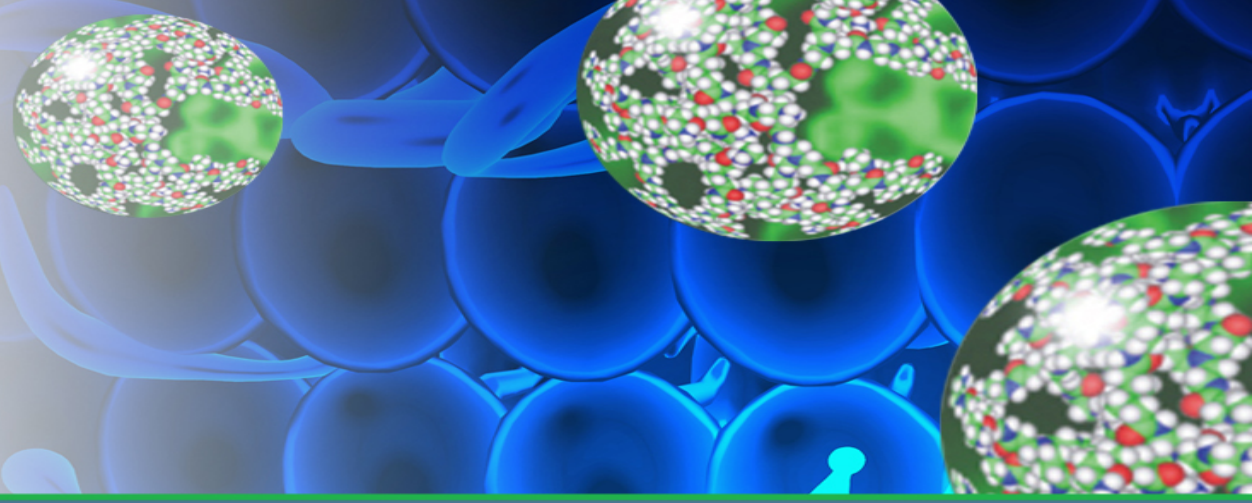
National Cancer Institute

NCI Alliance for Nanotechnology in Cancer



Towards Translation of Cancer Nanotechnology Interventions (Clinical Trial not Allowed) R01 PAR

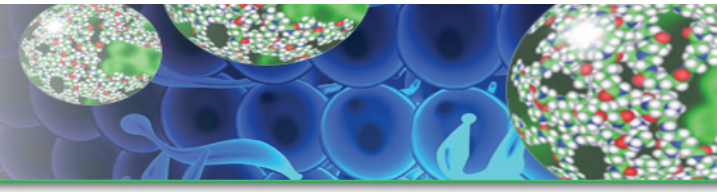
Piotr Grodzinski, Ph.D.

