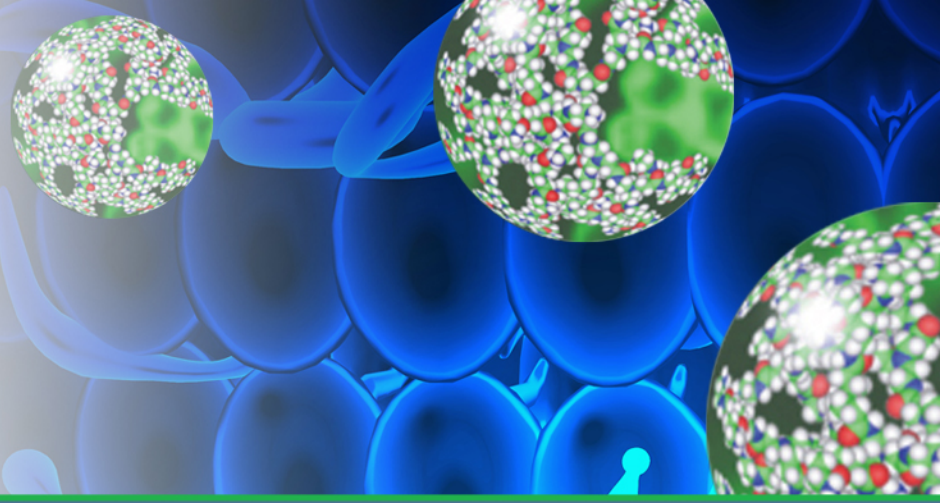
National Cancer Institute

NCI Alliance for Nanotechnology in Cancer



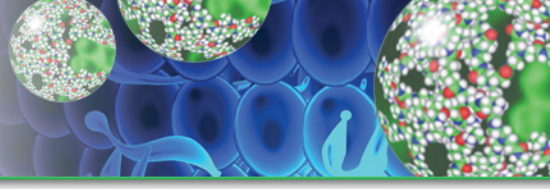
NanoWG - Introduction

Luisa Russell

Nanodelivery Systems and Devices Branch
Cancer Imaging Program
National Cancer Institute/National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

My Background



Research Background

- Graduate Research, Johns Hopkins University (Dr. Peter Searson): **Development of an *in vivo* benchmarking protocol for cancer nanomedicines and informed creation of a novel stealth nanomedicine for passive accumulation in solid tumors**

- Undergraduate Research, Stanford University (Dr. Robert Sinclair): **Electron microscopy of nanoparticles in biological samples**

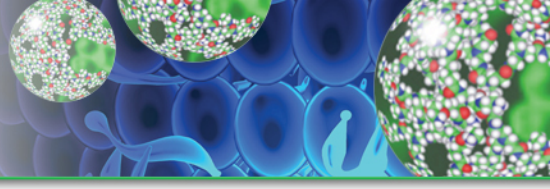
- Undergraduate Research, Freie Universitaet (Berlin, Germany): **Synthesis and functionalization of gold nanoparticles**

Nanoparticle Background

- Synthesis of…
  - Liposomes
  - Gold nanoparticles
  - Quantum dots
  - Silica nanoparticles
  - Silver nanoparticles
  - Graphene Oxide/Nano-diamonds
  - *Peptides

- Characterization of…
  - All of the above
    - PCC, *in vitro*, and/or *in vivo*
  - Magnetic nanoparticles
  - Polymeric nanoparticles
  - Micelles
  - Cell membrane vesicles
  - Antibody-drug conjugates
  - Peptide-drug conjugates
  - Thin films

