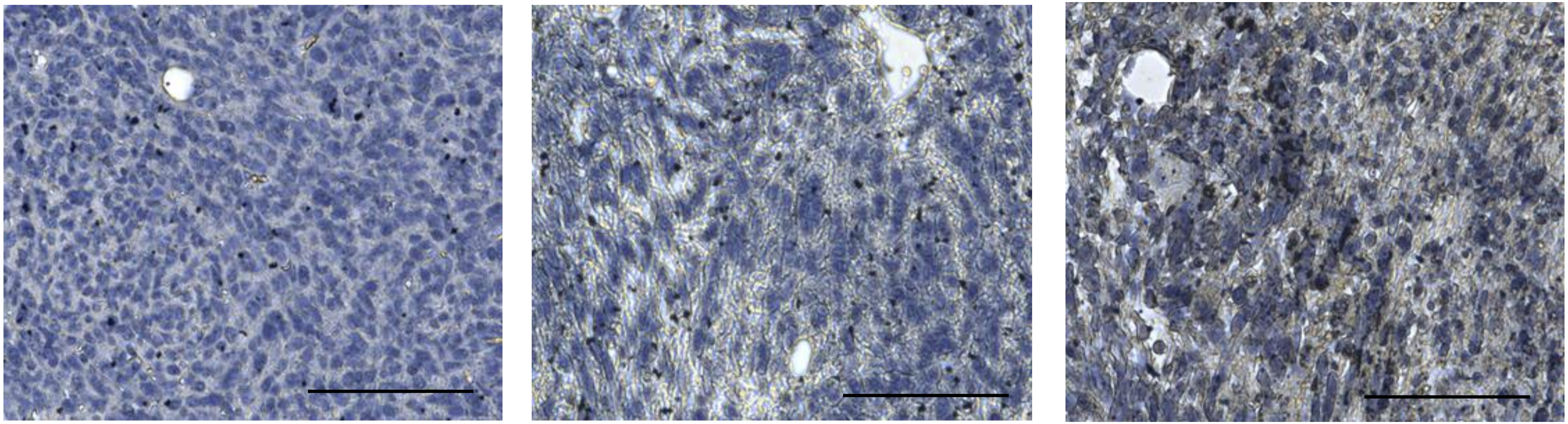
Scale bars=0.5 mm



*p<0.05

Silver Staining Confirms Increased Presence of MWNS Inside Tumors

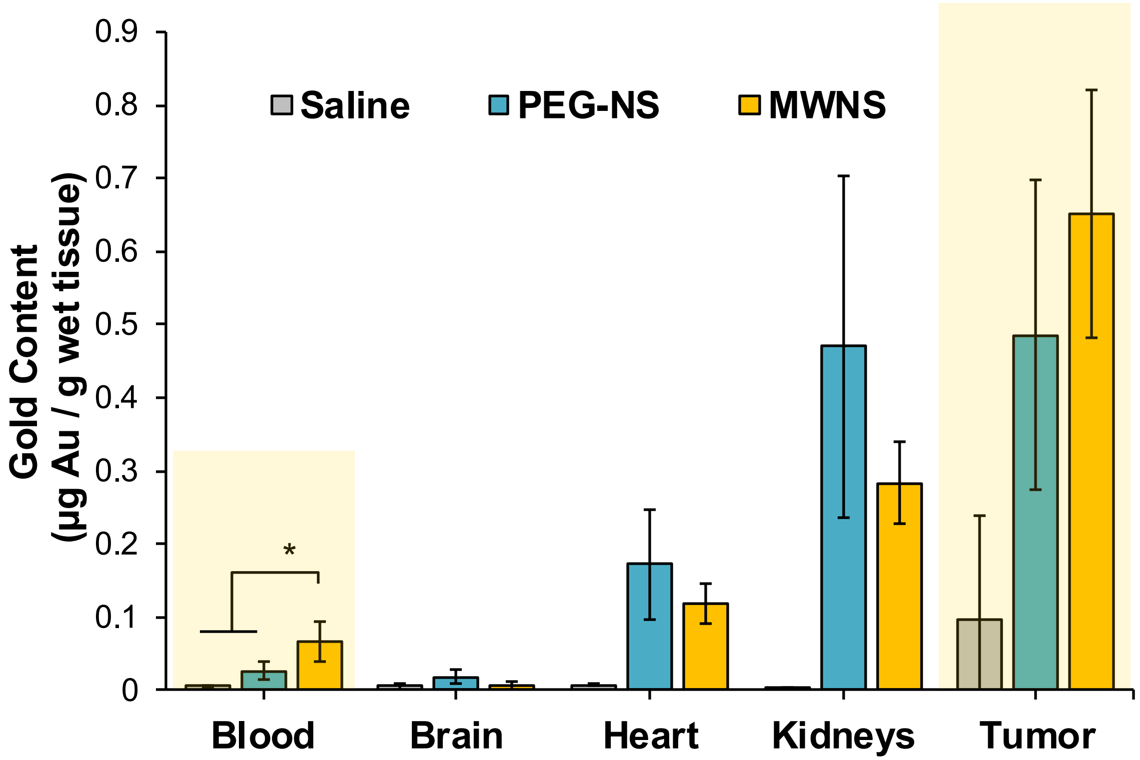
Saline | PEG-NS | MWNS

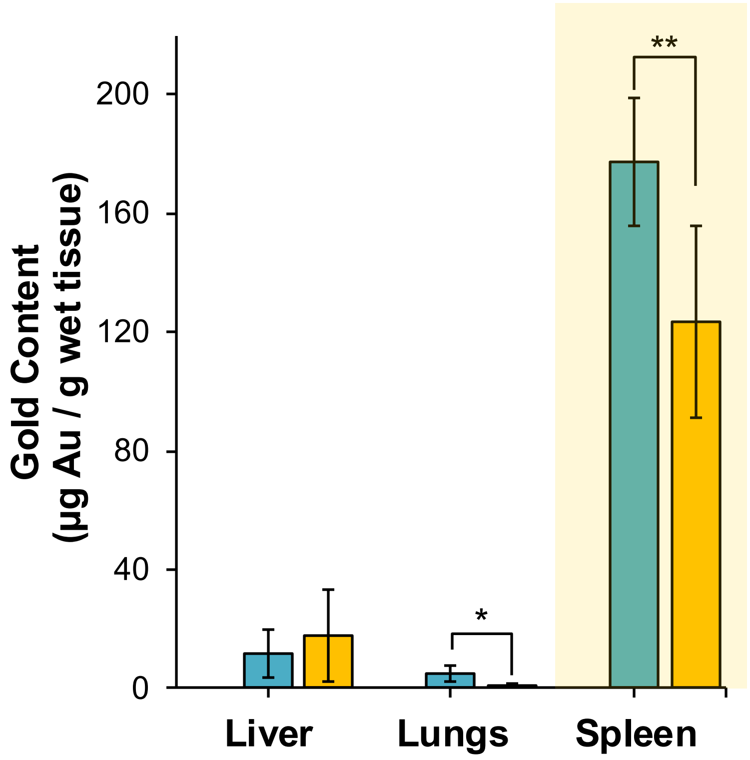


