Systematic Testing of Radionuclides in Preclinical Experiments

STRIPE Program
PAR Concept (R01, R21)

Michael Graham Espey, PhD
Jacek Capala, PhD

NIH NATIONAL CANCER INSTITUTE

BSA concept mtg. Dec. 9, 2021

Concept Snapshot

STRIPE: Systematic Testing of Radionuclides in Preclinical Experiments

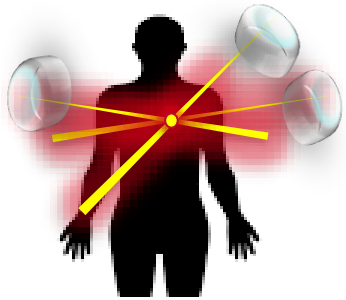
- Requesting a **PAR** to solicit proposals that address knowledge gaps in how **radiopharmaceutical therapy** (RPT) agents **affect the biology** of cancer cells, normal cells, and the microenvironment;

- Seeking to **catalyze interdisciplinary collaborations** across the fields of RPT and pre-clinical cancer biology;

- Will serve to **strengthen the pre-clinical foundation** of the RPT field and promote advances in biology-based targeting strategies;

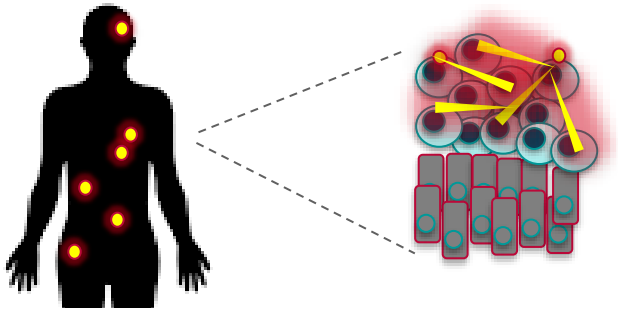
Two strategies in ionizing Radiation Therapy

External Beam Radiotherapy (XRT)



- Device manufacturers innovate to precisely deliver physical dose
- Spatial targeting limited by resolution of diagnostic imaging
- Efficacy limited by incidental injury to normal tissues

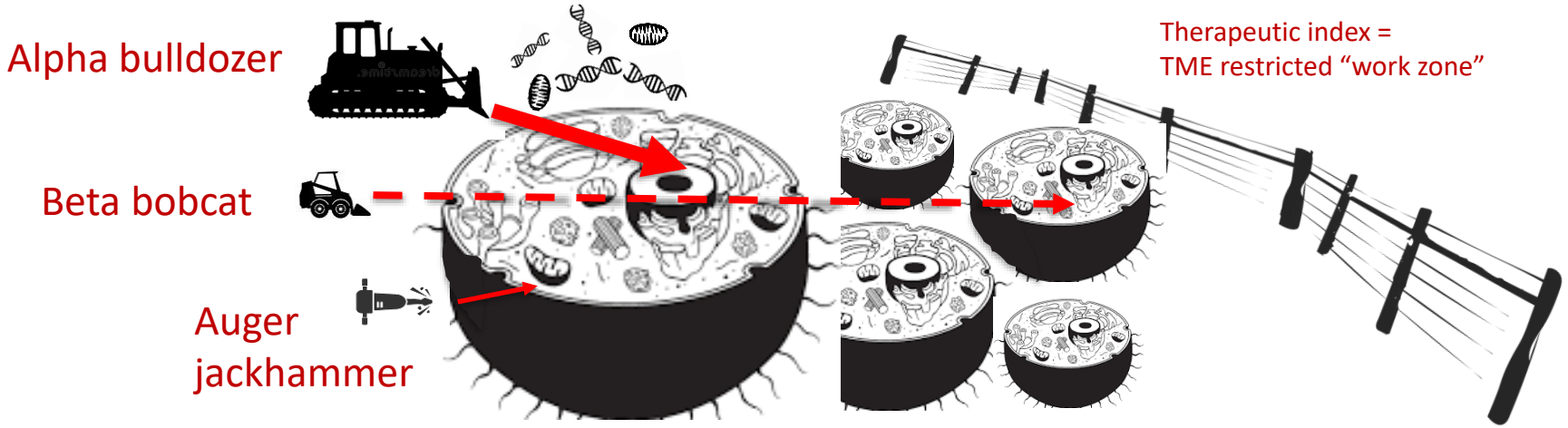
Radio Pharmaceutical Therapy (RPT)



- Targeting based on tumor biology
- Cellular-scaled drug delivery of a “cross-fire” dose to tumor and TME
- Utility in both local and micro-metastatic disease
- Potential to improve therapeutic index

