Imaging Heterogenous Tumor Accumulation and Intratumoral Distribution of Nanoparticles

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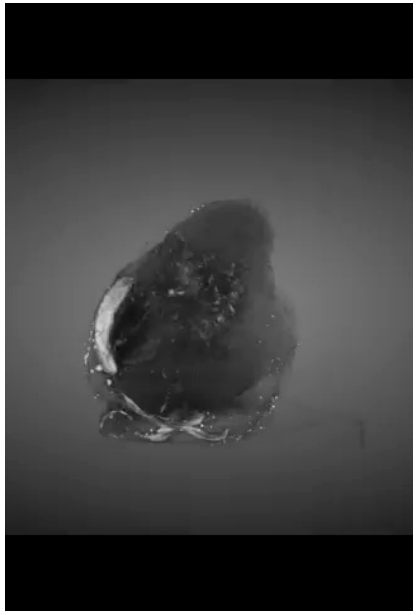
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

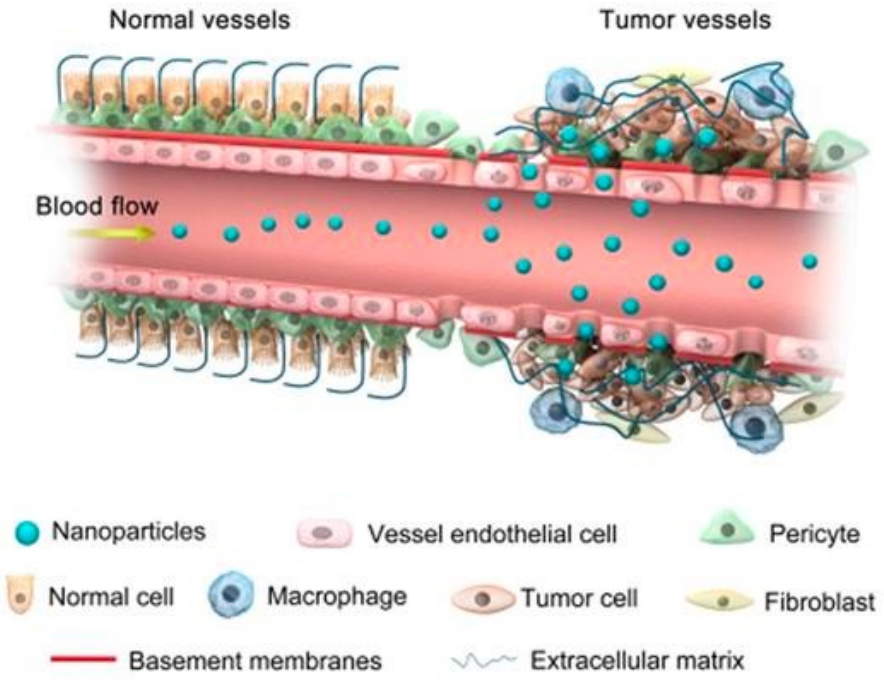
Revolution Needed for Cancer Nanomedicines

- Late detection
- Tumor heterogeneity and patient variation
- Needs image guided therapy
  ——precision medicine

EPR Effect and Tumor Leakiness

Enhanced Permeation and Retention (EPR) Effect





- Rapid angiogenesis leads to leaky vessels;
- Endothelial cells outline vessels without appropriate supporting basal layer;
  - 100 nm - 2 µm gaps.
- Tissue leakiness: interplay between tumor and nanoparticle properties.
- Special Entry through active pathway

Kalyane et al. Mater Sci Eng C (2019); Maeda et al. Adv Drug Deliv Rev (2015)

Sindhwani, S., Syed, A.M., Ngai, J. *et al. Nat. Mater.* **19,** 566–575 (2020).