Silver stain=NS
Hematoxylin=nucleus

Scale bars=75 μm

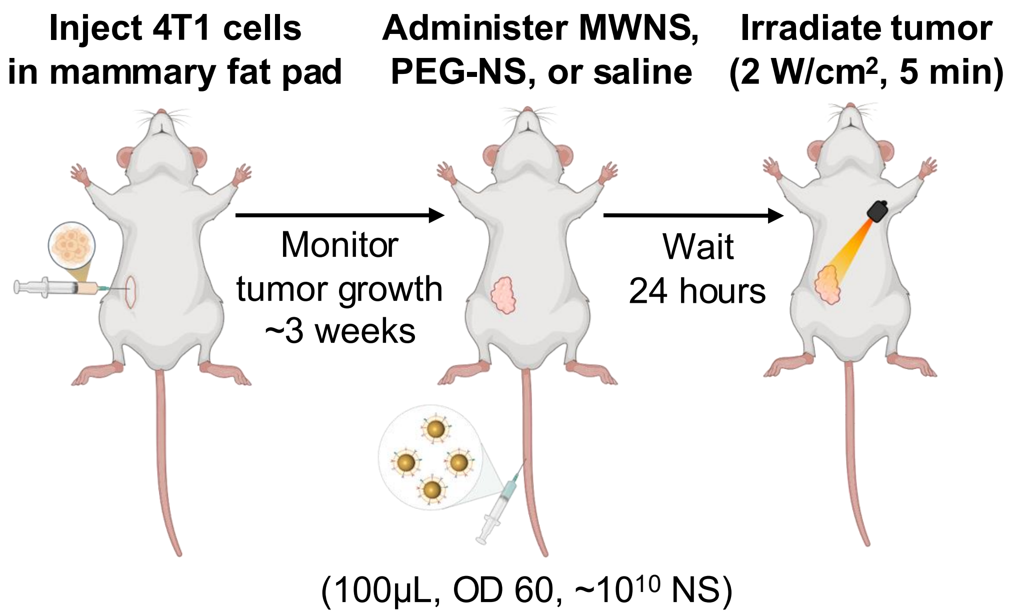
MWNS Exhibit ~147% Higher Blood Retention, ~30% Lower Spleen Accumulation, and ~34% Greater Tumor Delivery Than PEG-NS

