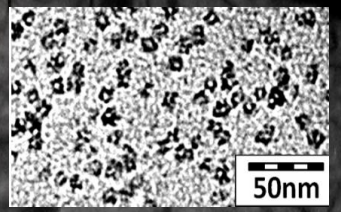
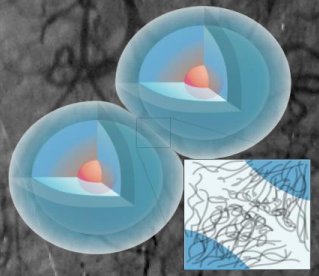
MC^{2}TCN
MSKCC-Cornell Center for Translation of Cancer Nanomedicines

Spotlight on Nanotechnology in the Biomedical Sciences



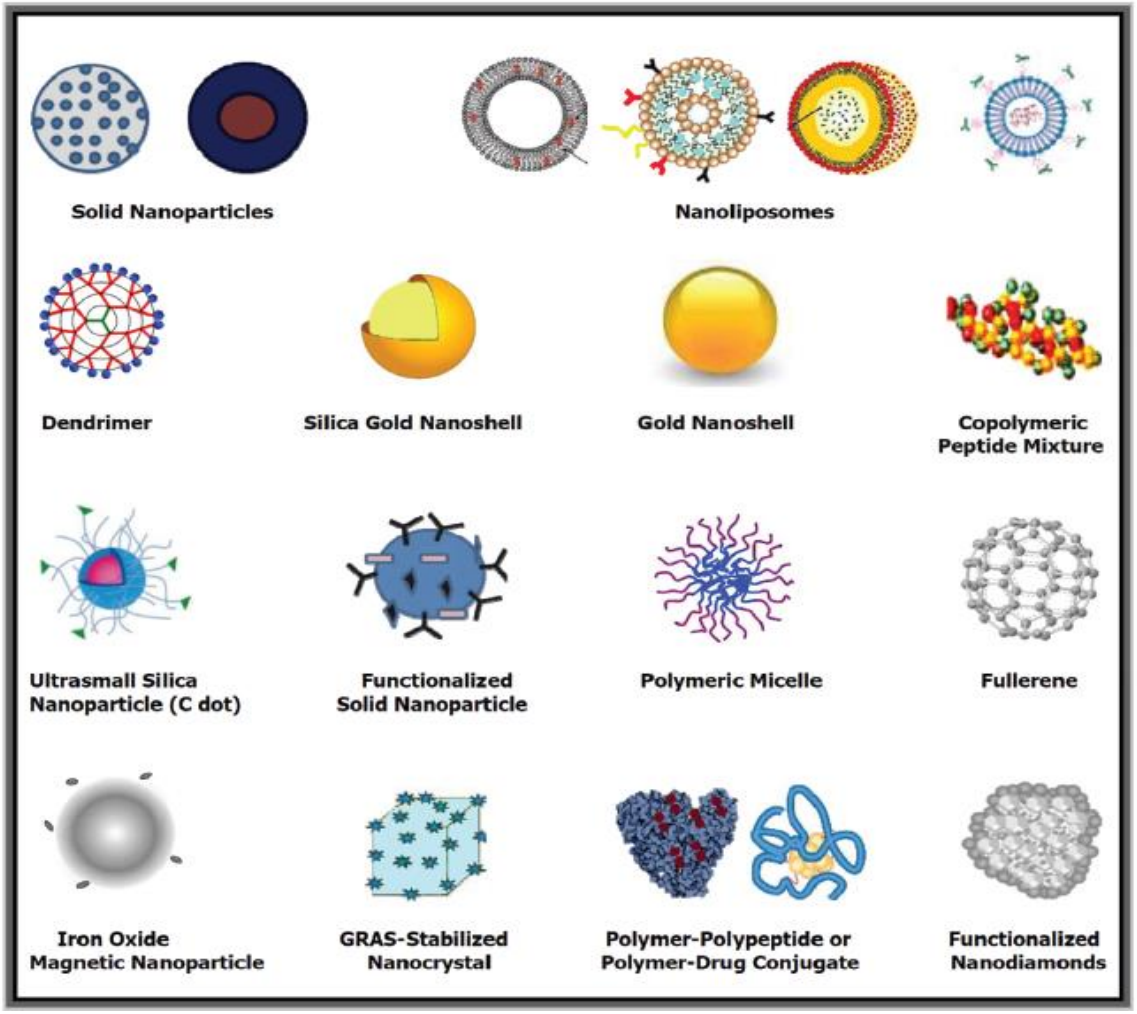
Michelle Bradbury MD, PhD

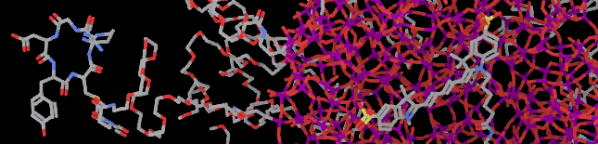
Director, Intraoperative Imaging
Department of Radiology
Molecular Pharmacology Program
Memorial Sloan Kettering Cancer Center &
Sloan Kettering Institute
New York, NY



NNI Bethesda, MD
May 19, 2016

Engineered Nanoprobes for Treating Disease





Overview

Paucity of targeted particle probes in the clinic

Paucity of particle-driven imaging tools

Translational Challenges

Probe Choice– nature of the application, biological questions of interest

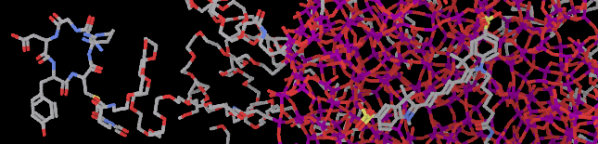
Ultrasmall dual-modality (NIR optical/PET) silica particle (C dots) –

- First ultrasmall targeted imaging platform of its class & properties
- Sub 10-nm size → facilitates renal excretion
- Successfully transitioned to clinic as dual-modality (PET-optical) platform
- Encapsulated dye
- Modular; can decorate surface with a variety of targeting ligands

Clinical Trials: First-in-Human/ Phase 1 Trials (INDs #110375, #121544)

Translational Applications Informed by Clinical Trial Developments

- Image-Guided Surgery Using Novel Optically-driven Ultrasmall Silica Particles
- Novel Ultrasmall Targeted Particle Therapeutics
- Biomarkers



MSKCC-Cornell Center for Translation of Cancer Nanomedicines

Michelle Bradbury MD, PhD
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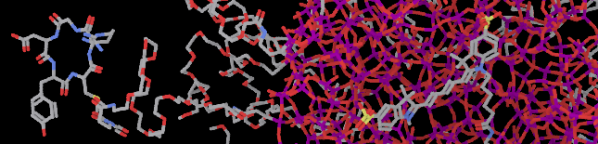
Materials Science and Engineering
Cornell University
Ithaca, NY



