

RFA Concept Proposal
BSA Meeting March 15, 2021

Radiation Oncology-Biology Integration Network

“ROBIN” U54 Program RFA Concept

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Division of Cancer Treatment and Diagnosis -
Division of Cancer Biology - joint concept



Thank you to all those who helped to advise & vet this concept:

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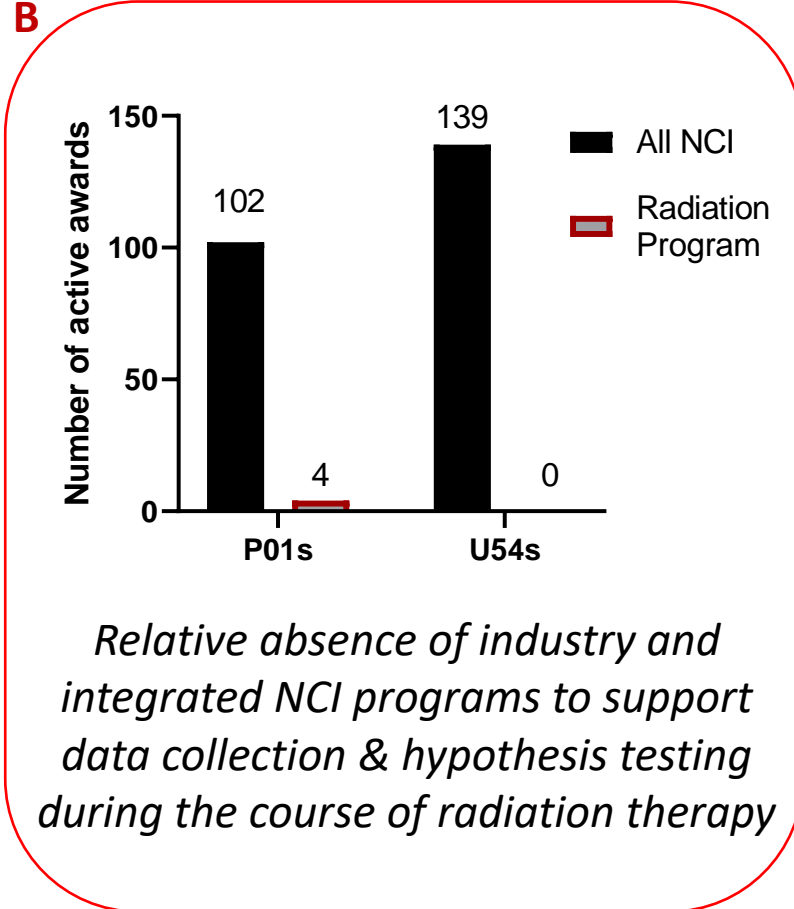
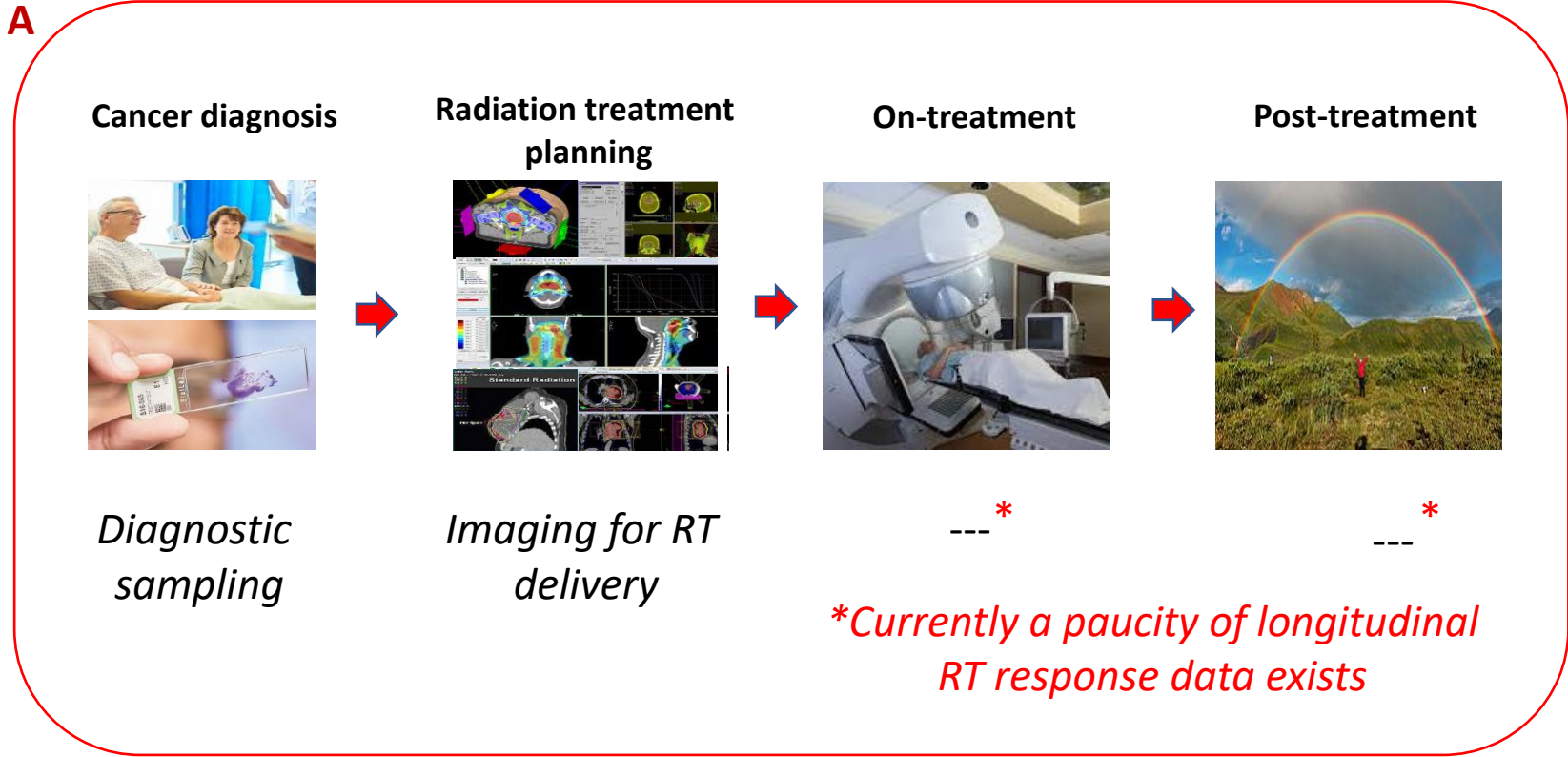
Dr. Keyvan Farahani, Cancer Research Data Commons, CBIIT