B.R. Kingston, Z. P. Lin et al. *ACS Nano 2021* DOI: 10.1021/acsnano.1c04510

Tool for Smart Therapeutic Decisions

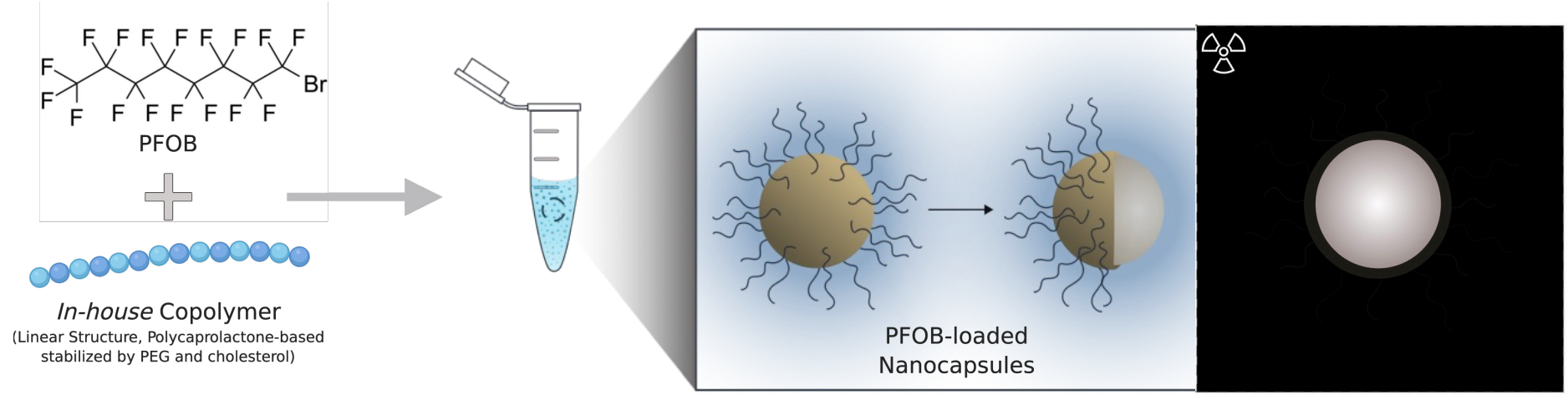
Imaging EPR

merrimack

- **^{64}Cu-labeled HER2-targeted PEGylated liposomal doxorubicin**;
- **PET/CT Imaging:** 35-fold (0.52-18.5 %ID/kg) variation;
- Patient selection for Phase II/III clinical trial based on cut-off value for nanoparticle deposition at cancerous lesions

Lee, H. et al., (64)Cu-MM-302 Positron Emission Tomography Quantifies Variability of Enhanced Permeability and Retention of Nanoparticles in Relation to Treatment Response in Patients with Metastatic Breast Cancer. *Clin Cancer Res* **2017,** *23* (15), 4190-4202.

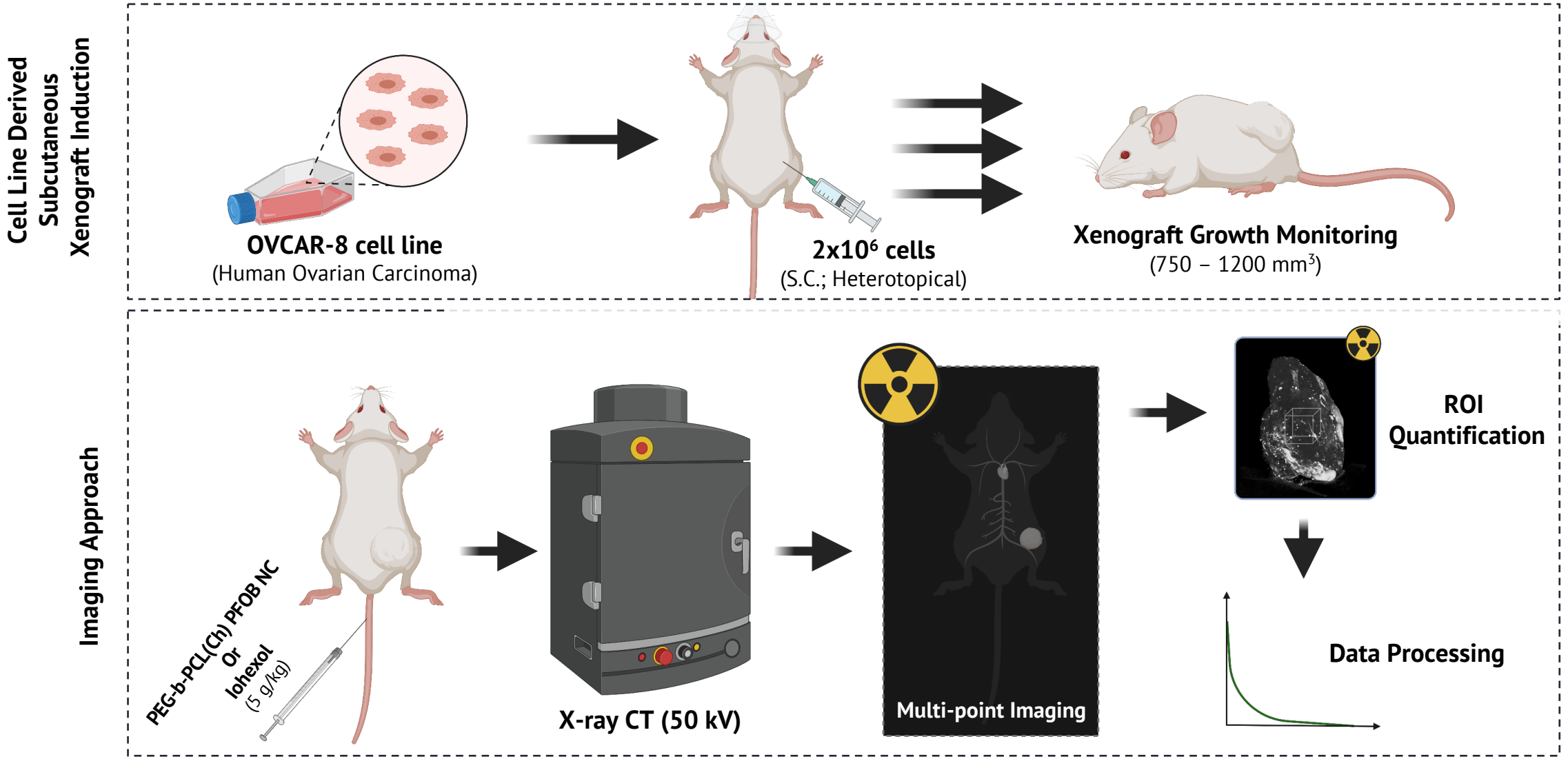
Generic Platform for Tumor Imaging via X-ray CT



BERINGHS, A.O.; NDAYA, D.; KASI, R.M.; LU, X. *Nanoparticles for Imaging and Therapy*. U.S. Patent and Trademark Office. Provisional Patent Application No. 62/812,944. Filed: 03/01/2019.