Common Overarching Problems Addressed in Oncology

Unmet needs:

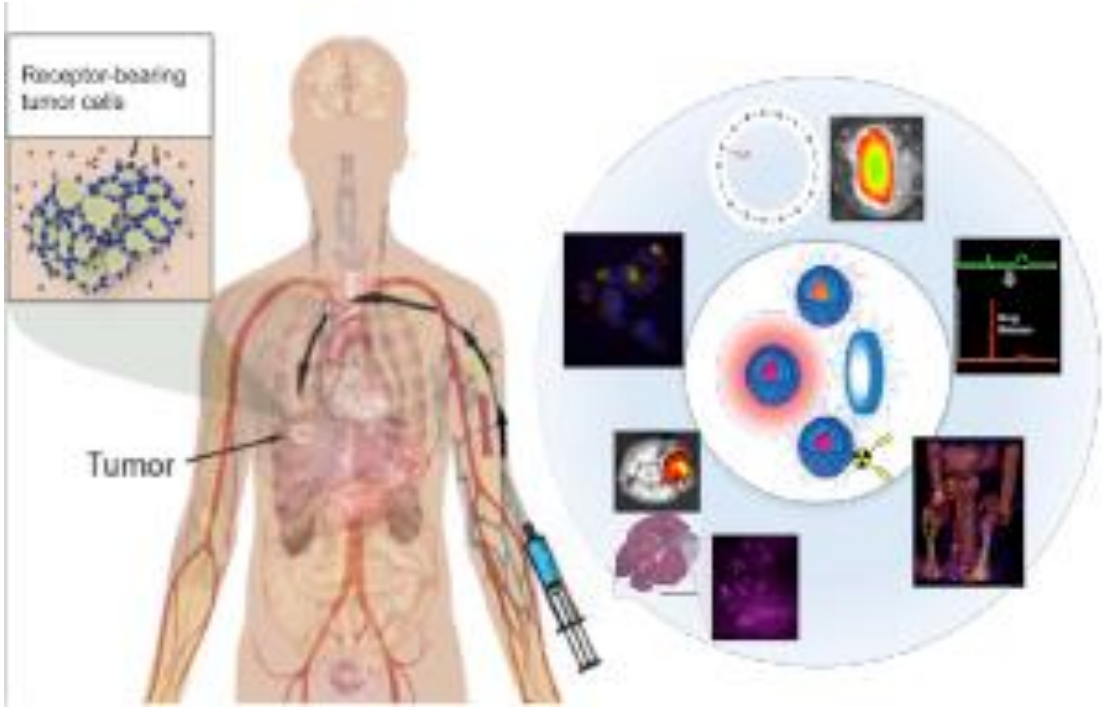
- Exquisitely bright optical visualization tools in the operating room to maximize contrast and detection sensitivity
- *Intraoperative* platforms for image-guided targeted treatment of metastases
- Cancer-directed particle therapies that potentially overcome unfavorable biological properties and dose-limiting toxicity

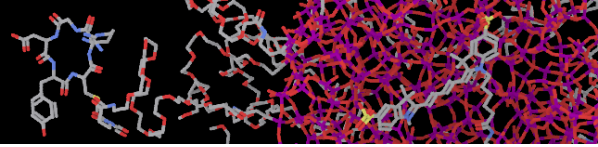
Advancing such novel platforms may:

- Enable tumor phenotyping, staging, and delineation of tumor versus normal tissue (i.e., nerves), which could change surgery-on-the-fly.
- Lead to pre-/intra-/post-operative paradigm shifts with single platform
- Maximize functional outcomes
- Enhance therapeutic efficacy to improve outcome measures

Long-Term Goal

Advance, translate, & disseminate a suite of ultrasmall (<10 nm) **silica organic hybrid nanoparticles (C dots)** with tunable size, brightness, and geometry whose favorable physicochemical, imaging, and biological properties may dramatically impact the way we diagnose & treat **melanoma** and **brain** tumors.





Nanomaterials as Enabling Technologies:
Linking with Larger-scale Clinical Initiatives in Oncology

"Five Reasons Why the Future Looks Bright for Humans and Bleak for Cancer"

Precision Medicine – vision that all people have access to customized care

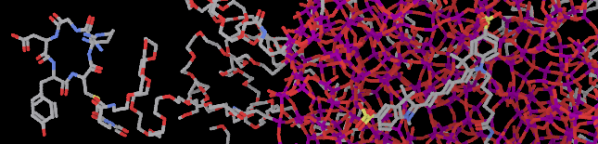
Use of particle imaging technologies that specifically coordinate imaging with therapeutic features of individual drugs to tailor cancer care

- Targeted therapy (target and reverse specific gene mutations)
- Radiogenomics (focuses on the correlation between cancer imaging features and gene expression)
- Imaging biomarkers of treatment response, staging

Immunotherapy – stimulate / mobilize the immune system to fight cancer

- Checkpoint inhibitors
- Vaccines
- Cytokines (interferons, interleukins)

Joan Massagué, Director of the Sloan Kettering Institute, MSKCC, 2016



Nanomaterials as Enabling Technologies:
Linking with Larger-scale Clinical Initiatives in Oncology

"Five Reasons Why the Future Looks Bright for Humans and Bleak for Cancer"

Cell-Based Therapy (used in combination with particle-based treatments)

- Adoptive immunotherapy with patient's tumor-targeted T cells
- Exploit T cells as delivery vehicles of therapeutic particle probes

Metastasis

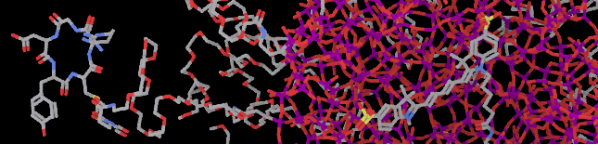
- Identification of genes and pathways driving the spread of certain types of cancer to various organs

•Engineering particles to interact with the genome and signaling pathway intermediates (i.e., engineered viral particles for delivery of proteins, genome editing)

Link with Epigenetic Therapies

- Drugs targeting epigenetic enzymes regulating the cells genetic programming.