BSA meeting, December 3, 2019

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

Purpose of Proposed PAR

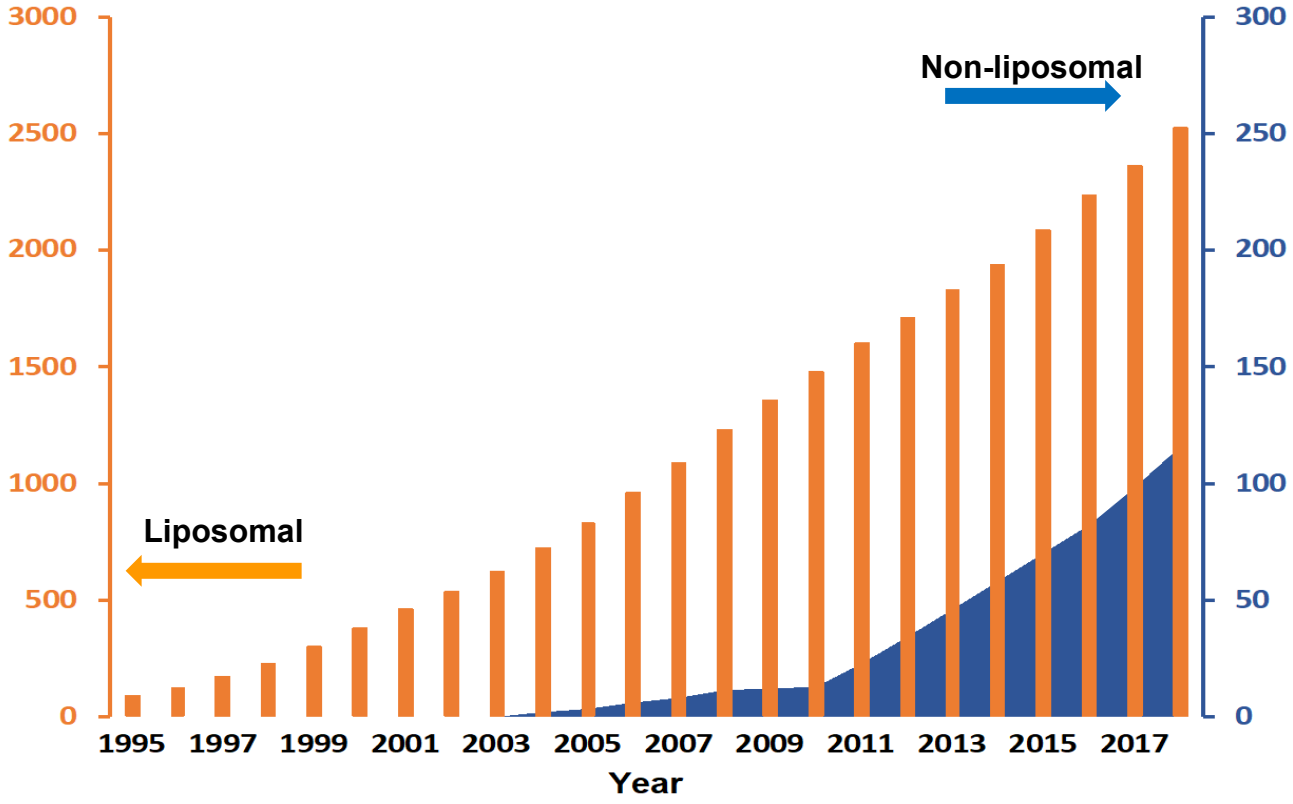
How does it Fit into Overall Nanomedicine Landscape?



- This Funding Opportunity Announcement (FOA) will support pre-clinical research on maturing nanomedicine formulations involving next generation nanoparticles with a strong clinical potential;
- Nanotechnology-based formulations require unique optimization process involving testing several nanoparticle and API combinations;
- FOA will prepare these nanomedicines for a successful entry to NExT program and other DCTD translational efforts;
- Interest in nanotechnology has been growing - over 700 R01 applications and 49 funded in 2018;
- Grant applications to this FOA will be best reviewed by Special Emphasis Panel (SEP) rather than standing study section. We already discussed this SEP review with CSR;
- PAR announcement - fair competition of applications for overall RPG pool funds, while maintaining SEP review benefit.

Nanoparticle Clinical Trials

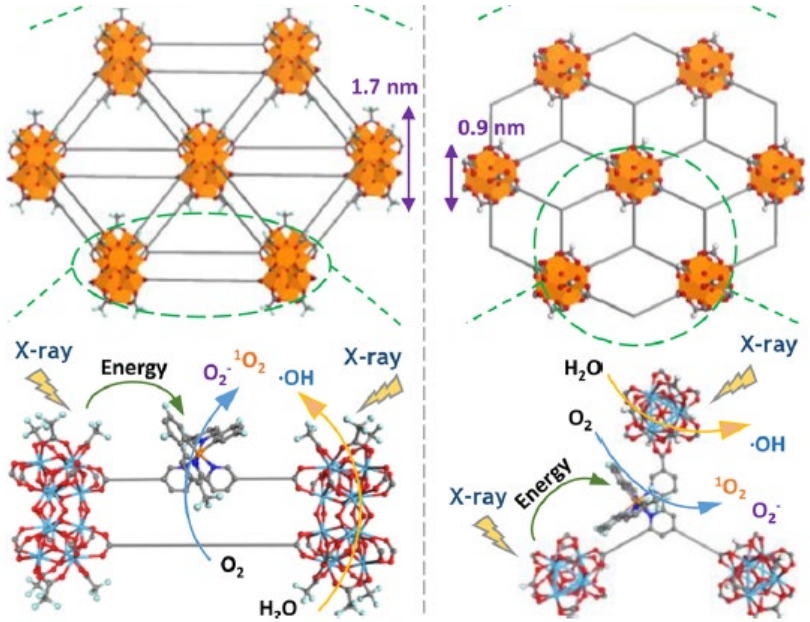
Cancer clinical trials conducted for liposomal and non-liposomal nanoparticles