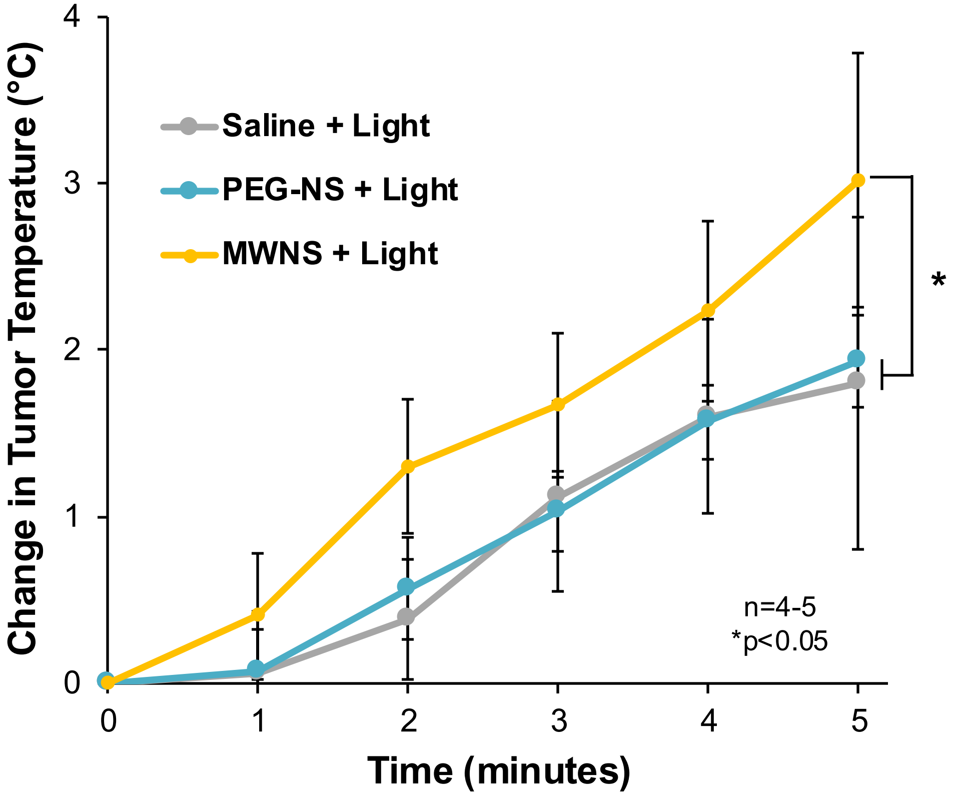




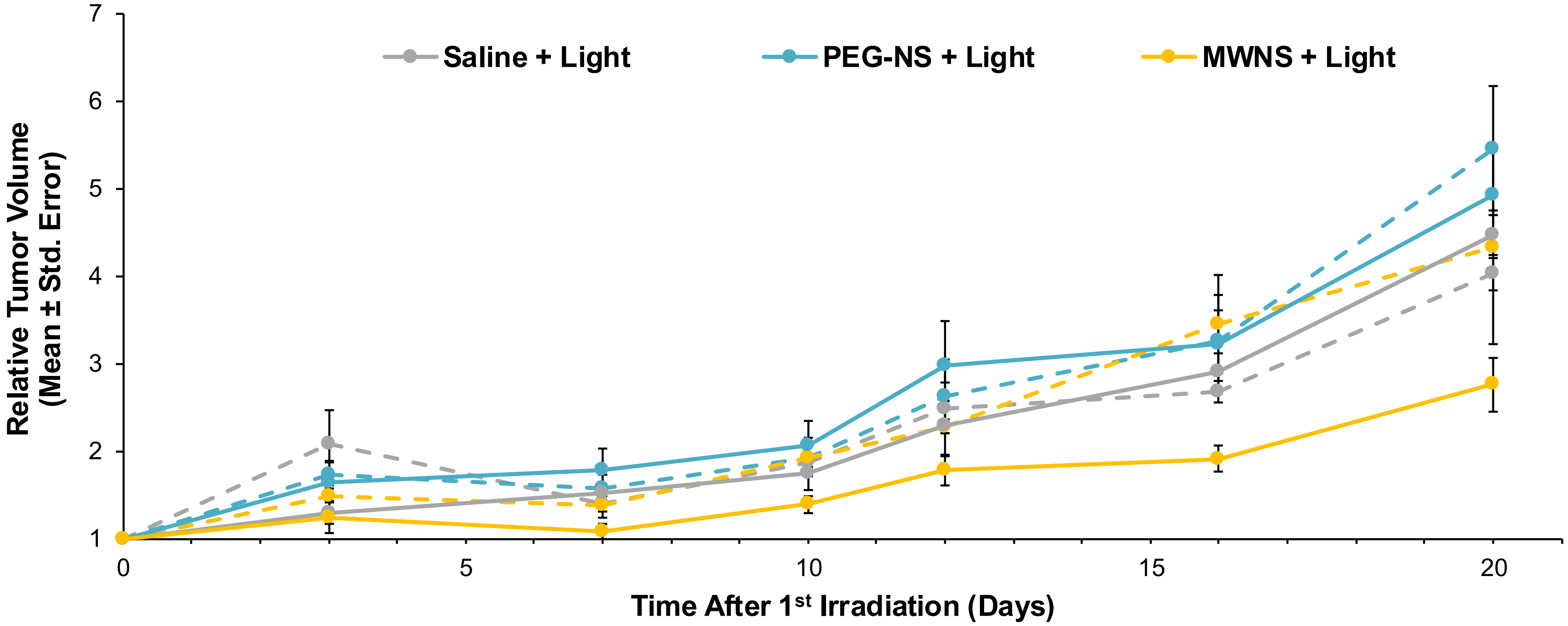
n=4-5
*p<0.05
**p<0.01

Evaluating the Phototherapeutic Effect of MWNS *In Vivo*