Joan Massagué, Director of the Sloan Kettering Institute, MSKCC, 2016



Translational Roadmap for Nanoparticle Imaging Platforms

Current and Future Directions for Cancer Detection & Treatment

Design, Synthesis Characterization

- Size, charge
- Surface chemistry
- Brightness
- Concentration
- Particle radiolabeling

Pre-Clinical Screens

- Particle binding
- Cellular internalization
- Inhibitory Profiles
- Toxicity testing
- Lysosome fn, Signaling
- Molecular Profiling

Pre-Clinical (Animal studies)

- Tumor model screen (transgenic, orthotopic)
- PK/Biodistribution
- Imaging/Targeting
- Plasma, Urine sampling Histology

GMP (formulation

Preclinical studies (regulatory)

CMC Pharm/Tox

Clinical Imaging

Pilot clinical trial 'Safety/PK' study

Phase 1 Image-Directed Surgery/Interventions

- SLN Mapping
- Residual Tumor (post-op)
- Nerve, Tissue-Sparing Proc.
- Clinical Multiplexing

Intraoperative NIR Fluorescence Camera Developments

-Open, -Laparoscopic

Clinical Imaging

Advanced Phase Trials

Commercial Dev. New Venture

Therapeutics (Systemic/Local Administration)

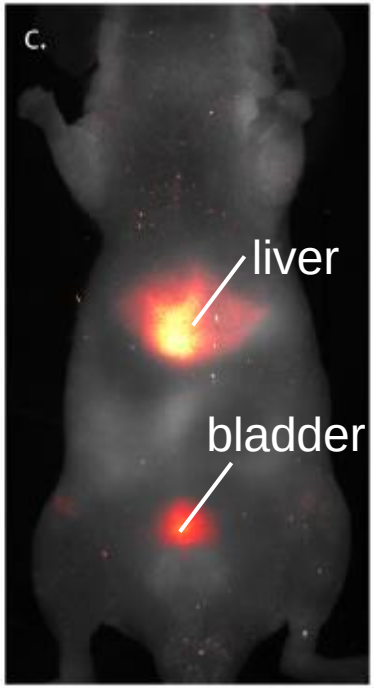
- Nanoparticle drug conjugates
- Radiotherapeutics

Pre-/Post-op PET, MRI

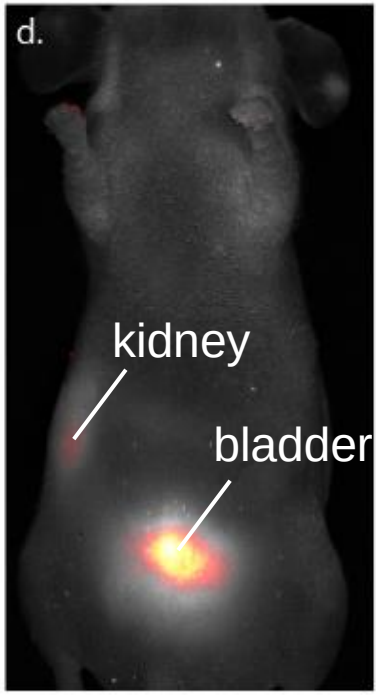
Particle Design Criteria: "Target or clear" via sizes < 10 nm

Efficient urinary excretion

> 10 nm



< 10 nm



Advantages of small size < 10 nm

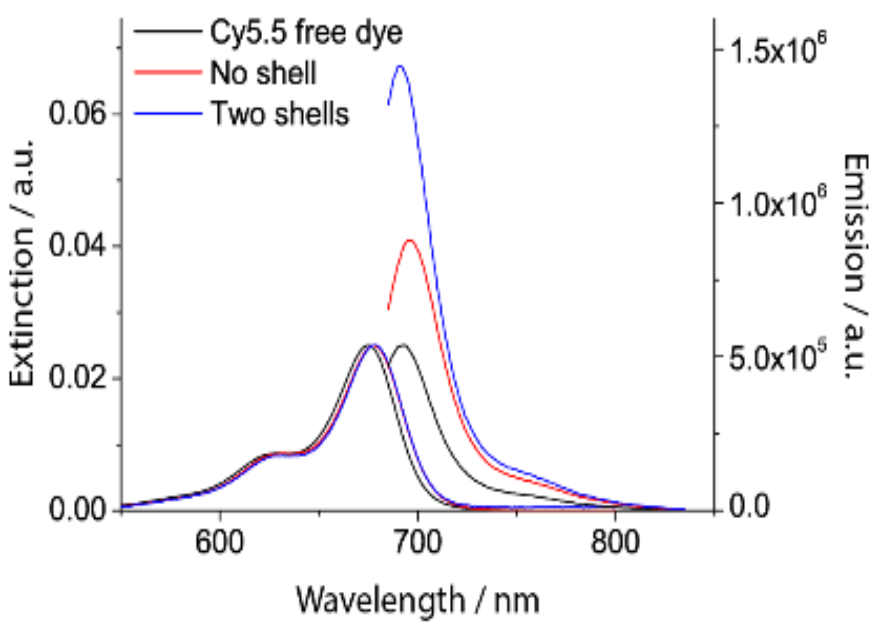
- Favorable biodistribution and PK
- Enables in-depth characterization
- Enhances particle diffusion
- Still enables multifunctionality

Essentially an unexplored size regime for nanoparticles

H. Ow, UW *et al.*, *Nano Letters* **5** (2005), 113
A. Burns, U.W., M. Bradbury *et al.*, Nano Letters **9** (2009), 442

Particle Design Criteria:
Exceptional brightness for high sensitivity detection

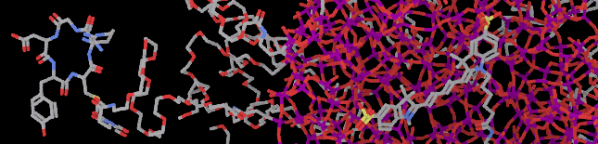
Encapsulated dye: 300% brighter than the native dye



K. Ma *et al.*, *Chem. Mater.* ***27*** (2015), 4119

Advantages of silica dye matrix

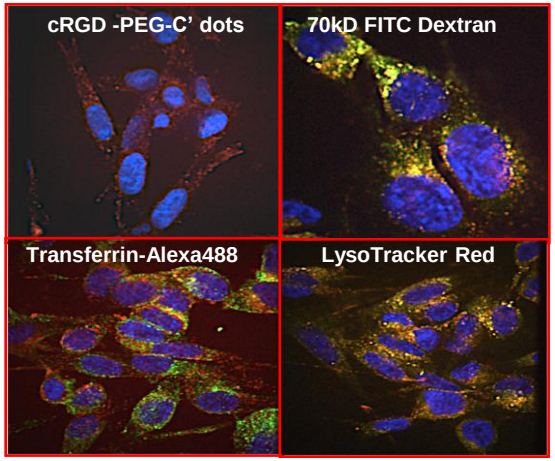
- Protects dye from environment
- Provides exceptional rigidity
- Can be further tuned
- Less than 10 nM per patient