RPT construction site analogy

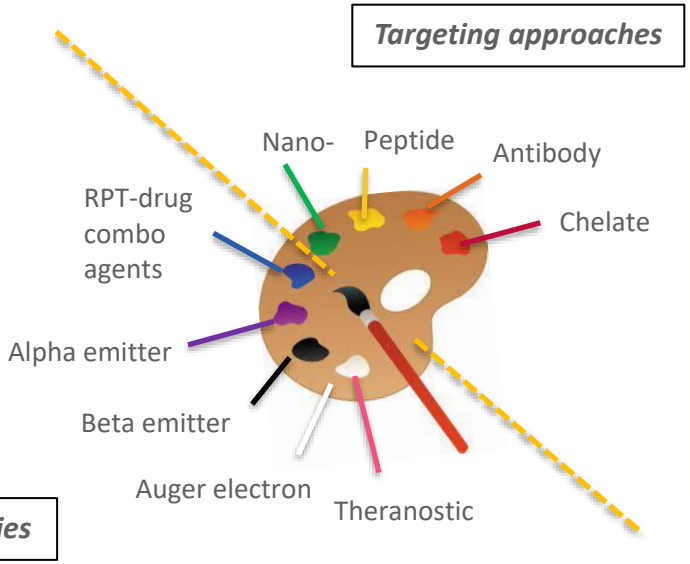
- Physics of radionuclide emissions is well known:
  - **Alpha**: high energy (He^{2+}), short range (50-100 µm), highly ionizing LET (DSB)
  - **Beta**: lower energy (electrons), longer range (1-5 mm), low LET
  - **Auger/conversion:** electrons, short range (500 nm), high LET

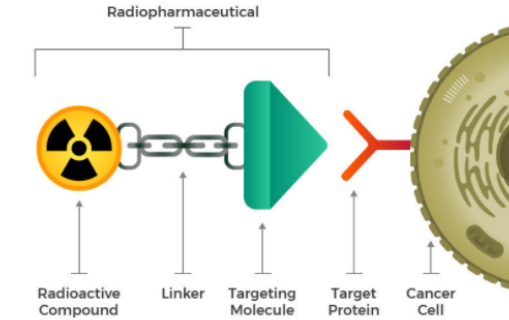


RPT modular designer flexibility

- Customizable drug targeting:
  - Flexible delivery system (nanoconstruct, peptide ligand, antibody, chelate)
  - RPT payload can be added to existing/known targeting agents
  - Wide range of possible new biology-based strategies for innovative RPT targeting

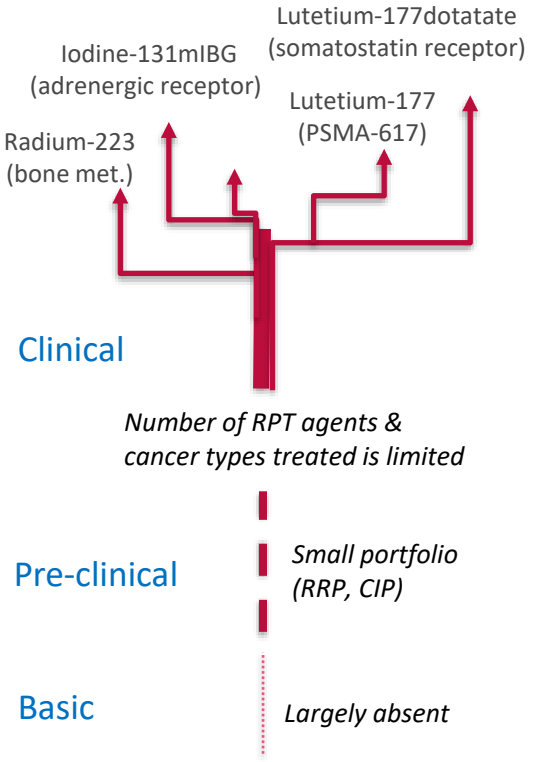
Radionuclide	Particle Type	Half-life
Bismuth-212	alpha	1 hour
Astatine-211	alpha	7 hours
Yttrium-90	beta	64 hours
Lutetium-177	beta	6 days
Iodine-131	beta	8 days
Actinium-225	alpha	10 days
Radium-223	alpha	11 days
Thorium-227	alpha	19 days





Radiopharmaceuticals consist of a radioactive molecule, a targeting molecule, and a linker that joins the two.
Credit: National Cancer Institute

Portfolio – RPT state of the field



- Clinical track record of successes
  - Commercially viable pipeline of several RPT agents in the clinic;
  - Development of new agents by big pharma is limited;
  - Focused so far as monotherapy;
  - **Reliance on empirical data, lack of pre-clinical dev.**

- Current NCI-supported "radiopharmaceutical therapy" awards
  - Few, spread between either therapeutic- or imaging-based objectives
    - ✓ DCTD: R01 = 15; U01 = 1; P01 = 2; P50 = 1
    - ✓ CTEP: ETCTN = 4; NCTN = 2
    - ✓ SBIR: R42/44 = 5
  - **Minimal support to examine the biologic effects of radionuclides and investigate new targeting strategies**