And our BSA subgroup mentors:

Dr. Sylvia Plevritis, Dr. Eileen White, and Dr. Otis Brawley

ROBIN concept: Gap Analysis

Unmet Need: While approximately 50% of all cancer patients receive radiation therapy, few data are collected to test hypotheses on the biological basis for patient responses to radiation therapy.



ROBIN concept: Unmet Needs & CTAC WG Recommendations

Unmet Need: While approximately 50% of all cancer patients receive radiation therapy, few data are collected to test hypotheses on the biological basis for patient responses to radiation therapy.

**NCI Clinical Trials and Translational Research Advisory Committee
*Ad hoc Working Group on Radiation Oncology***

Recommendation:

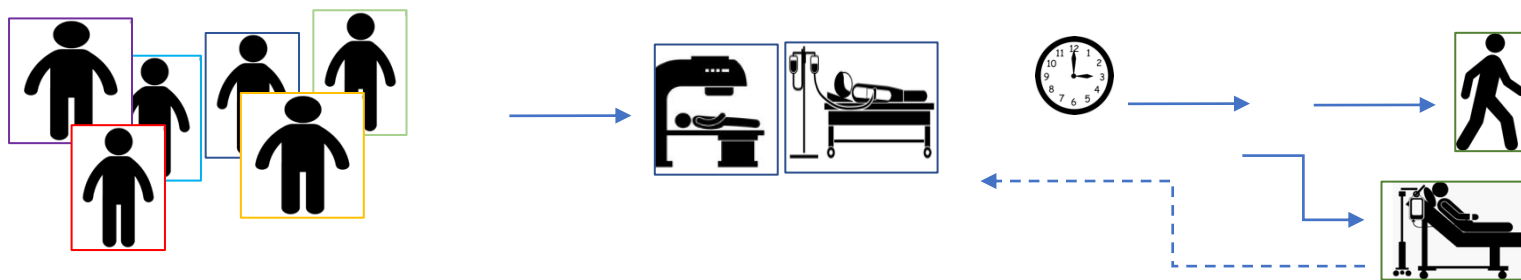
*“Establish an agile and effective **national radiation oncology consortium** to advance the study of the biologic mechanisms of radiation therapy through preclinical research and translational research studies to develop promising radiotherapeutic approaches to advance cancer care.”*

- Prioritize and support research to investigate the biological consequences of radiation treatment;
- Support longitudinal collection of clinically annotated research biospecimens before, on-treatment, and after radiation therapy;
- Develop a multidisciplinary workforce to best inform clinical radiation oncology studies.