Graduate Work - Main Research Thrusts



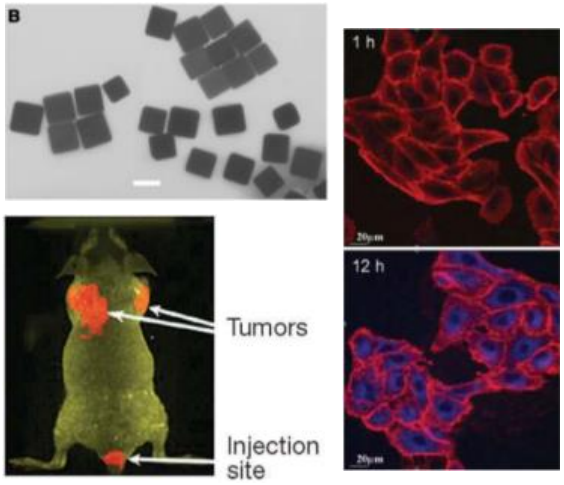
- ***Overview and Analysis of the field of Cancer Nanomedicine***
  - *Dawidczyk, C. M.*, Kim, C.*, Park, J. H.*,* ***Russell, L. M.****, Lee, K. H., Pomper, M. G., & Searson, P. C. (2014). State-of-the-art in design rules for drug delivery platforms: lessons learned from FDA-approved nanomedicines.* Journal of Controlled Release*, 187, 133-144.*
  - *Dawidczyk, C. M.*,* ***Russell, L. M.****, & Searson, P. C. (2014). Nanomedicines for cancer therapy: state-of-the-art and limitations to pre-clinical studies that hinder future developments.* Frontiers in Chemistry*, 2, e69.*
  - *Dawidczyk, C. M.*,* ***Russell, L. M.****, & Searson, P. C. (2015). Recommendations for Benchmarking Preclinical Studies of Nanomedicines.* Cancer Research*, 75(19), 4016-4020.*
  - *Dawidczyk, C. M.,* ***Russell, L. M.****, Hultz, M., & Searson, P. C. (2017). Tumor accumulation of liposomal doxorubicin in three murine models: Optimizing delivery efficiency.* Nanomedicine: Nanotechnology, Biology and Medicine*. Epub.*
  - ***Russell, L M****., Dawidczyk. C. M., & Searson, P.C. (2017). Quantitative Evaluation of the Enhanced Permeability and Retention (EPR) Effect.* Methods in Molecular Biology, 1530, *247-254.*
  - *Dawidczyk, C. M.*,* ***Russell, L. M.****, & Searson, P. C. (2017). Nanomedicines for cancer therapy: state-of-the-art and limitations to pre-clinical studies that hinder future developments.* Cancer Nanotheranostics: What Have We Learned So Far? *35-47.*

- ***Nanoparticle Characterization***
  - ***Russell, L. M.****, Hultz, M., & Searson, P. C. (2018). Leakage kinetics of the liposomal chemotherapeutic agent Doxil: The role of dissolution, protonation, and passive transport, and implications for mechanism of action.* Journal of Controlled Release, 269, 171-176
  - *Submitted: Wong, A. D.,* ***Russell, L. M.****, & Searson, P. C. (2017). Quantitative Analysis of Proliferation, Apoptosis, and Migration in a Tissue-Engineered 3D Microvessel Model of the Tumor Microenvironment Following Chemotherapeutic Delivery.*
  - *Mukherjee, A., Kumar, B., Hatano, K.,* ***Russell, L. M.****, Trock, B. J., Searson, P. C., & Lupold, S. E. (2016). Development and Application of a Novel Model System to Study "Active" and "Passive" Tumor Targeting.* Molecular Cancer Therapeutics*, 15(10), 2541-2550.*

- ***Development of stealth liposomes***
  - *In preparation:* ***Russell, L. M.,*** *Komin, A., Xu, Z., Hultz, M., Gallagher, E., Searson, P. C. (2018) Tumor drug delivery using a PEG-less stealth liposome based in marker-of-self technology.*
  - *In preparation:* ***Russell, L. M.*,*** *Gallagher, E.*, Searson, P. C. (2017) Targeted liposome delivery of novel neurotoxin antidotes to the brain.*

Simplified Informatics Framework

Data → Data Collection/ Analytics → Outcomes



NANOPARTICLE INFORMATION LIBRARY

NIH NATIONAL CANCER INSTITUTE Center for Biomedical Informatics & Information Technology

caNanoLab

InterNano Resources for Nanomanufacturing

nanoHUB

???