The Gap

- Unmet needs in foundational pre-clinical RPT research
  - **Limited knowledge on radionuclide radiation biology effects in tumor and normal tissues**
    e.g., guide particle choice, low dose-rate exposure, optimizing combinations (RPT+ chemo, timing), late effects
  - **Inadequate level of pre-clinical research to catalyze targeting strategy development**
    “Beyond” DSB-cytotoxicity, few new targets investigated
  - **Integration of RPT with –omic, molecular characterization, and enabling technologies**
  - **As noted by the CTAC Rad Onc Working Group**

- Threshold for wider adoption of RPT into cancer research
  - Radioactivity license (open-source lab) can be an impediment for non-RPT researchers;
  - Isolating effect on RPT field in leveraging full range of cancer modeling for discovery, optimization, and validation;

Concept Purpose

Catalyze interdisciplinary projects that intersect the fields of RPT and pre-clinical cancer biology;

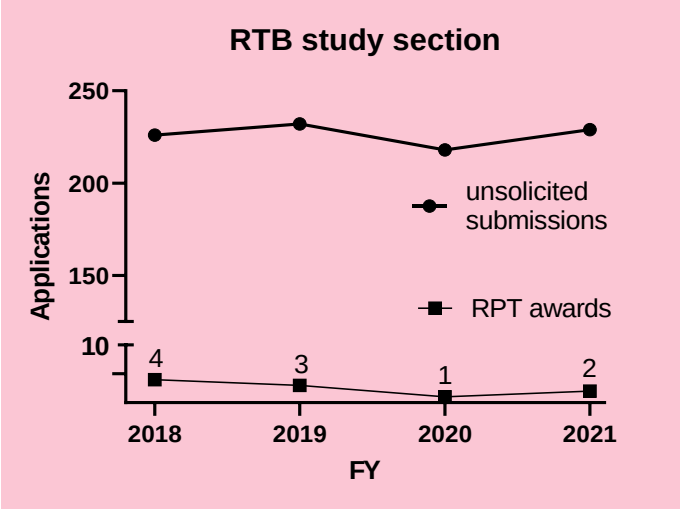
- **Scope: <u>Pre-clinical experiments</u> aimed to understand <u>RPT effects on the biology</u> of cancer cells, normal cells, and the microenvironment toward development of targeted interventions;**

- **Identify new targeting strategies for RPT**
  - Selectively target cancer-specific pathway, organelle, or processes
  - Develop synthetic lethality approaches
  - Advance PD biomarkers or microdosimetry based on RPT theranostic capabilities

- **Testing and optimization of novel RPT-molecular targeted therapy combinations**
  - Maximize opportunities to couple new pre-clinical cancer biology research in resistance & metastatic dis. to RPT clinical translational concepts
  - Understand polypharmacy mechanisms for RPT-drug combinations

Proposed Initiative: PAR

- Mechanism: PAR soliciting R01 and R21 applications
  - RPG funding source (no set-aside)
- Seeking interdisciplinary collaborative projects
  - e.g., cancer biology underpinnings of radionuclide targeting
- Review
  - Clustered together in a chartered CSR study section
  - Anticipated number of PAR applications (7-10/round for 3 years)

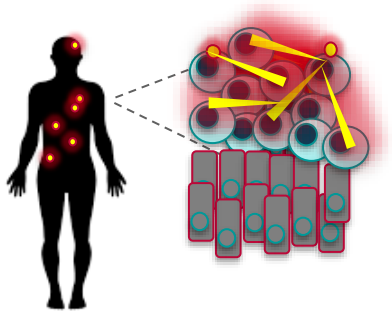


- Justification for PAR mechanism:
  - Incentivize high quality applications not seen with unsolicited route
  - Nucleate the portfolio
  - Affords FOA language that highlights topical priority areas of unmet need and can serve as a timely catalyst to drive the field with strong potential forward

Summation: New RPT Trajectory

Final slide

- Radionuclide toolbox exists
  - Physics, conjugate radiochemistry, and RPT dosimetry modeling are well established;
  - Targetable to achieve a high therapeutic index (tumor/normal);
  - Theranostics have desirable properties (dual function as imaging agent and drug);
  - Complementary to combined modality treatments, resistant or metastatic disease;



- *BSA subcommittee points of emphasis*
  - **PAR's scope: Pre-clinical biology of RPT**;
    - ✓ Coupling RPT to new enabling cancer biology tools & modeling approaches
    - ✓ Understanding RPT effects on tumor & TME; new targets
    - ✓ Timing and optimization studies with chemo- other targeting strategies
  - **PAR's goal: Expand & diversify the RPT field**;
    - ✓ Encourage cross-over projects in RPT biology and molecular targeting
  - **What does success look like;**
    - ✓ Establish a research portfolio (e.g., 6 - 8 awards) on biology-based RPT targeting
    - ✓ Data will form the rationale for new clinical trial concepts (e.g., ETCTN);