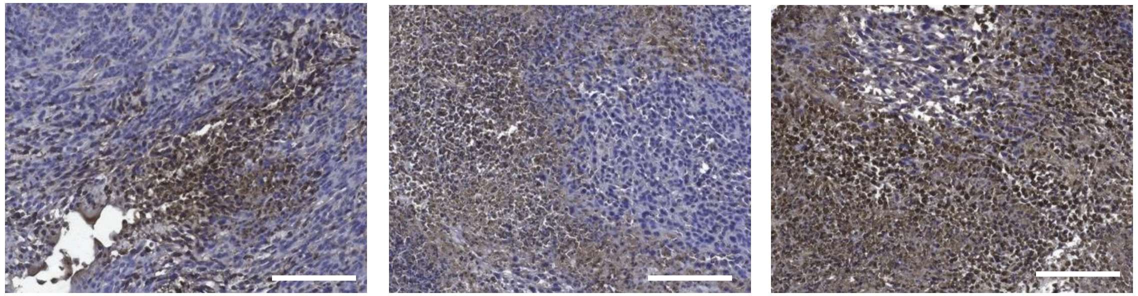
MWNS-Mediated PTT Slows Tumor Growth



MWNS-Mediated PTT Increases Tumor Cell Apoptosis and Decreases Tumor Cell Proliferation