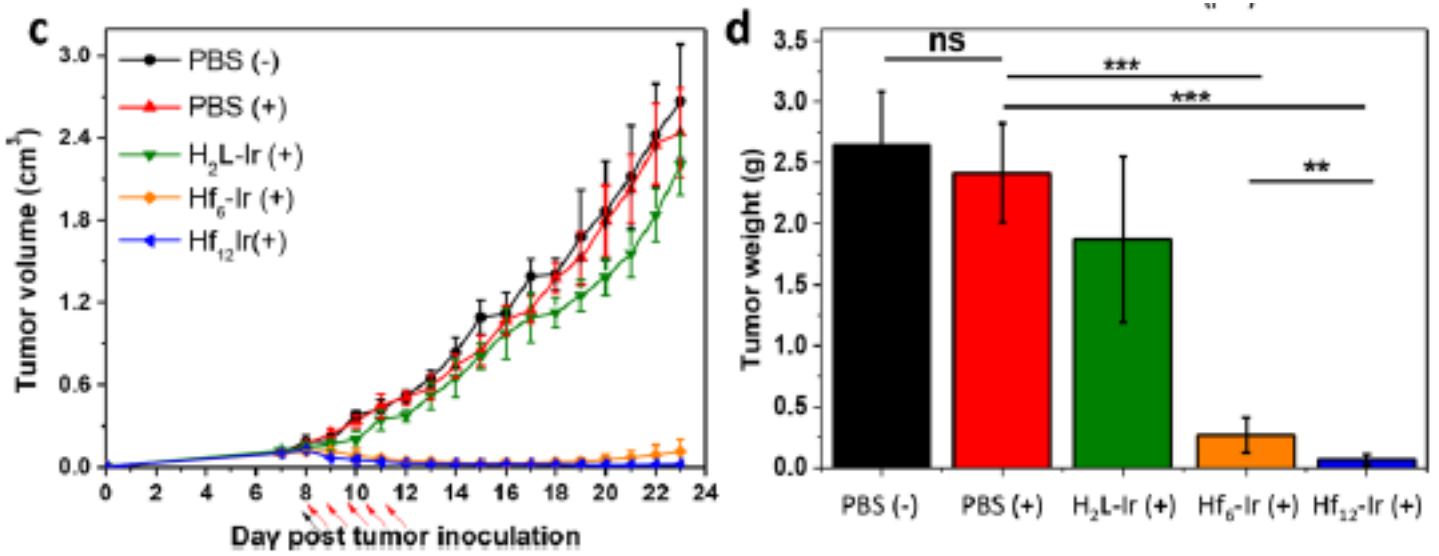
- Several nanomedicines have been approved by FDA to-date, but majority of them rely on liposomal delivery of known (previously FDA-approved) APIs;
- These nanomedicines resulted in significant reduction of side effects, but demonstrated only modest improvement in survival;
- Quest for new nanoparticle designs and delivery of wider range of therapeutic molecules is on-going.

The information was derived from clinicaltrials.gov based on the following keyword searches 'Cancer and – liposomal, Caelyx, Myocet, Lipodox, Onivyde, Depocyt, Daunoxome, Marquibo, Vyxeos, or Mepact' and for non-liposomal 'Cancer and nanoparticle or nanotechnology'.

Radiodynamic (RDT) Therapy Using Nanoscale Metal–organic Frameworks (nMOFs)



Lan G, Ni K, Veroneau SS, Song Y, Lin W. Nanoscale Metal-Organic Layers for Radiotherapy-Radiodynamic Therapy. J Am Chem Soc. 2018; 140:16971-16975.



- Nanoscale metal–organic layers (nMOLs) are based on Hf12 and Hf6 building units and photosensitizing Ir(bpy)[dF(CF3)ppy] ligands;
- Upon X-ray irradiation, the Hf12 or Hf6 building units efficiently absorb X-rays and produce hydroxyl radicals;
- Energy transfer from heavy metal building units to Ir ligands results in generation of singlet oxygen and superoxide anions;
- Low X-ray doses of <5 Gy are required.
- **Entered Phase I trial to treat advanced tumors (head and neck and prostate cancers).**

Intra-operative Imaging with Ultra-small C-dots

Pre-operative PET and real-time optical imaging for detection and dissection of nodal metastases in spontaneous melanoma miniswine model