Design rules to increase tumor accumulation

Sun, Y., and Xia, Y. *Science* (2002), Liu, Y., et al. *International journal of cancer* (2007)

Simplified Informatics Framework

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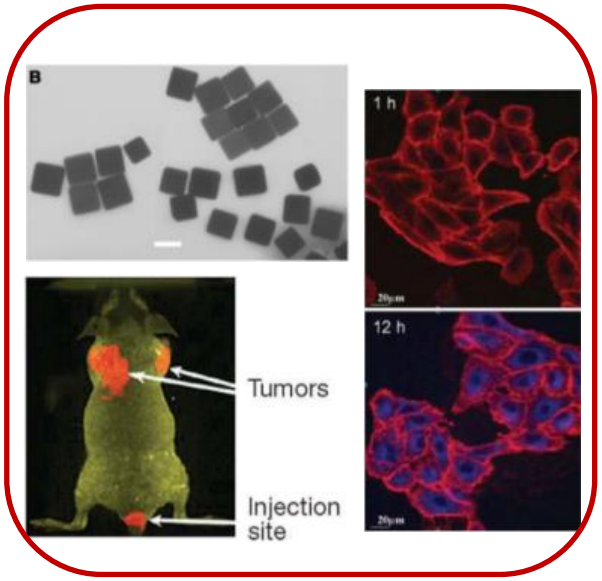

Graduate Focus

NANOPARTICLE INFORMATION LIBRARY

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Current Focus

???

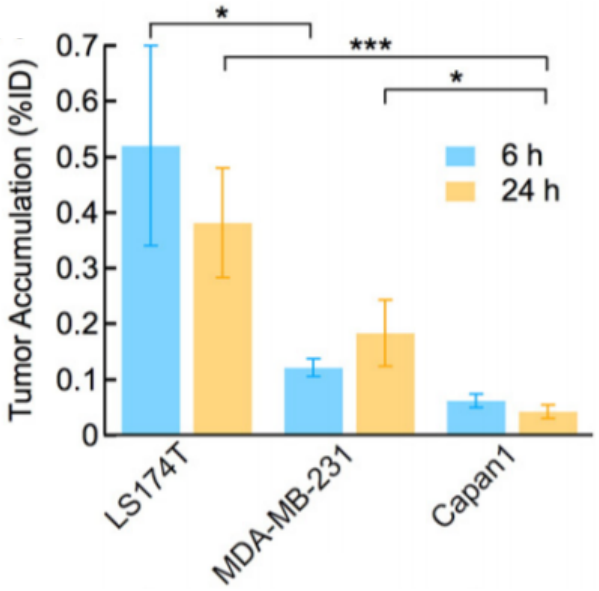
Design rules to increase tumor accumulation

Sun, Y., and Xia, Y. *Science* (2002), Liu, Y., et al. *International journal of cancer* (2007)