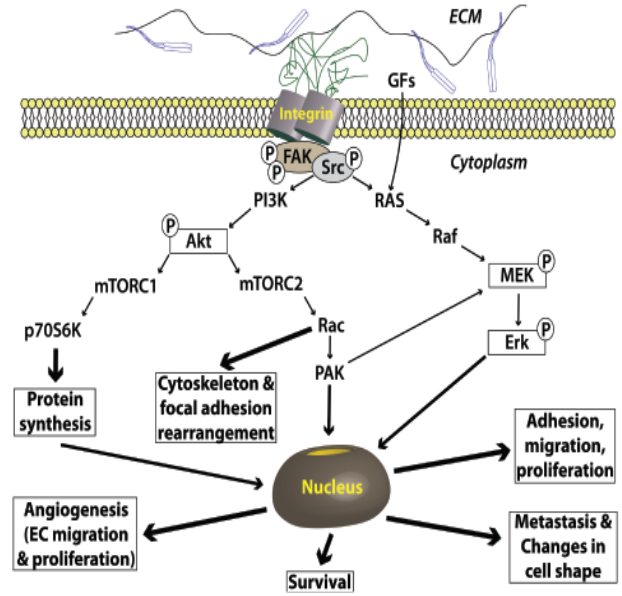


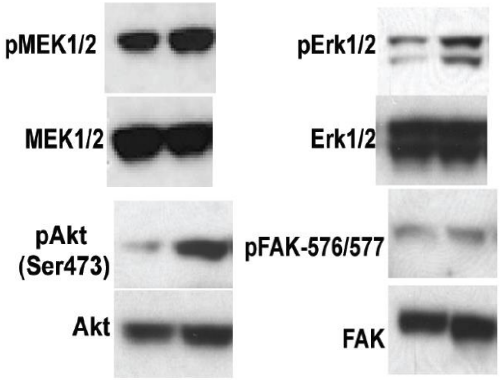
Biological Characterization of Targeting Moieties and Therapeutics

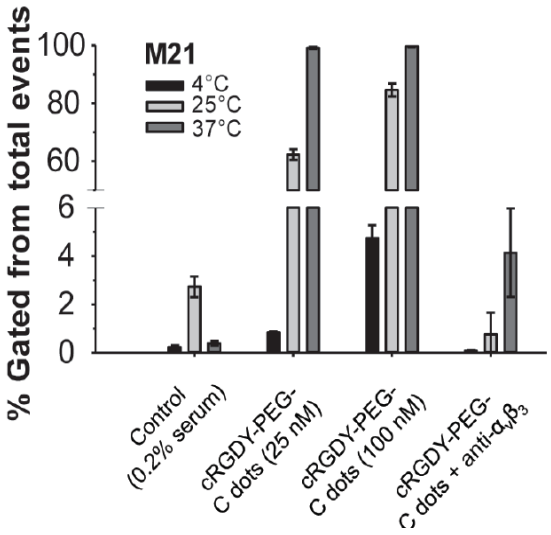
- Competitive binding assays
- Dose-response assessments
- Specificity
- Particle stability
- Internalization routes
- Assays for assessing cellular/molecular function
- Activation/inhibitory profiles
- Expression levels of signaling pathway intermediates
- survival/proliferation, adhesion, cell cycle, etc
- Biodistribution, PK
- In vivo targeted uptake, target-to-background ratios
- Dosimetry
- Toxicological profiles

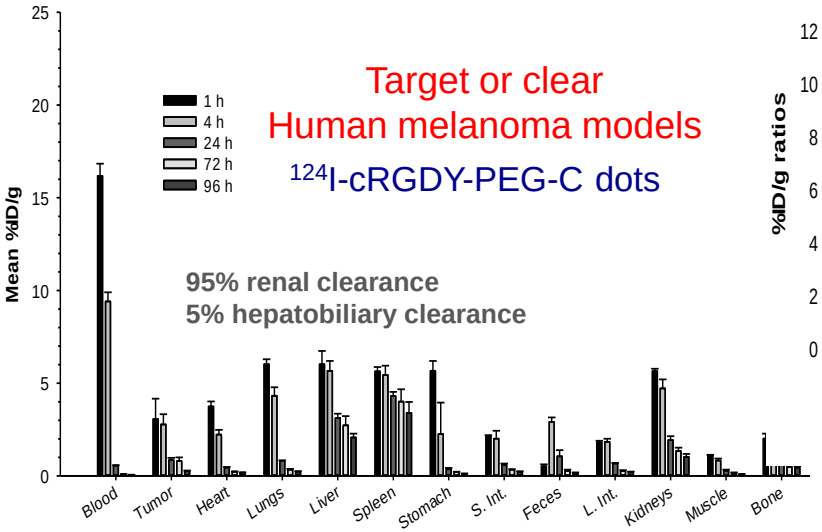
Integrin-targeted C' dot Modulation of Biological Properties