Pre-surgery

PET-^{124}I-cRGDY-CW800-C'dot

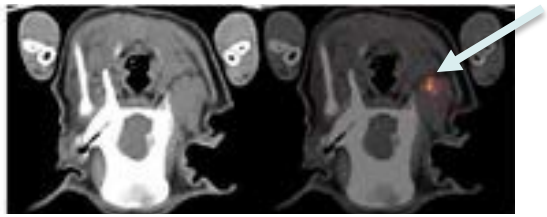
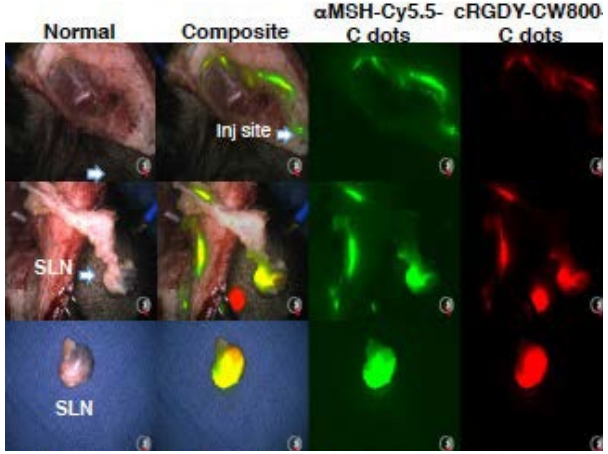
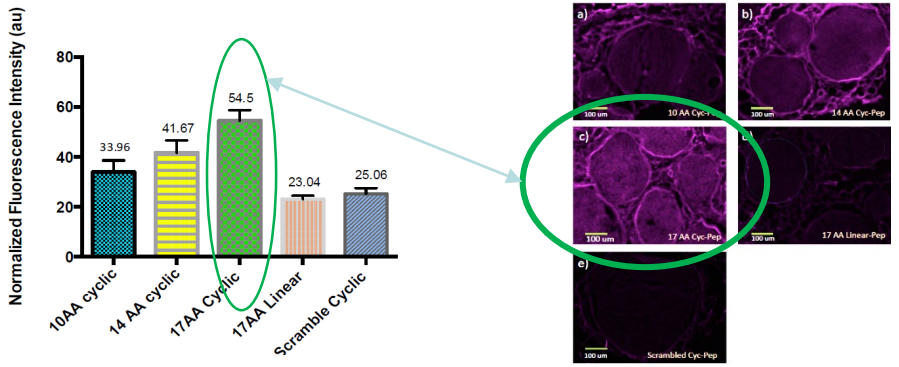


Image-guided surgery

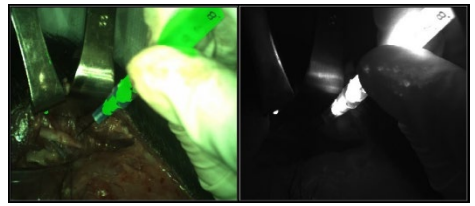


Identify peptide sequence with strong nerve binding/uptake and link to C dots for sciatic nerve visualization during surgery

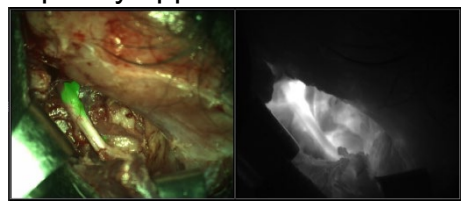


Miniswine Sciatic Nerve Binding Study

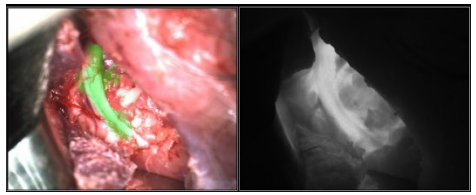
1 - Sciatic nerve exposure



2- 17AA cyclic pep-C dots topically applied



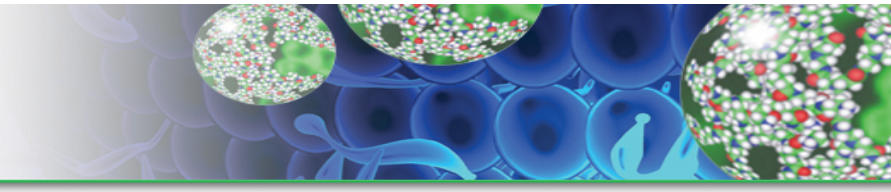
3- Sciatic nerve was dissected



Phase I and II clinical trials for guiding surgery of solid tumors (head and neck, melanoma, breast, cervical).