Trouble with nanomedicine databases – Incomparable data

Consider tumor accumulation…

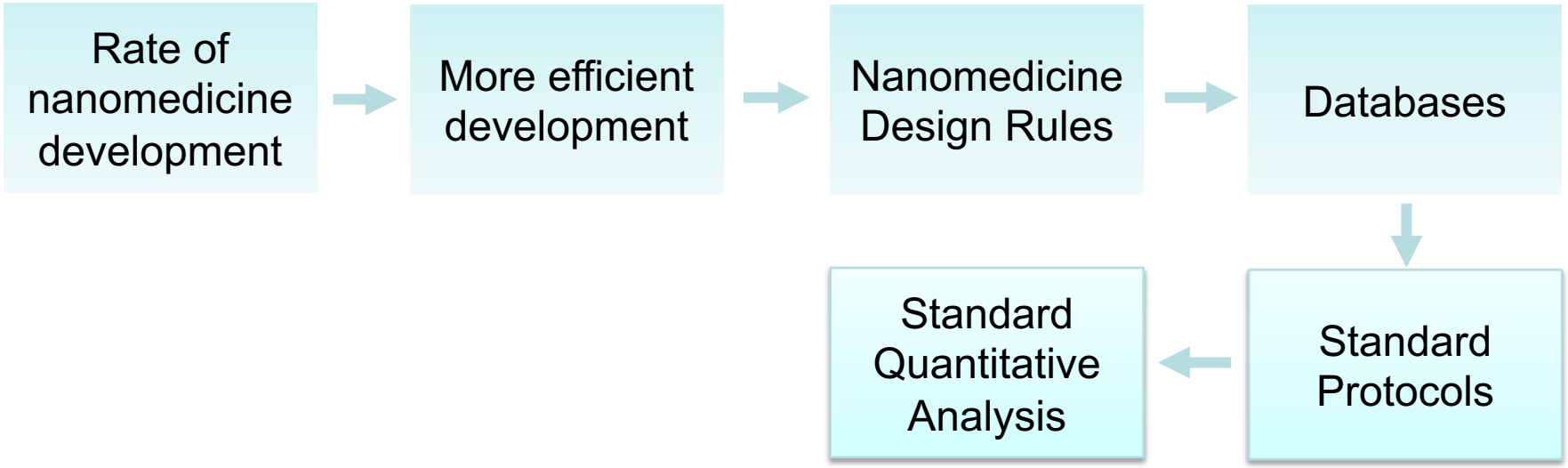
- Variability in controls
- Mouse model
- Dose
- ***Tumor type*** *(35 types in 68 studies)*
- Quantitative measurement of tumor accumulation
- Inconsistent reporting



LS174T: colorectal adenocarcinoma, high EPR
MDA-MB-231: breast cancer, medium EPR
Capan1: pancreatic cancer, low EPR

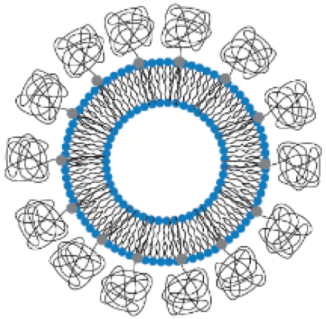
Dawidczyk et al, *Nanomedicine: NBM* (2017), Dawidczyk et al, *Frontiers in Chemistry* (2014)

Critical need for new tools

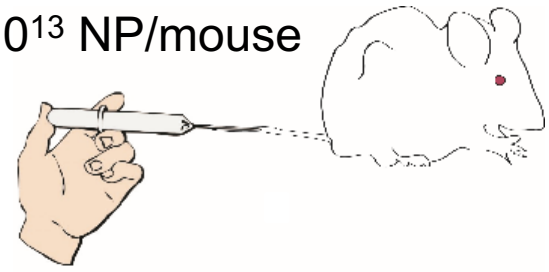


Proposed standardized experiment for benchmarking

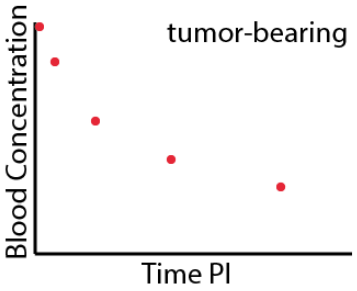
Physicochemical properties:
Size (nm)
Shape
Composition
Surface chemistry