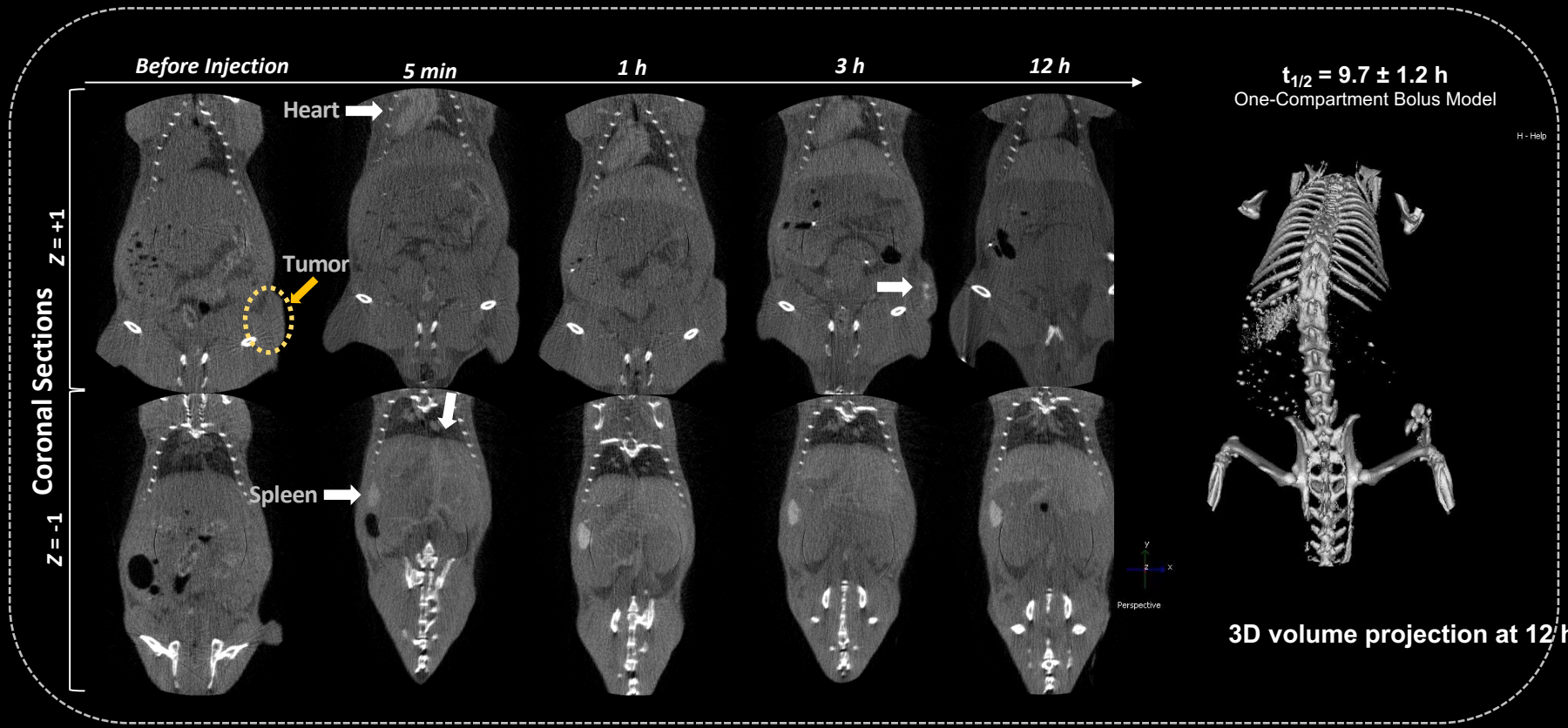
Beringhs AO, Ndaya D, Bosire R, Kasi RM, Lu X. AAPS PharmSci Tech. 2021 Mar 5;22(3):90.