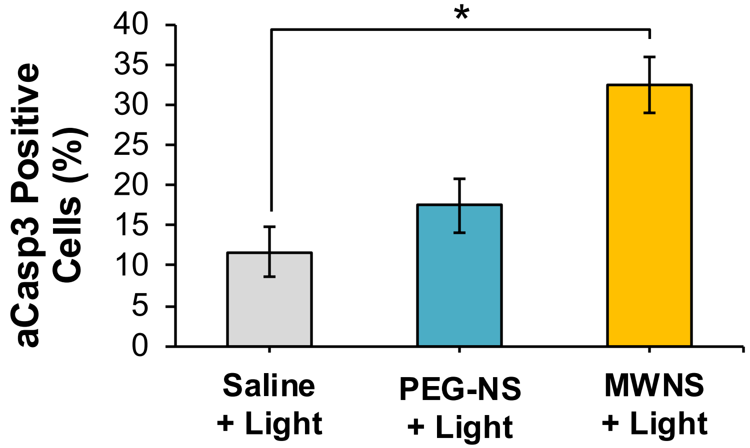
Saline + Light | PEG-NS+ Light | MWNS + Light

Apoptosis (aCasp-3)



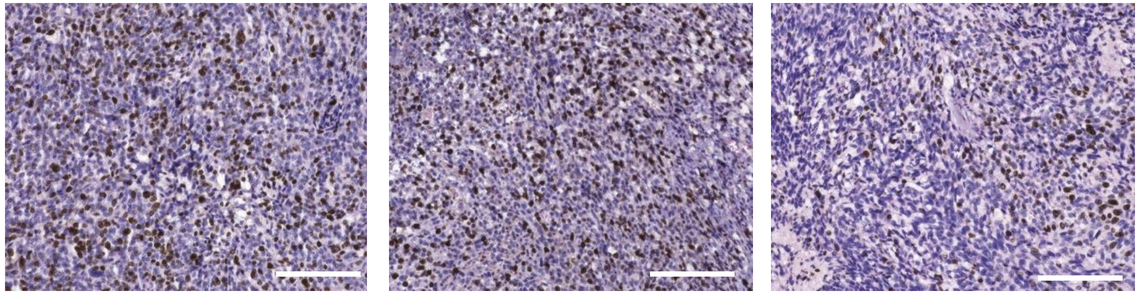
Hematoxylin=blue/purple
aCasp-3=maroon/brown

Scale bars=150 µm



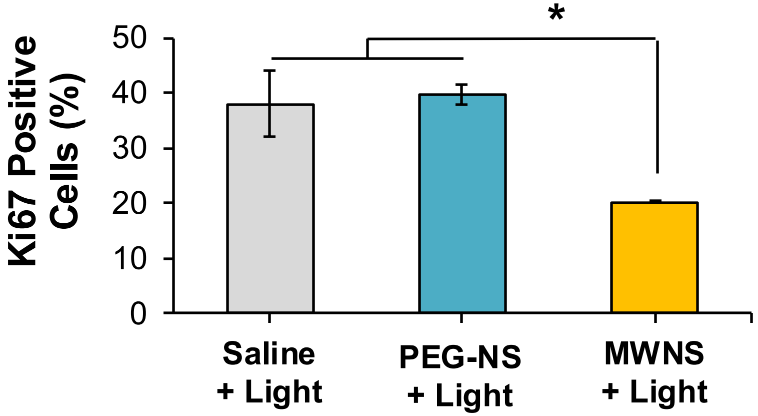
Saline + Light | PEG-NS+ Light | MWNS + Light

Proliferation (Ki67)