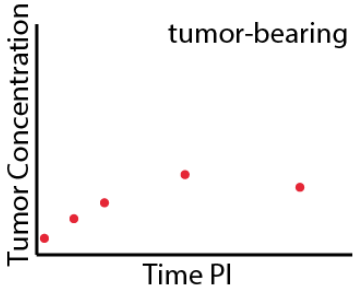


Dose:
10^{13} NP/mouse



Animal model:
Athymic nu/nu mice
LS174T xenografts
8-10 mm
Report weight/
diameter of tumor

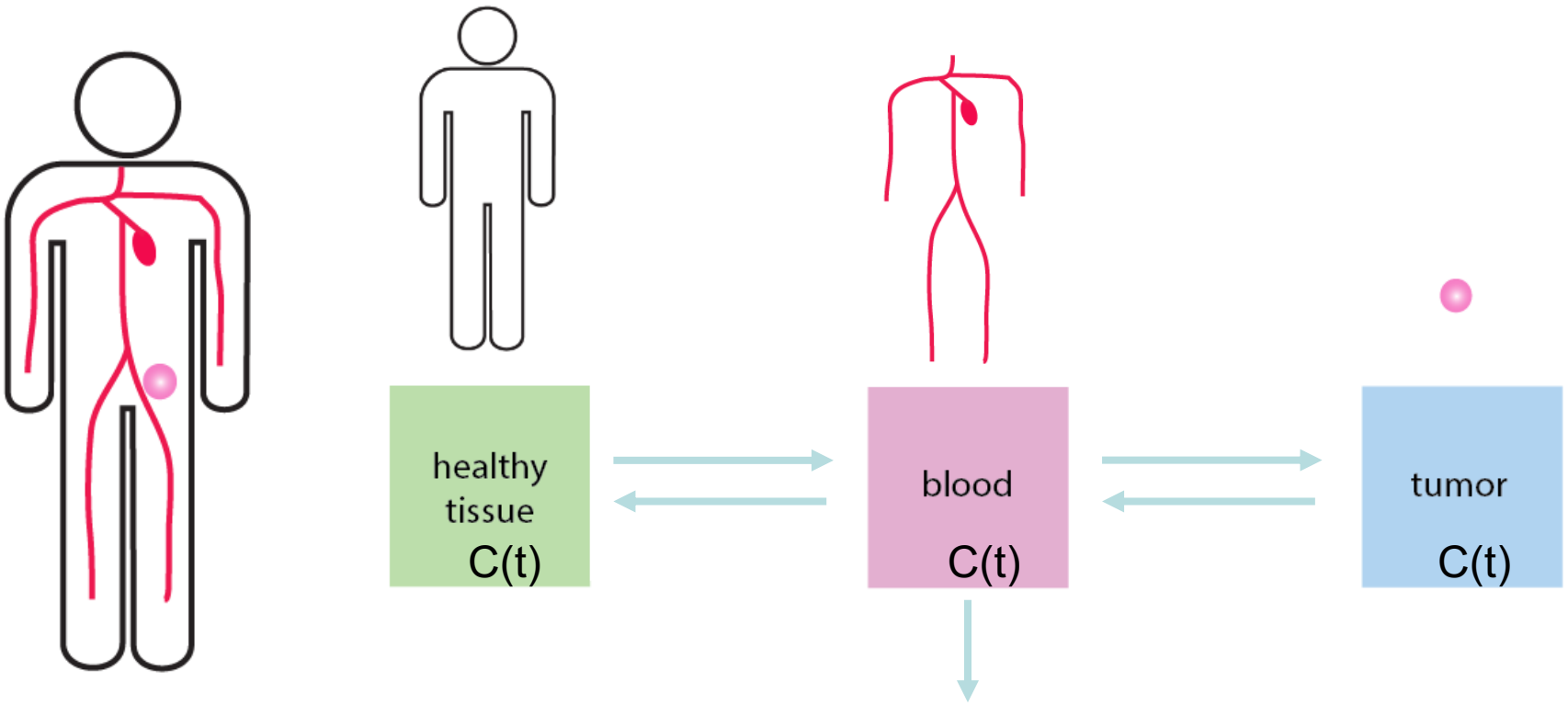