Xenograft Induction, Imaging and Kinetic Assessment



PEG-b-PCL(Ch) NC Promote Differential Tumor Contrast

PFOB-loaded PEG-b-PCL(Ch) NC – OVCAR-8 subcutaneous xenograft tumor model
5 g PFOB/kg tail vein injection (n=4)



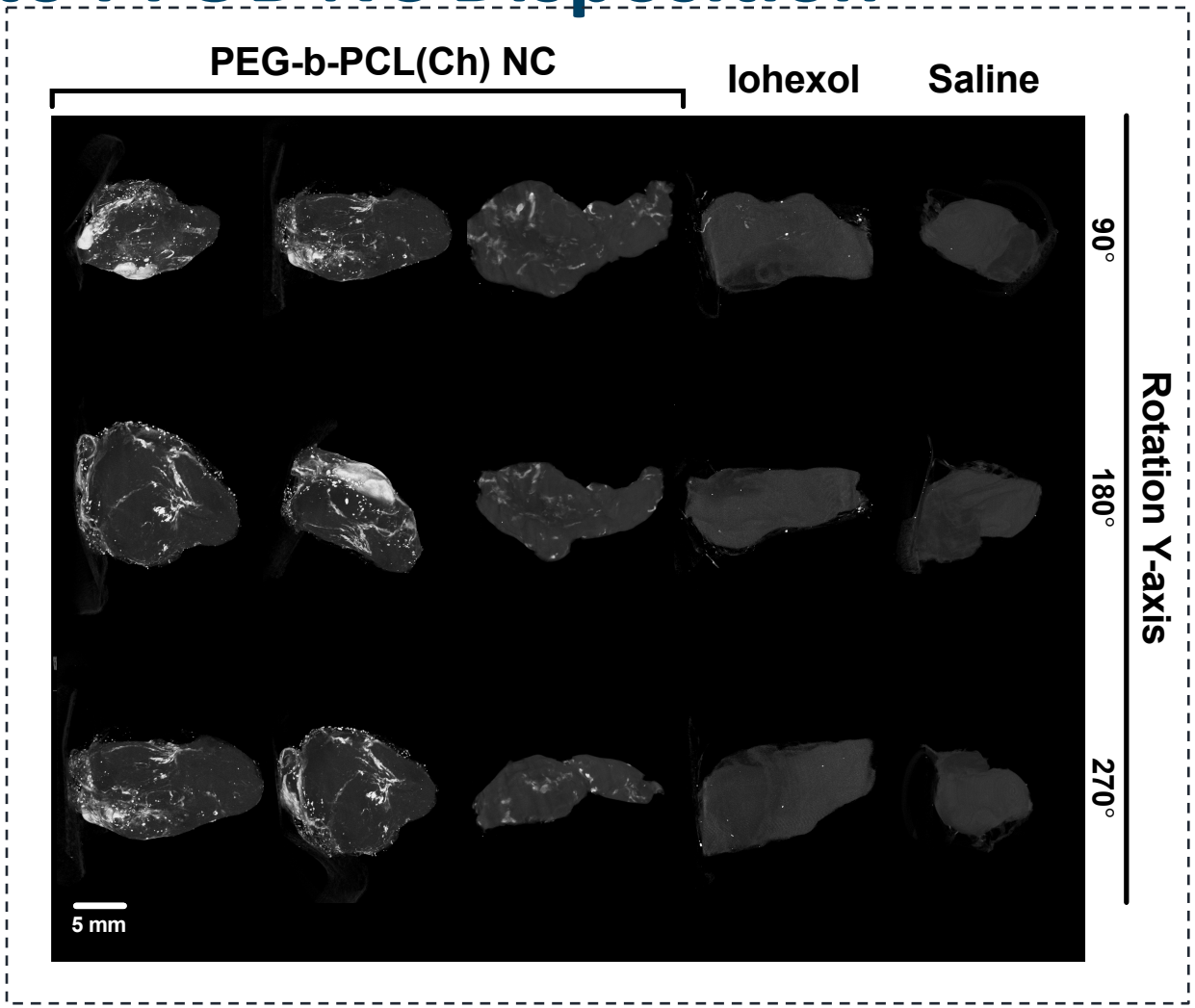
$t_{1/2}$ = 9.7 ± 1.2 h
One-Compartment Bolus Model