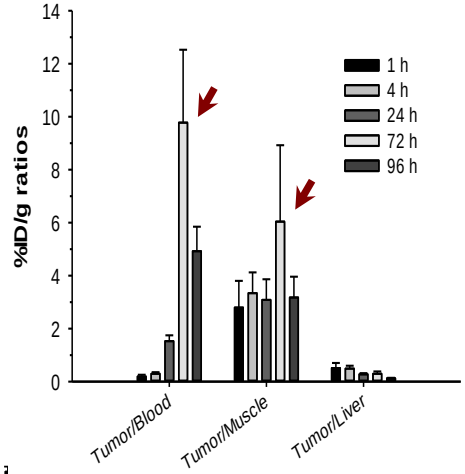


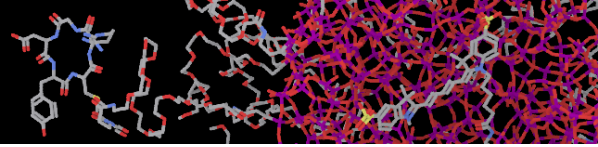


Target or clear
Human melanoma models
^{124}I-cRGDY-PEG-C dots

95% renal clearance
5% hepatobiliary clearance

Tumor-to-Background





FDA-Approved IND (#110375) First-in-Human Clinical Trial

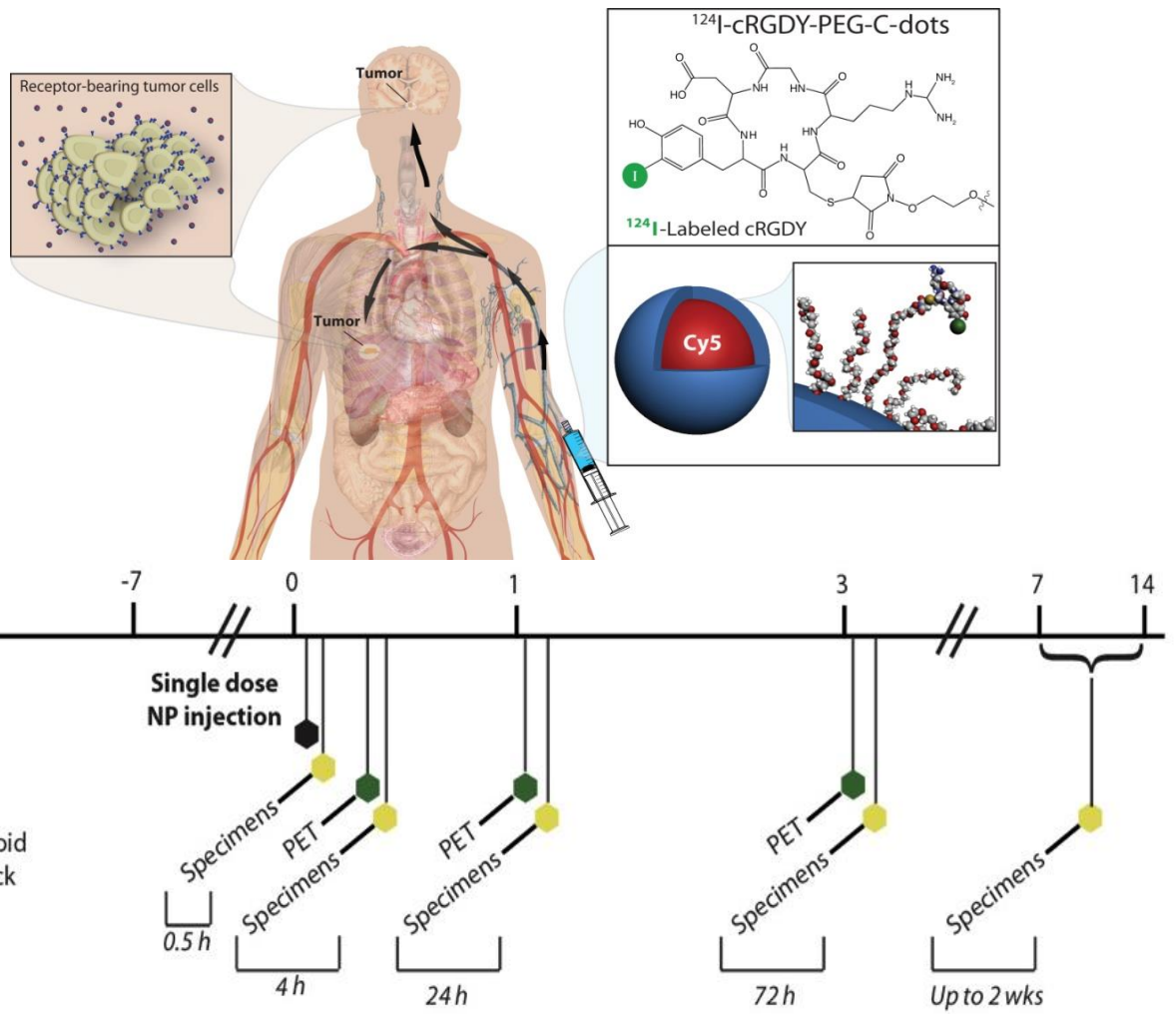
First inorganic particle of its class / properties to be cleared as a "drug" for clinical use

- Efficient renal clearance
- Favorable targeting kinetics
- Lack of toxicity over a 14 day recovery period
- Multimodal (PET-optical) – quantitation, cellular assessments
- Potential utility in a variety of integrin-expressing tumors

C dot particle tracer for first-in-human studies (microdosing) of metastatic melanoma

- Safety
- Biodistribution/Pharmacokinetics
- Dosimetry
- Metabolic profiles, chemistry, hematology
- Uptake in tumor, normal tissues

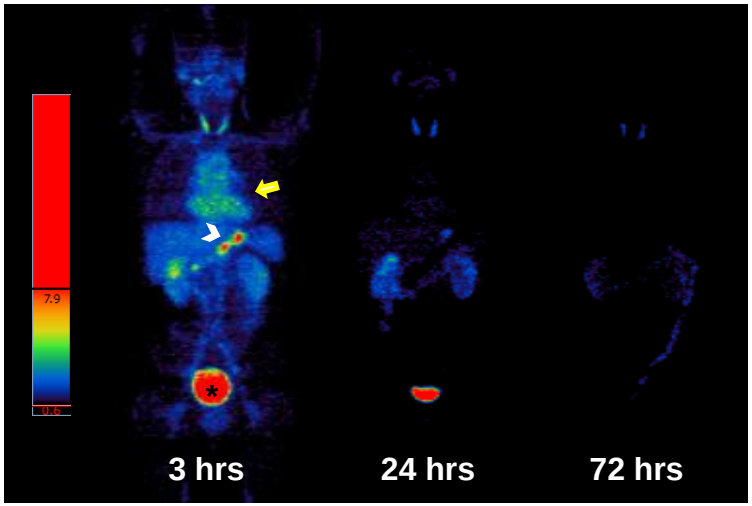
FDA-Approved IND (#110375) First-in-Human Clinical Trial Molecular Cancer Imaging