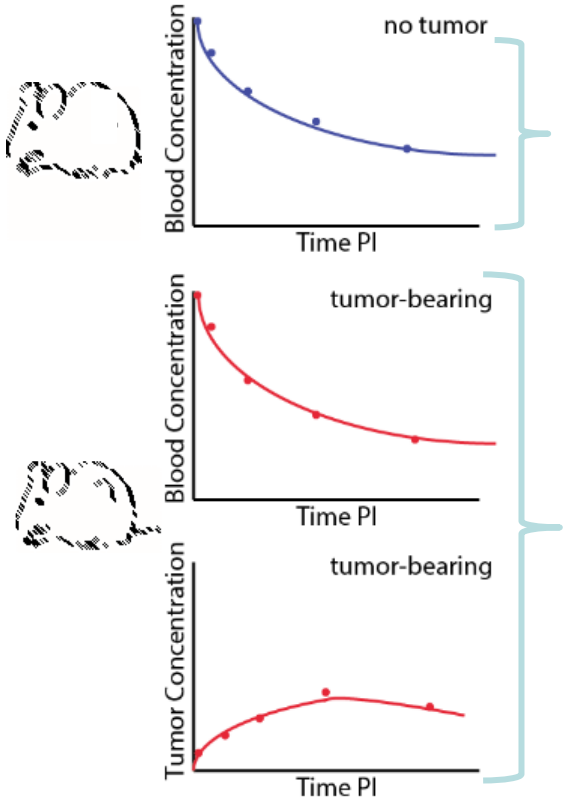
Pharmacokinetics/Tumor Accumulation:
Time points: 6, 24, 48 h PI
%ID, mg of drug
%ID/g

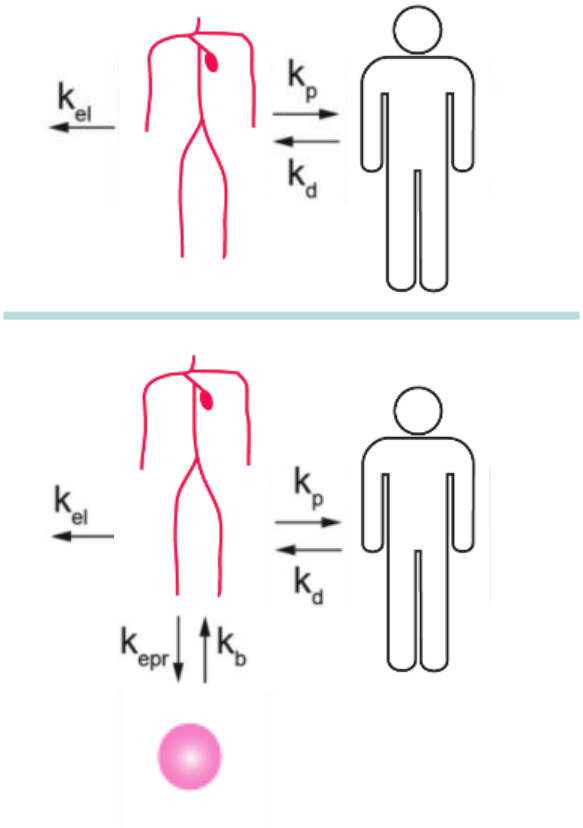
C.M.Dawidczyk*, ***L.M. Russell****, P.C. Searson, *Cancer Research* (2015)