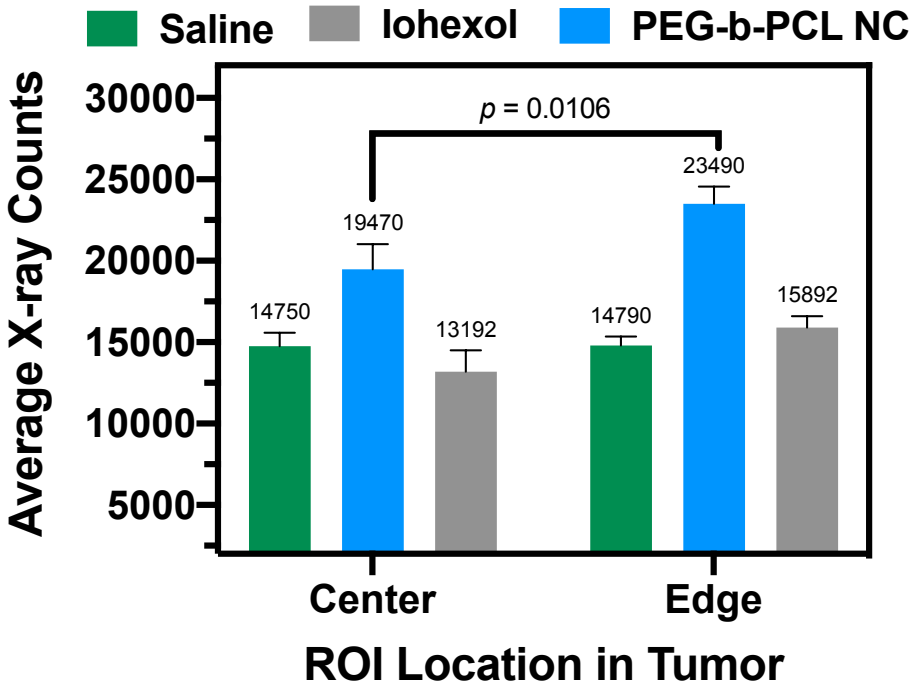
3D volume projection at 12 h

High-load PFOB nanocapsules display **improved colloidal stability** when stabilized with in-house copolymer, enabling **real-time *in vivo* imaging** and assessment of **solid tumor leakiness** for **imaging-guided nano-therapy**

BERINGHS, A.O.; NDAYA, D.; KASI, R.M.; LU, X. *Nanoparticles for Imaging and Therapy*. U.S. Patent and Trademark Office. Provisional Patent Application No. 62/812,944. Filed: 03/01/2019.

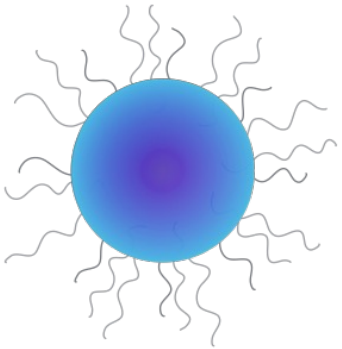
Ex Vivo Imaging Reveals Tumor Heterogeneity with Respect to PFOB NC Disposition

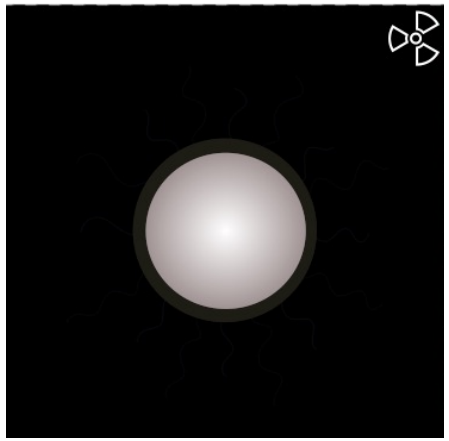




PFOB NC **intratumoral distribution** is **heterogeneous** and concentrated within **peripheric regions**

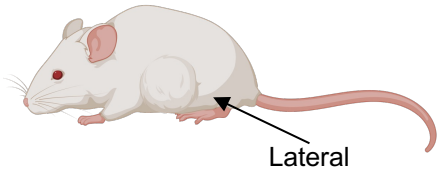
Can PFOB Nanocapsules Differentiate tumors as a Function of Leakiness?



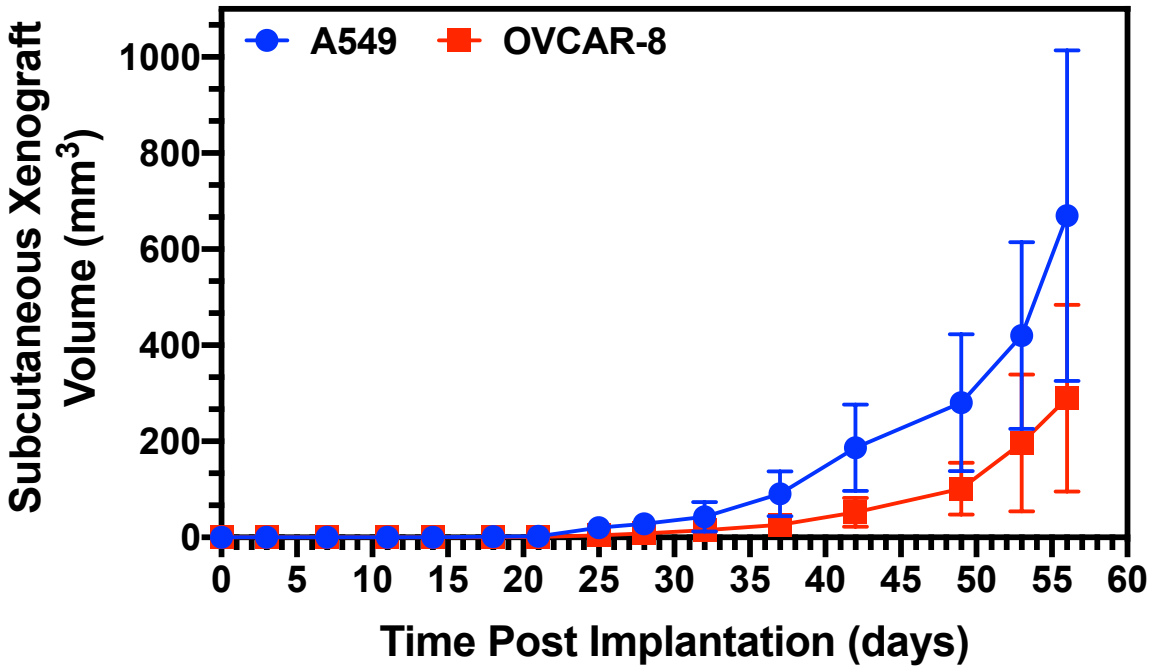


40% (v/v) PFOB-loaded PEG-b-PCL(Ch) NC + DiR' label

- **Double-lateral xenograft tumor model:**
  - **A549** (human alveolar adenocarcinoma)
  - **OVCAR-8** (human ovarian carcinoma)