Foundation of the ROBIN concept: Deep multidimensional characterization trials of RT

Small study cohorts of radiation treatment (BOA)

A BEFORE Treatment Assessments ON Treatment Assessments AFTER Treatment Assessments
Pre-treatment baseline *During treatment course* *Hours, days, months...*



C Possible types of invasive and non-invasive assessments

- Serial biopsies of tumor and blood;
- Functional genomics, proteomics;
- cfDNA, extracellular vesicles;
- Imaging tools (MRI, CT, PET);
- Sensor technologies;
- PROs, meta data

B Generate longitudinal molecular characterization datasets of biological responses to RT

- Each patient serves as their own control (pre-, on-treatment, post-)
- Characterization of the biological complexity underlying RT responses;
- Hypothesis-driven multimodal high-content analysis

D Cancers most amenable to “BOA”-RT pilot trials:

- Gastrointestinal;
- Head & Neck- Oral;
- Sarcoma;
- Cervical;
- Lung;
- Pediatric & CNS tumors

Utility of “small N” “data dense” characterization studies

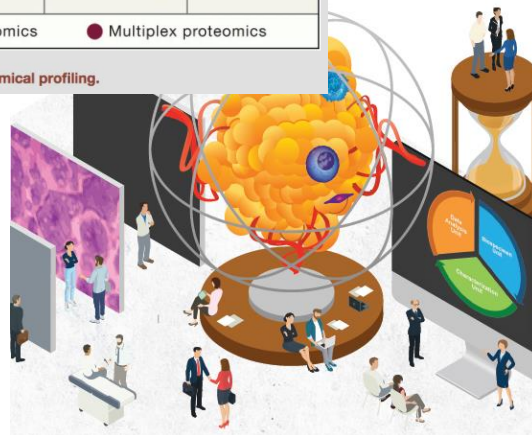
- Commonly used in early-phase clinical trials;
- Allows for deep multidimensional characterization of treatment responses;
- Advantages opportunity for serial sampling from devoted patient volunteers;
- Nimble. Can be completed rapidly and allow for hypothesis testing and progress.

Molecular		Spatiomolecular	Histological	Anatomical
● sc/snRNA-seq	● RNA-seq	● EM	● H&E	MRI
● sc/snEpigenomics	● Epigenomics	● Sequencing-based		CT
● CITE-seq	● WES	● Fluorescence-based		PET
	● Metabolomics	● Antibody-based		
	● Proteomics			
	● Microbiome			
● Single cell	● Bulk	● Multiplex transcriptomics	● Multiplex proteomics	

The HTAN toolbox includes molecular, spatiomolecular, histological, and anatomical profiling.

HTAN is an example of a “high-content” characterization program

- Deep dive on as few as 20 subjects per tumor type;
- Atlases molecular-cellular scale features by combining multiple approaches;
- Longitudinal with respect to chemo/IO treatment;
- Hypothesis generating (not biomarker validation-driven)

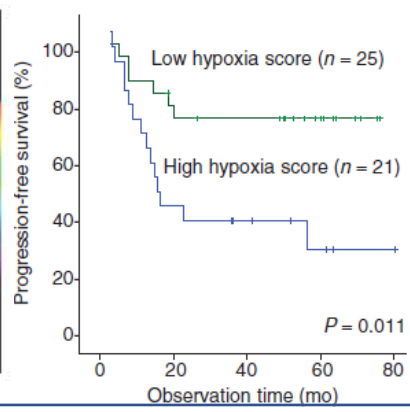
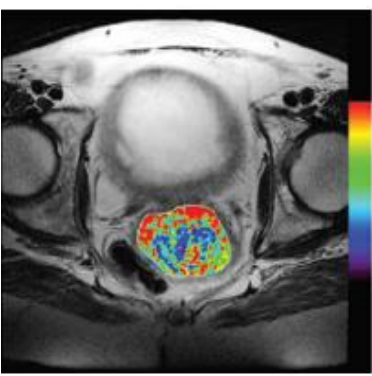


Molecular Characterization of RT responses

- Longitudinal data can be obtained from small N pilot trials;
- Assays/biomarkers exist that have not been systematically applied to RT;
- Orthogonal, multimodal, data dense approaches are feasible in an RT setting.