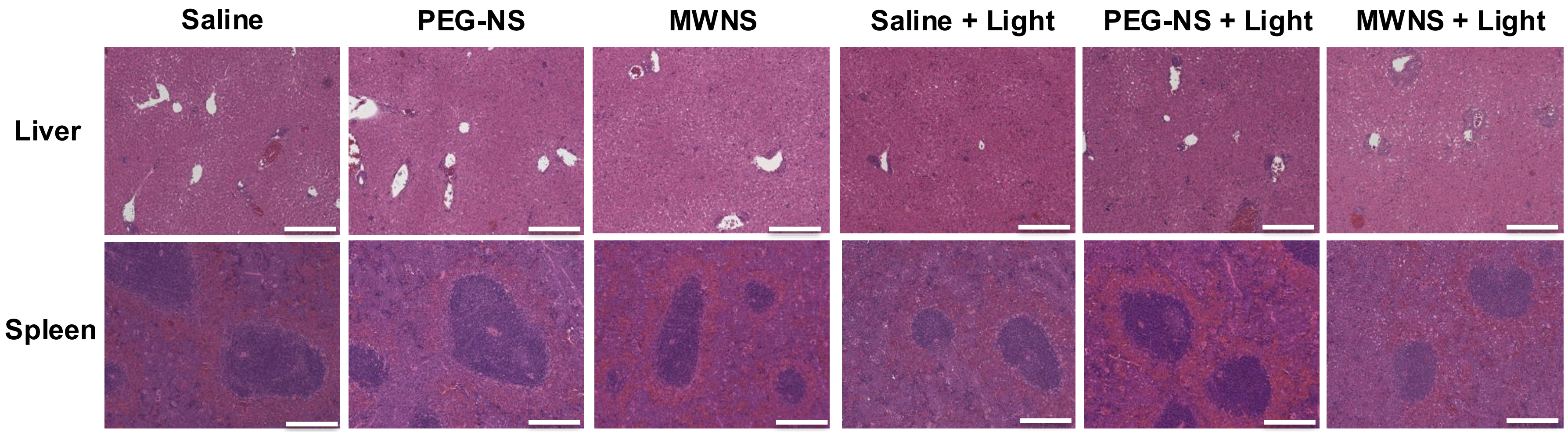


Hematoxylin=purple
Ki67=maroon/brown

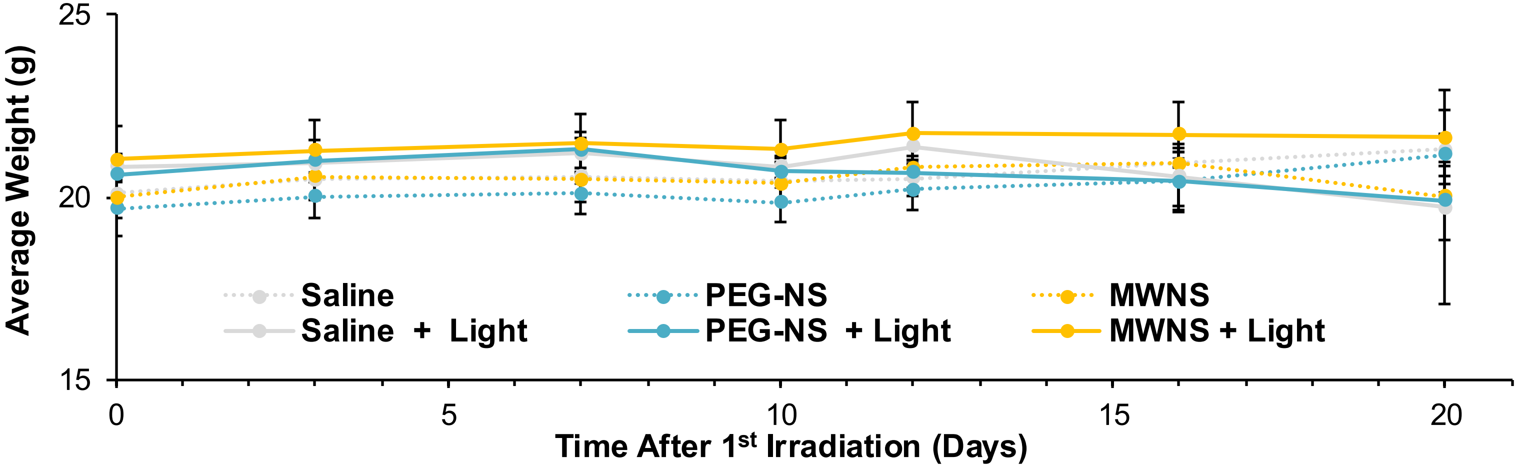
Scale bars=150 µm



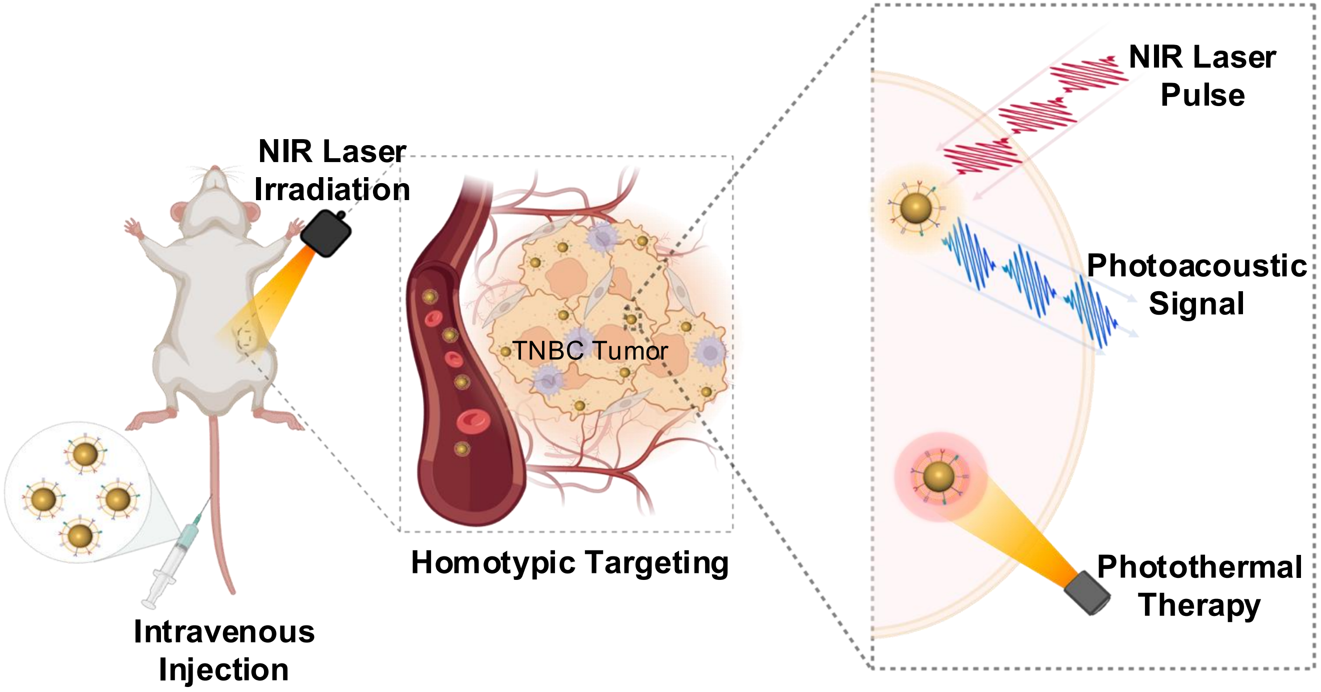
MWNS are Well Tolerated *In Vivo*



Scale bars=275 µm



Summary: MWNS Can Enhance Photoacoustic Imaging and Photothermal Therapy of TNBC



- ✓ Coating NS with cell membranes does not alter their optical properties
- ✓ MWNS enter cancer cells and tumors more efficiently than PEG-NS
- ✓ MWNS enhance tumor imaging and PTT as compared to PEG-NS

Acknowledgements

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Thank You!

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