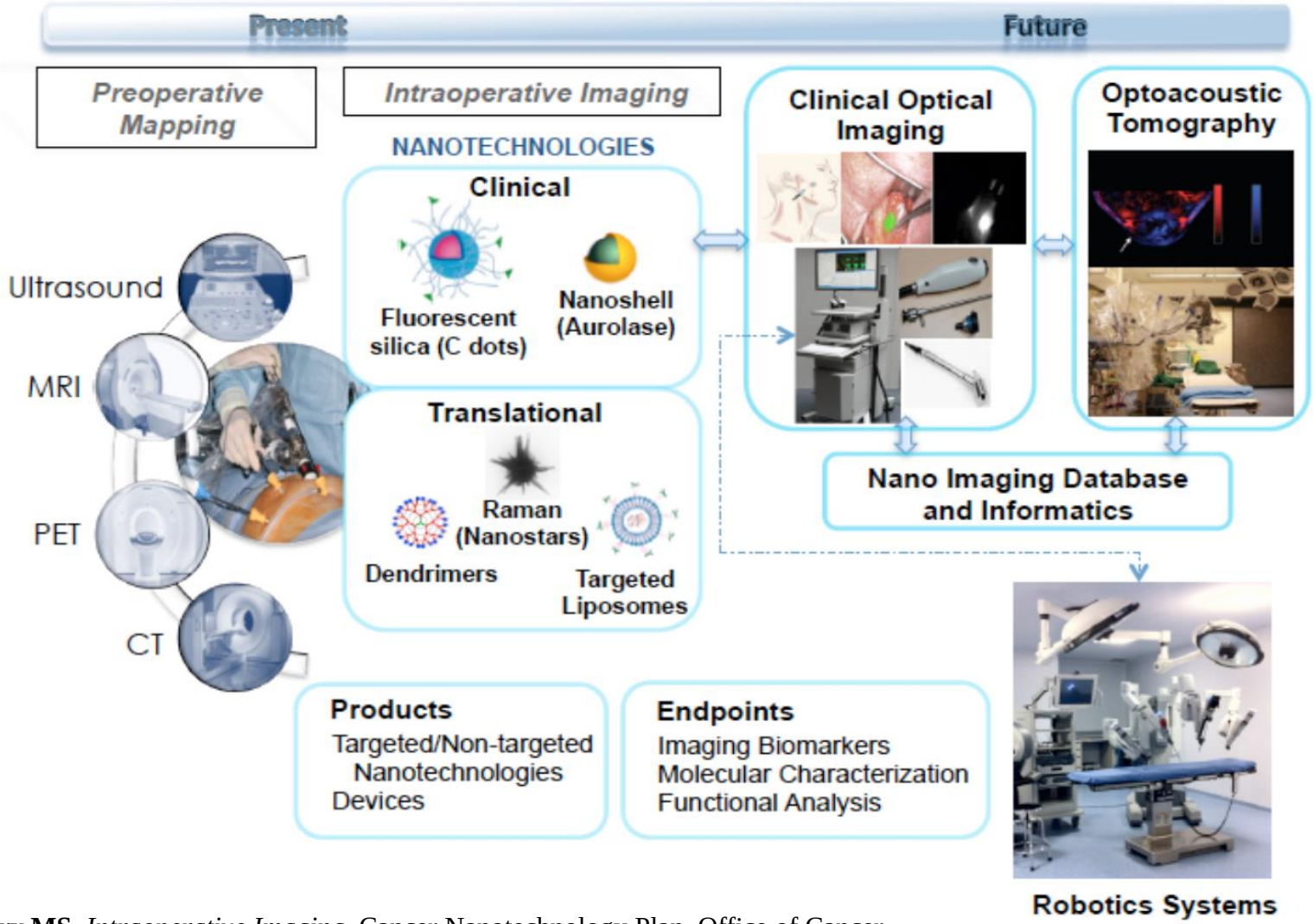
E. Phillips, P. Zanzonico, J. Humm, S. Larson, U. Wiesner, M. Bradbury *et al. Sci Trans Med 6, 260ra149 (2014)*

FDA-Approved IND (#110375) First-in-Human Clinical Trials

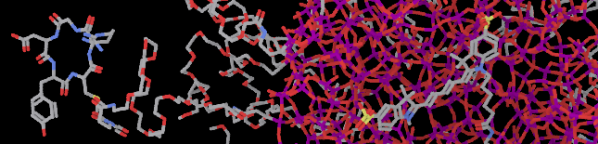
Biodistribution of ^{124}I-cRGDY-PEG-C dots in Metastatic Melanoma Patients



Present and Future of NanoOncology Image-Guided Surgical Suite



Bradbury MS. *Intraoperative Imaging*. Cancer Nanotechnology Plan. Office of Cancer Nanotechnology Research, Center for Strategic Scientific Initiatives, NCI/NIH, 36-42, 2015



Limitations and Solutions

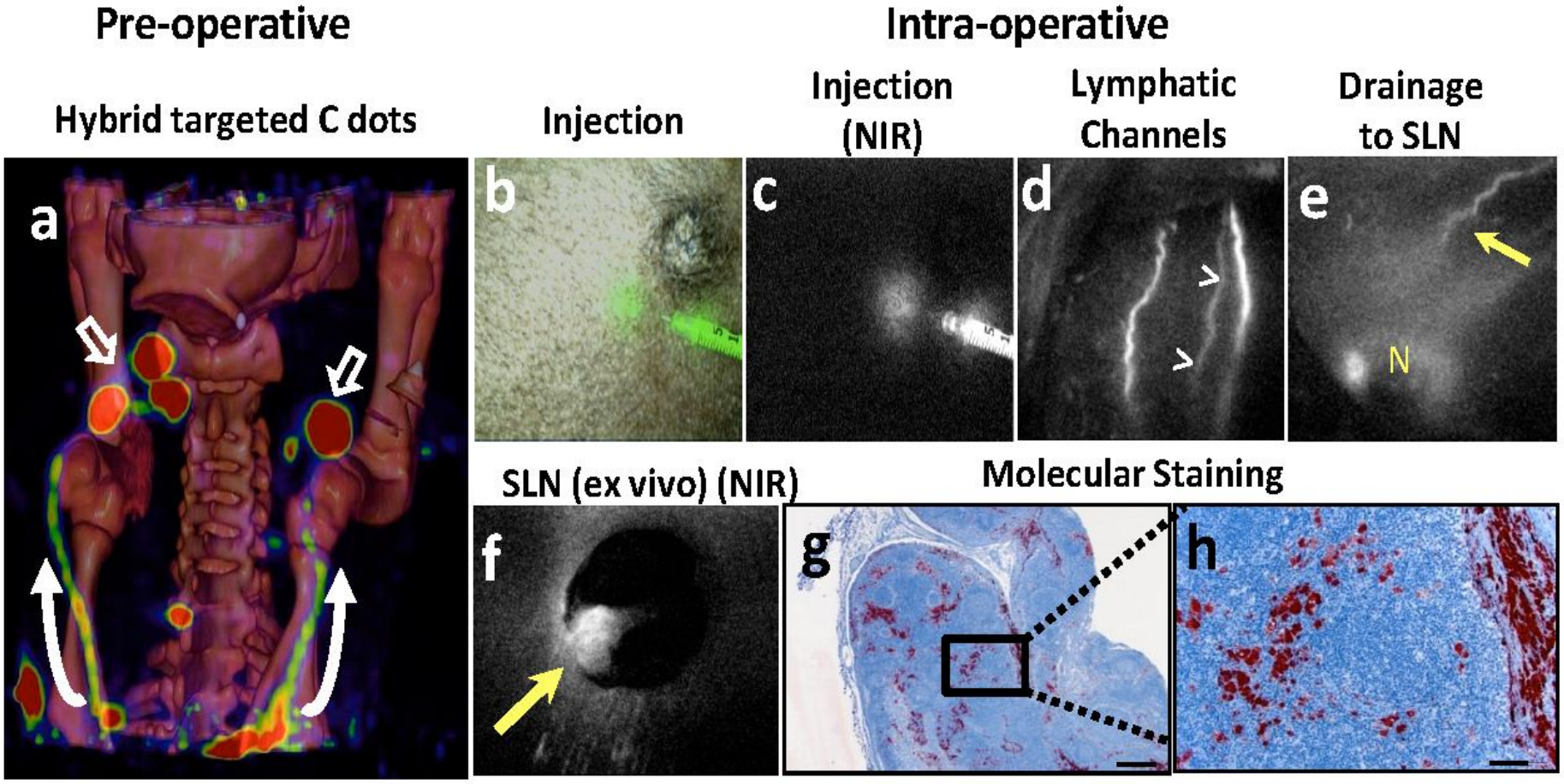
Intraoperative optical imaging approaches have been hampered by:

- small number of imaging agents available in the NIR spectrum
- high background autofluorescence - restricts depth, contrast, sensitivity
- large spectral overlap between optical agents may prevent concurrent detection of multiple targets (i.e., multiplexing)
- rapid photobleaching that reduces imaging duration

Solution*:* Emergence of new, diverse, and clinically promising NIR fluorescence probes, including particle-based agents

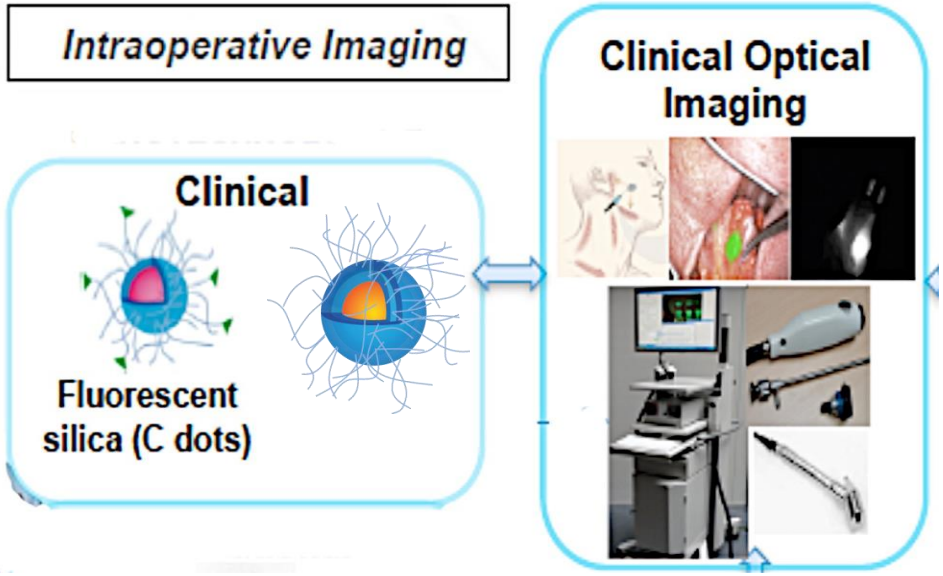
- Enhance soft tissue contrast, detection sensitivity, and depth penetration
- Enable specific detection and direct visualization of disease
- Improve staging and facilitate surgical management
- Maximize functional outcomes, reduce surgical risks

Volume-rendered pre-operative PET imaging of metastatic nodal disease

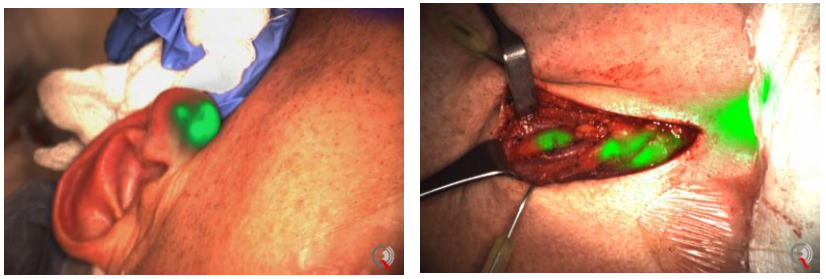


Bradbury MS, Phillips E, Meester R, Wiesner U, Patel S. *et al., Integr Biol 5: 74 – 86, 2013*
Bradbury MS, Pauliah M, P. Zanzonico, Wiesner U, and Patel S. Intraoperative mapping of SLN metastases using a clinically translated ultrasmall silica nanoparticles. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*., 2015 (in press)

Ongoing Phase 1 Clinical Trials (INDs #110375, #121544) in Metastatic Melanoma and Malignant Brain Tumors



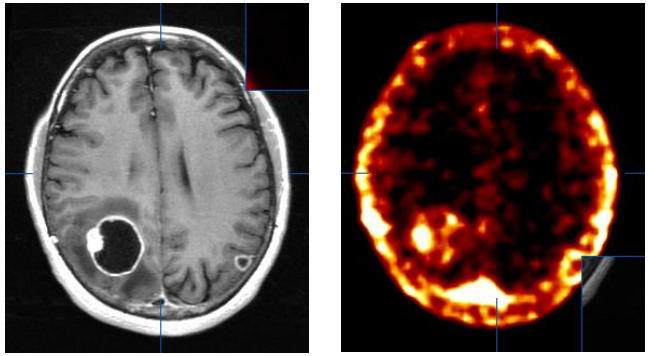
Real-time Intraoperative Optical Imaging of SLN Metastases