Bradbury MS, Pauliah M, Zanzonico P, Wiesner U, Patel S. Intraoperative mapping of sentinel lymph node metastases using a clinically translated ultrasmall silica nanoparticle. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2016; 8:535-53.

Path to Nanomedicine Translation



Where we Are → **Technology maturation** → **Translation**

- R01s and U01s @ technology demonstration
- Less mature U54s @ technology demonstration
- Mature U54s @ GMP and early clinical trials (via start-up companies)

→ **Proposed PAR**
'Towards Translation of Cancer Nanotechnology Interventions'

- Stabilizing nanomedicine synthesis
- *In vivo* testing in multiple animal models
- New cancer indications and drugs for mature particle concepts

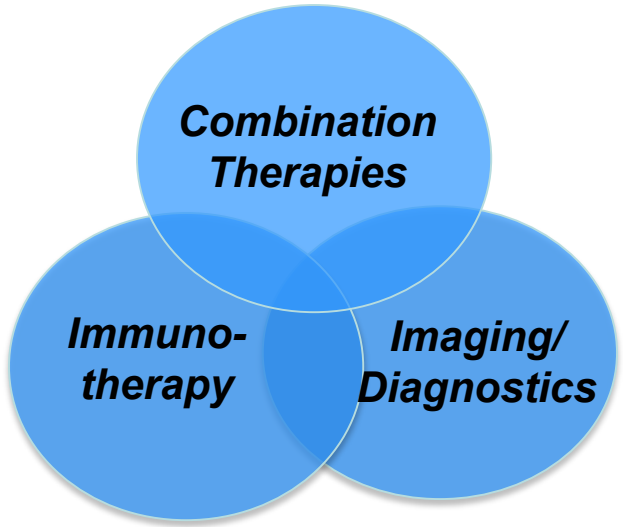
→ Future entry to NExT and ETCTN

U54 Centers of Nanotechnology Excellence will be discontinued in 2020

New PAR Proposal:
Towards Translation of Nanotechnology-based Cancer Interventions

Applications:

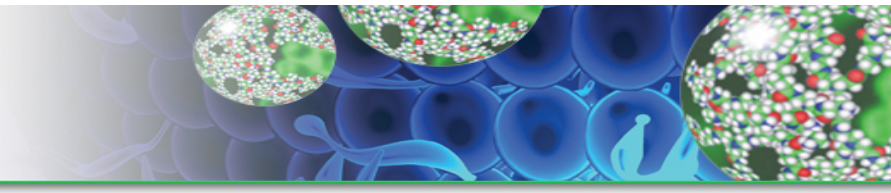
- Demonstrate efficacy of next generation (non-liposomal) nanoparticle construct (nanomedicine) in two animal models;
- Propose compelling cancer indication for the nano-therapy with a promise of durable response;
- Describe why nanotechnology-based solution is expected to perform better than other existing, contemporary approaches.



Research plan:

- Perform extensive physicochemical characterization;
- Perform efficacy studies in additional *in vivo* cancer models. The use of non-rodent species (larger animals) is encouraged, but not required;
- Perform biodistribution, safety pharmacology and toxicokinetics studies;
- Develop the model explaining mode of action of the nanomedicine;
- Leverage NCI services in Frederick through collaboration with Nanotechnology Characterization Laboratory and Laboratory of Animal Sciences Program.

Summary and Outcomes



- Proposed FOA is expected to advance translation of nanotechnology-based cancer interventions;
- Focus on next generation nanoparticles and strategies to improve treatment efficacy;
- FOA will warrant maturation of pre-clinical nano-concepts and will position them better for entry to NExT program and ETCTN network;
- Data collection and its sharing from systematic studies in multiple animal models will advance understanding of nanomedicines and enable further standardization of their synthesis and characterization;
- DCTD programs (CIP, DTP, CTEP, TRP, RRP, CDP) expressed strong interest in co-sponsoring this FOA and co-managing the program – benefit of collective expertise;
- CSR will review applications submitted to this FOA via SEP;
- PAR - fair competition of applications for overall RPG pool funds, while maintaining SEP review benefit.