A

Functional Radiogenomics

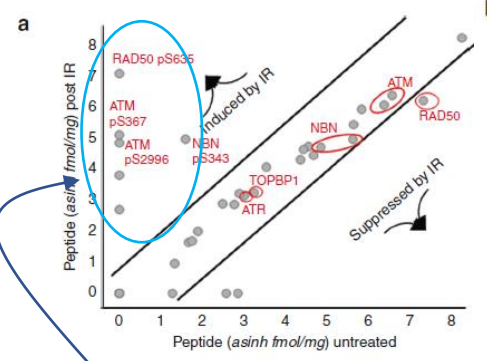


Cervical ca. patients;
pairwise DCE-MRI + hypoxia gene set
analysis on “before” RT tumor biopsy
was prognostic for PFS

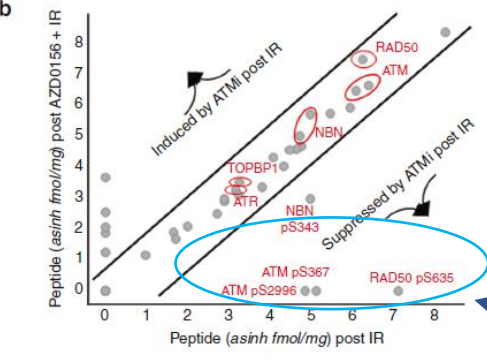
N = 46 patients
Halle, Can Res 72:5285; 2012

B

Phospho-proteomic DNA damage-repair panel



Induced by RT



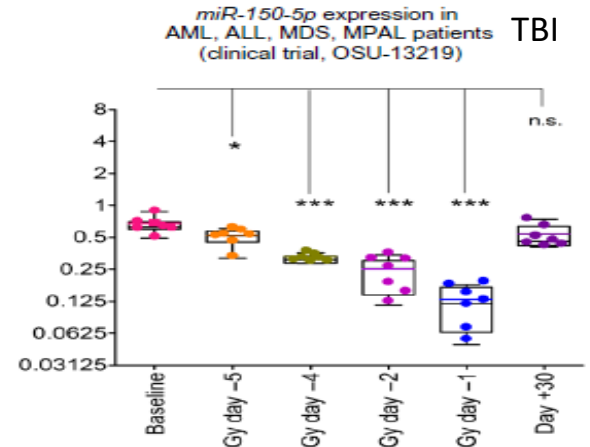
Suppressed w/ATMi post-RT

DNA damage panel showing ATMi
drug blocks RT-induced phospho-
activation of key repair pathway
proteins

N = 4 patients
Jones, BJ Cancer, 119:1233; 2018

C

Blood fingerstick ratiometric miR assay

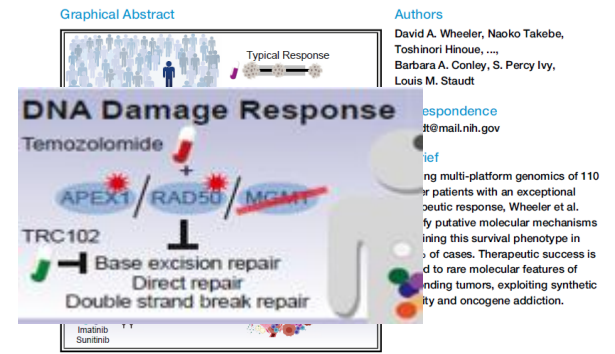


RT-responsive PBMC derived miR 150-5p /
RT-non-responsive lung secreted miR23a-3p