https://clinicaltrials.gov/ct2/show/NCT02106598

Melanoma, Breast, GYN malignancies

Pre-operative MRI-PET Imaging of a Brain Metastasis - ^{124}I-cRGDY-PEG-C dots

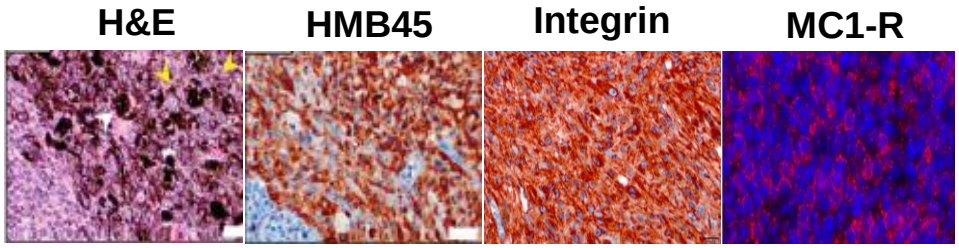


https://clinicaltrials.gov/ct2/show/NCT01266096

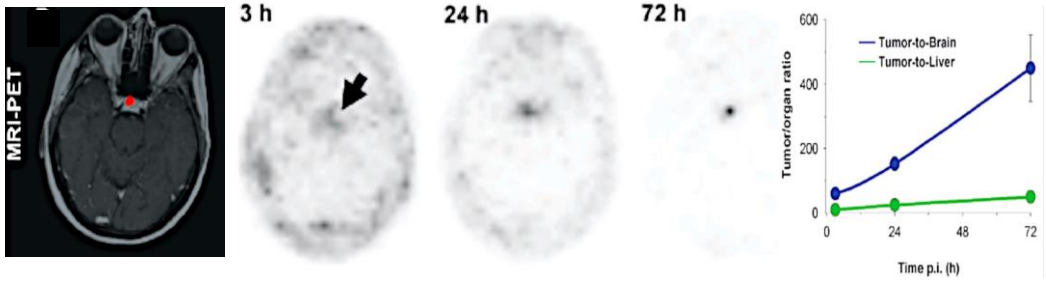
Melanoma, Malignant Brain Tumors

Precision Medicine

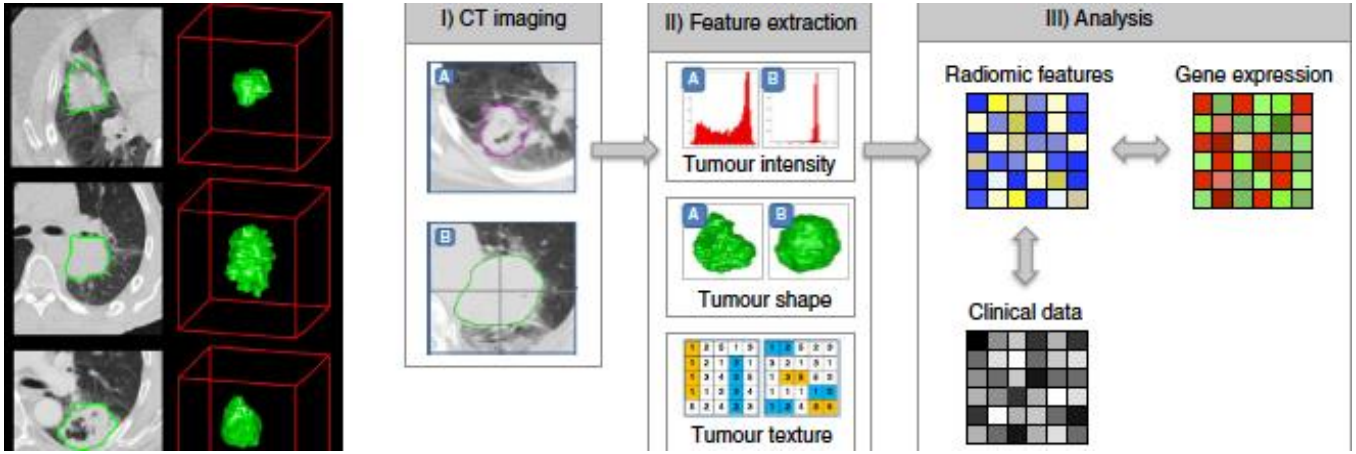
Biomarker Screening

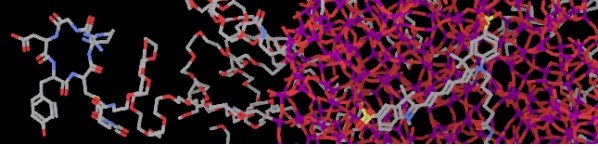


Targeted C' dot Tracers for Therapeutic Management



Particle-driven Radiogenomics





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U. Wiesner (Cornell-Ithaca)

Collaborators

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Core Facilities, MSKCC

Investigational Products Core Facility
Antitumor Assessment
Cyclotron-Radiochemistry
Molecular Cytology
Small Animal Imaging
Research Engineering
Pathology

SKI-MSKCC Assistant Lab Members/ Sr Scientists/Research Fellows

M. Benezra, B. Yoo, P. Mohan, F. Chen, S. Cheal, S. Carlin, P. Montero, L. Zhang, D. Karassawa, N. Chen

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The Netherlands

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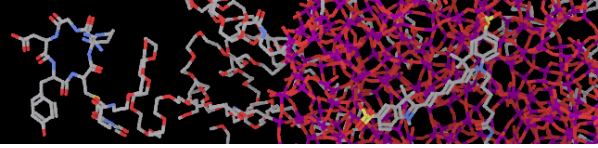
Cornell Nanobiotechnology Center
NSF, STC Program



Questions for the Panel

- Are there any obvious gaps in the draft goals and objectives (attached)? Are there any objectives that are no longer among the top priorities that need to be addressed?
- What will be the new/hot areas of research or challenges in the next 5-10 years?
- Outside of additional funding, what can the Federal Government do to support activities or address challenges in the areas above?
- How will we know when the nanotechnology enterprise is successful in this area? How do we measure this?

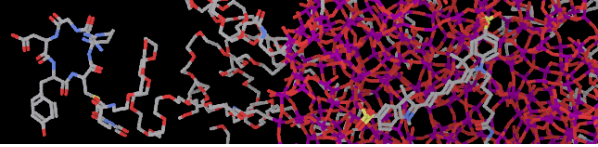
Panel Members

Zhen Gu, Associate Professor / NC State Univ & UNC Chapel Hill

- Ph.D., UCLA
- Postdoctoral Associate (Langer Lab): MIT / Harvard Medical School
- Recipient of several awards: Sloan Research Fellowship (2016), Pathway Award of the American Diabetes Association (2015), Young Innovator of Cellular and Molecular Bioengineering of BMES (2015)
- Expertise – Polymer Science & Engineering, Biomedical Engineering
- Top innovators under 35 (TR35), MIT Technology Review, 2015

Katia Karalis, Professor, Pediatrics / Emulate, Inc

- M.D., Athens University Medical School; Cedars-Sinai Medical Center, UCLA
- National Institutes of Health, postdoctoral fellow, Endocrinology
- Children's Hospital, Harvard University, postdoctoral fellow in Pediatrics and Medicine at the Division of Endocrinology.
- **Expertise**: Physiology and pathophysiology, the biology of the stress response in mammals and the crosstalk between the endocrine, the nervous and the immune system in the development and progress of the inflammatory response.



NNI R&D Centers & Networks to Support Multidisciplinary Activities & Address Challenges

NNI Research and Development (R&D) Centers and Networks

http://www.nano.gov/centers-networks
http://www.nano.gov/userfacilities
http://www.cleanroom.byu.edu/Links_university.phtml (nanofabrication facilities)

Department of Defense

Center for Nanoscience Innovation for Defense (U. CA, Riverside) Institute for Nanoscience (NRL)

Institute for Soldier Nanotechnologies (MIT)

National Institutes of Health

Nanotechnology Characterization Laboratory (NCL)

NCI Centers of Nanotechnology Excellence (CCNE)

NCI Cancer Nanotechnology Training Centers

National Institute for Occupational Safety

National Institute of Standards and Technology (NIST)

National Science Foundation with the EPA

supports a number of major nanotechnology user facilities