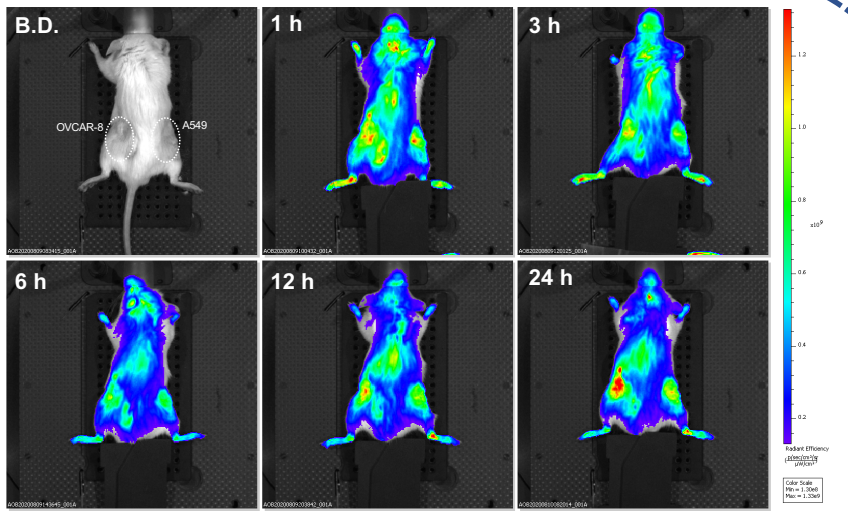


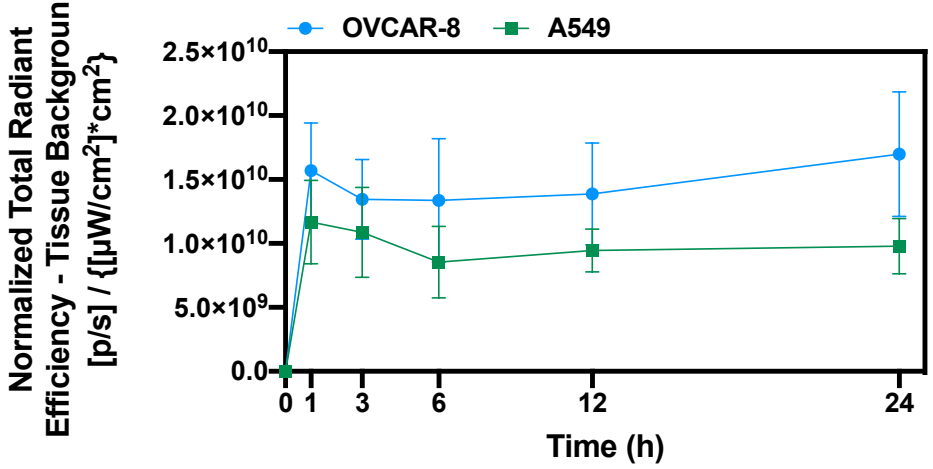
Lateral xenograft representation



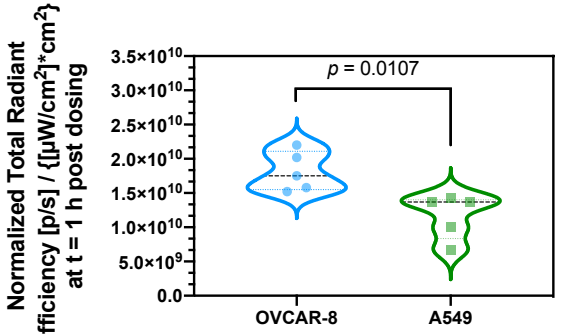
Optical Imaging Reveals Differences in Vascular Supply and Tissue Exposure