Novel Tool: *In vivo* standardized experiment, tumor accumulation kinetics



Information we can *use*: Analytical Model





Mass Balance Equations

$$\frac{dN_{bl}}{dt} = k_d N_p - k_p N_{bl} - k_{el} N_{bl} + k_b N_t - k_{epr} N_{bl}$$

$$\frac{dN_p}{dt} = k_p N_{bl} - k_d N_p$$

$$\frac{dN_t}{dt} = k_{epr} N_{bl} - k_b N_t$$

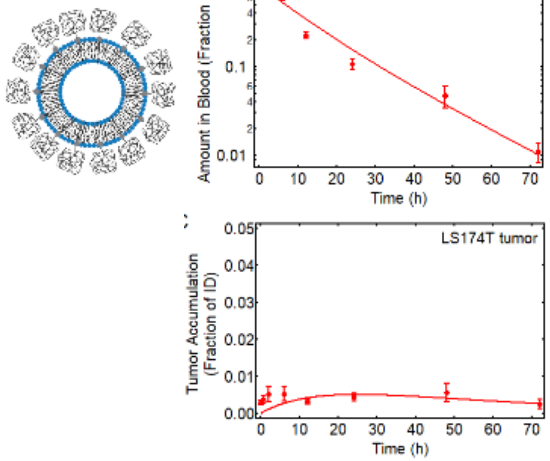
$$\frac{d(N_{bl} + N_p + N_t)}{dt} = -k_{el} N_{bl}$$

Tumor-free	LS174T Tumor-bearing
k_p	
k_d	
	k_{el}
	k_{epr}
	k_b

Dawidczyk et al, *Nanomedicine: NBM* (2017), Wong et al., *PLoS One* (2015)

A (very) small-scale nanoinformatics approach

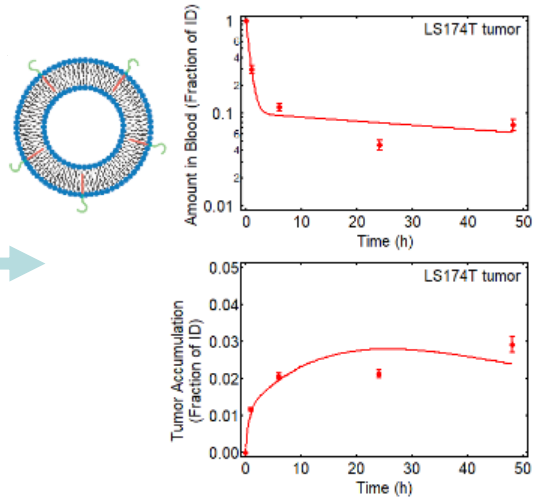
Data → Data Collection/ Analytics → Outcomes



PEGylated liposome

Parameter	PEG
A	0.072
B	0.078
Alpha	5.6
Beta	0.05
k_p	2.62
k_d	2.94
k_{epr}	0.0011
k_b	0.022
k_{el}	0.124

Rate constants in h^{-1}

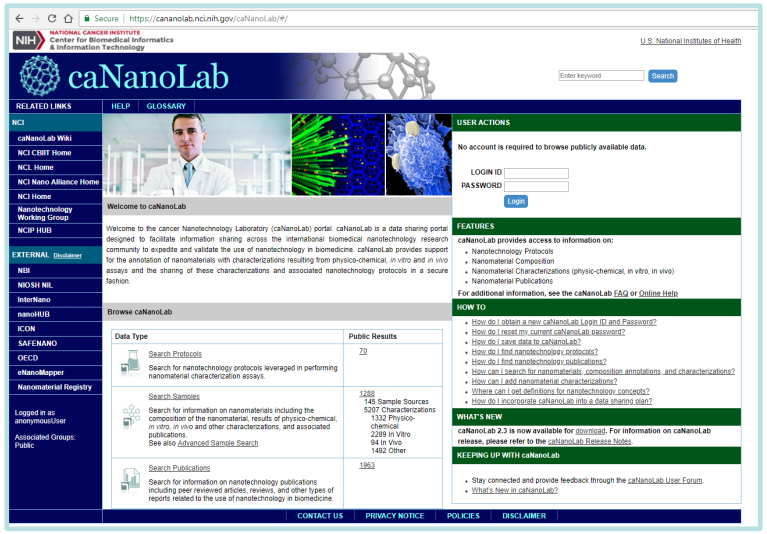


Newly Developed:
CD47*-functionalized liposome

Current Focus: caNanoLab

caNanoLab Goal

To provide a nanotechnology resource that facilitates data sharing in the community to expedite and validate the use of nanomaterials in biomedicine



Philippa Barnes
Developmental Technical Project Manager

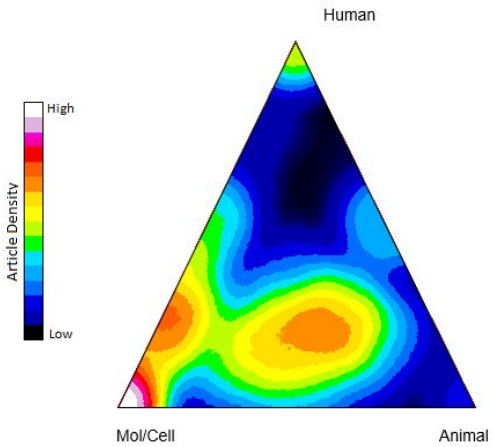
Michal Lijowski, PhD
Curator

Mervi Heiskanen, PhD
CBIIT Team Lead

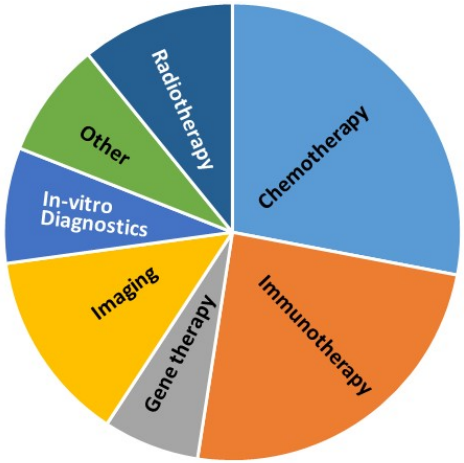
Luisa Russell, PhD
NSDB Team Lead

Current Focus: Alliance for Nanotechnology in Cancer

NCI Alliance for Nanotechnology in Cancer



Translatability



Shifting Focus in the field

Piotr Grodzinski, PhD
Branch Chief

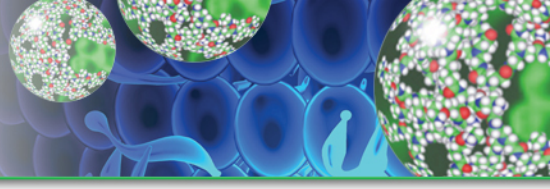
Christina Liu, PhD, PE
Program Director

Chris Hartshorn, PhD
Program Director

Luisa Russell, PhD
CRTA Fellow

http://www.cancer.gov/sites/nano

My Focuses Looking Forward

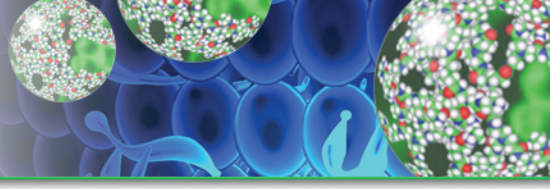


- Keep focus on concerted efforts in nanoinformatics across fields, with emphasis on *nanomedicine* and *nanomaterial development through informatics*
  - *Emphasis on cancer relevance*

- Bring together efforts in nanoinformatics to advance them all
  - Catalogue of existing databases and tools
  - Continued development and expansion of the NPO and ISA-TAB Nano
  - Develop realistic requirements for data and metadata collection
  - Enable global collaborations across databases and tools

- Bring together nano fields – Nanomedicine and nanotoxicology
  - Much to learn from each other, not just from a informatics perspective
  - Acknowledge individual needs of each field while finding a fundamental base

Questions?



Thanks everybody!