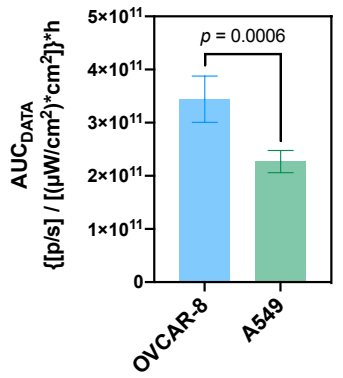
In vivo Biodistribution



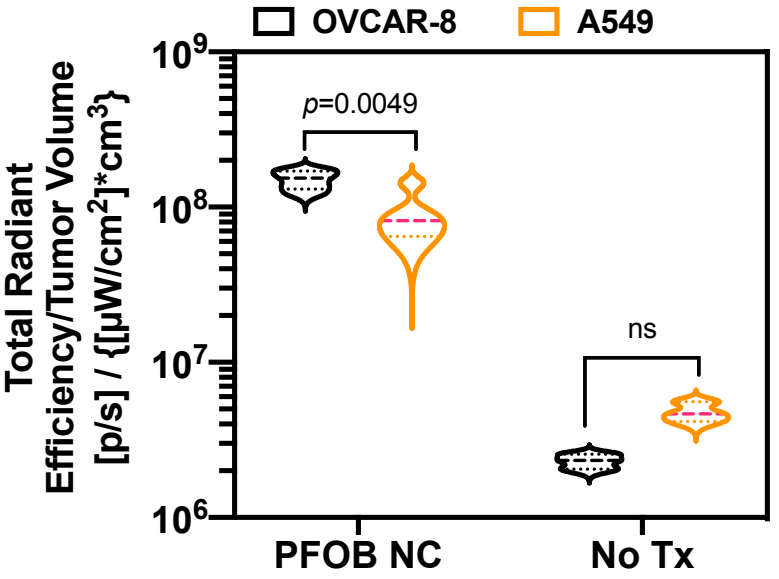


In Vivo Exposure



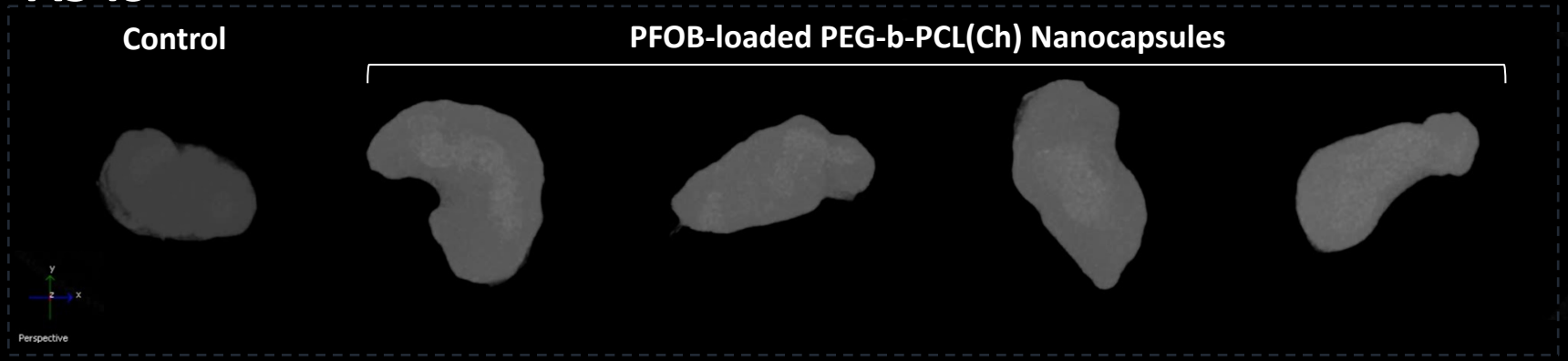


Ex vivo Exposure

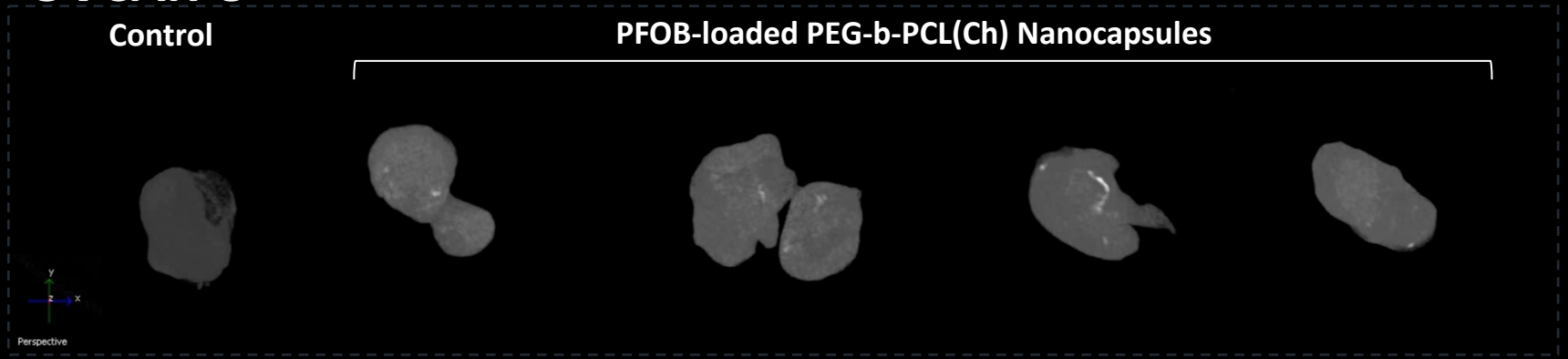


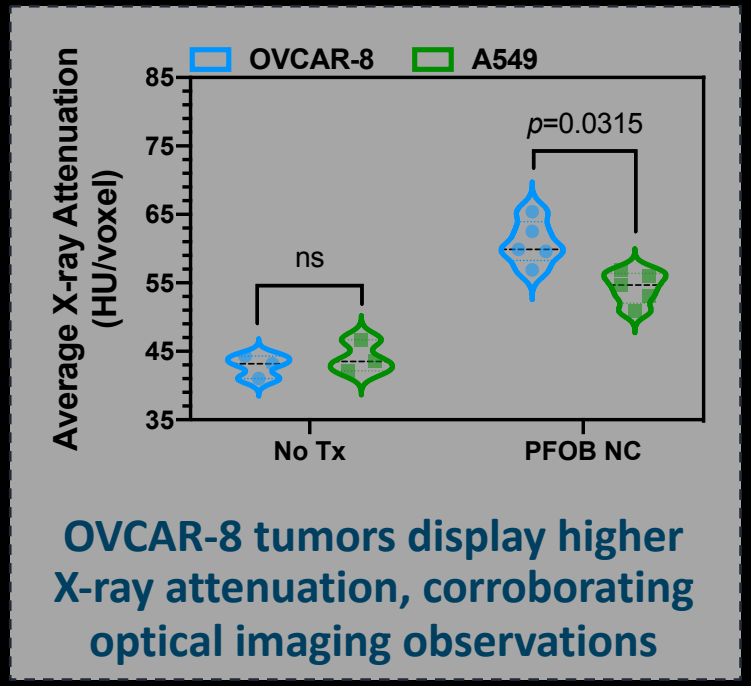
X-ray CT Enables Precise Nanocapsule Localization and Quantification in Tumors

A549



OVCAR-8





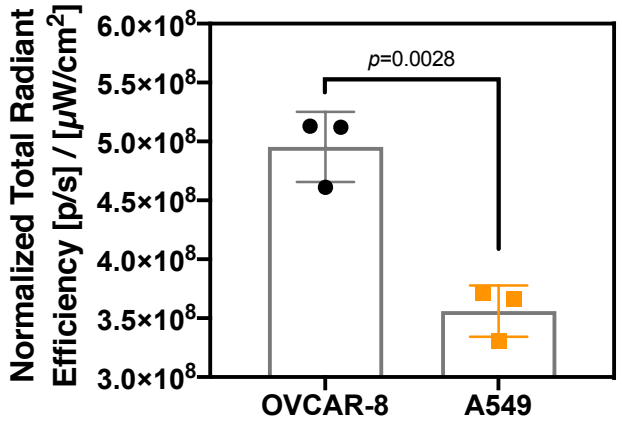
OVCAR-8 tumors display higher X-ray attenuation, corroborating optical imaging observations

A549 tumors displayed lower overall tumor exposure to nanocapsules *in vivo*, reflecting in lower X-ray attenuation and diffuse-like pattern of accumulation. OVCAR-8 showed higher attenuation with "spot-like" perivascular accumulation.

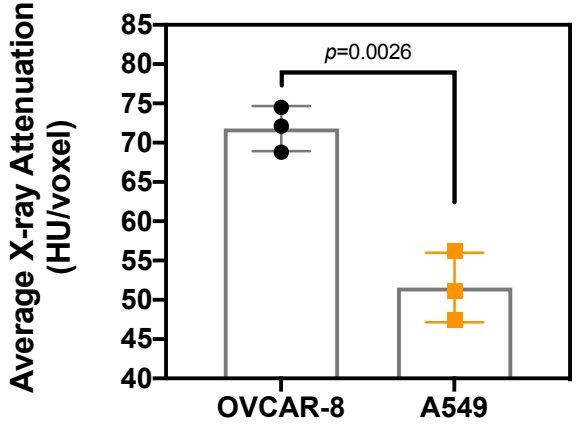
PFOB-loaded Nanocapsules Provide Insights for Nanoparticle Therapy

Co-administration of PFOB-loaded nanocapsules and generic liposomal doxorubicin

Optical Imaging
(Doxorubicin Quantification)



X-ray CT
(PFOB Quantification)



Agreement between X-ray CT observations and liposomal doxorubicin accumulation in tumor tissues

- OVCAR-8 tumors are smaller than A549, but vascularization and increased leakiness provide optimal conditions for nanoparticle extravasation;
- PFOB nanocapsules can facilitate the further understanding of delivery and therapeutic outcome.

Beringhs AO. Ndaya D, Bosire R, Kasi RM, Lu X. Imaging Tumor Heterogeneity and the Variations in Nanoparticle Accumulation using Perfluorooctyl Bromide Nanocapsule X-ray Computed Tomography Contrast. Advanced Therapeutics. April 2022, 5 (8)

Key Observations & Conclusions

Nanomedicine for Cancer Therapy is not a one-size-fits-all approach

- The high variability in tumor biology is a major limitation to the delivery of colloidal structures;
- PFOB-loaded nanocapsules show high X-ray attenuation and adequate colloidal stability for *in vivo*;
- The ability of nanoparticles to accumulate in a tumor can be better assessed using CT imaging with the nano-contrast;
- Preclinical correlation between PFOB nanocapsule accumulation and liposomal doxorubicin has been established;
- Precise localization and quantification of nanoparticles within tumor tissue can be achieved by employing image-guided therapy and can potentially be used as a screening tool for future clinical applications.

Thank you!

71 Dr. Lu's Lab 174.967