N = 7 patients
Yadav, SciTransMed 12: 2020

Cancer Cell

Molecular Features of Cancers Exhibiting Exceptional Responses to Treatment

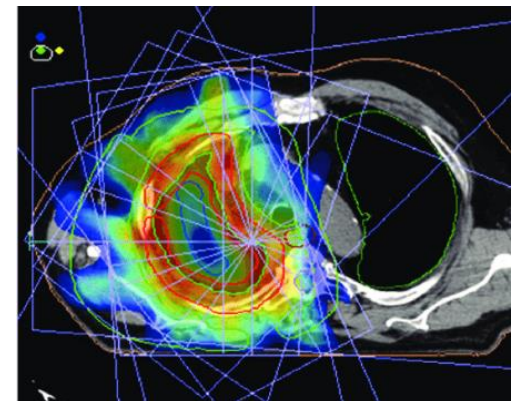
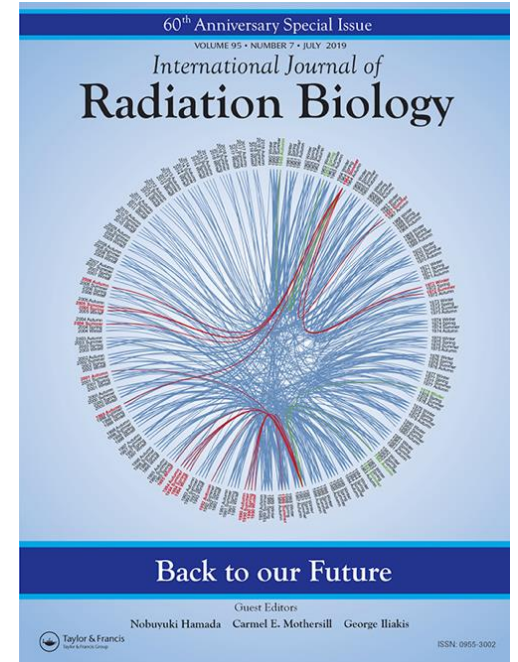


Wheeler, Cancer Cell, 39:1-16; 2021

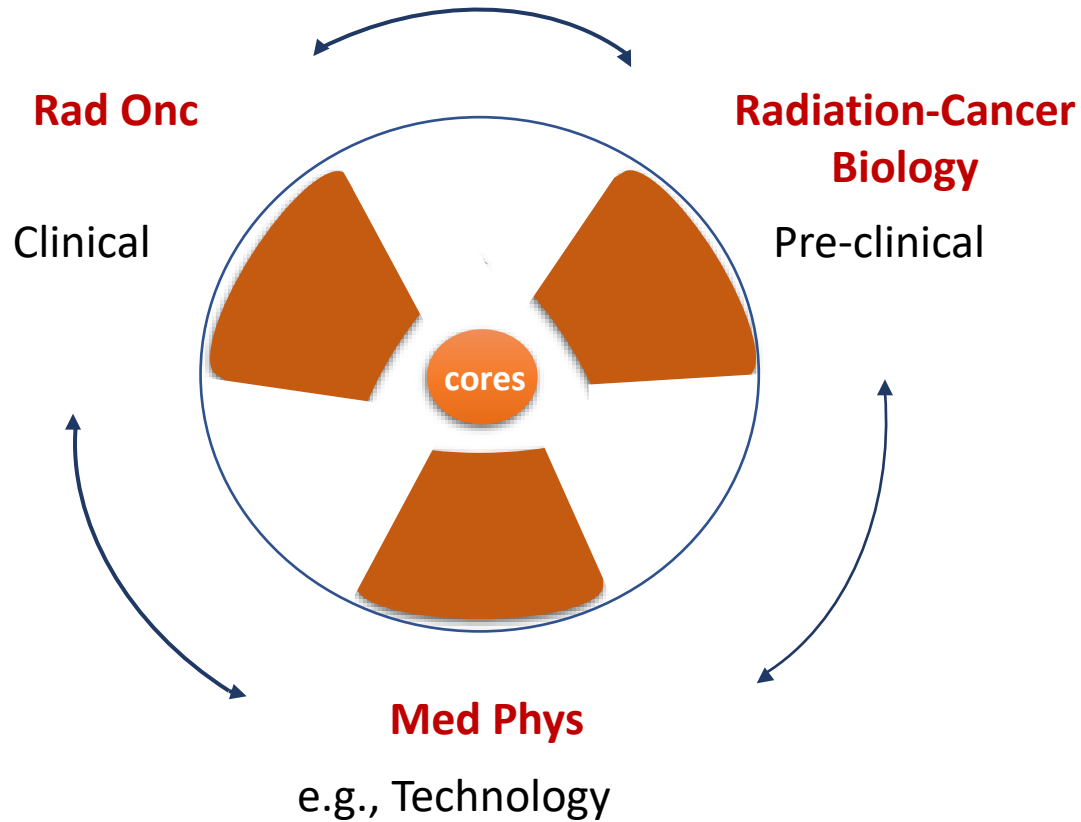
Radiation Oncology-Biology Integration Network (ROBIN) Program

A network of U54 Centers best achieves these goals:

- Collect data that describes the **biological basis** of radiation responses;
- Spur innovation to provide a multiscale **holistic view of radiotherapy** in both tumors and normal tissue;
- Grow a sustainable RT scientific **workforce** within the cancer research community;



Proposed U54 *ROBIN* Center Structure



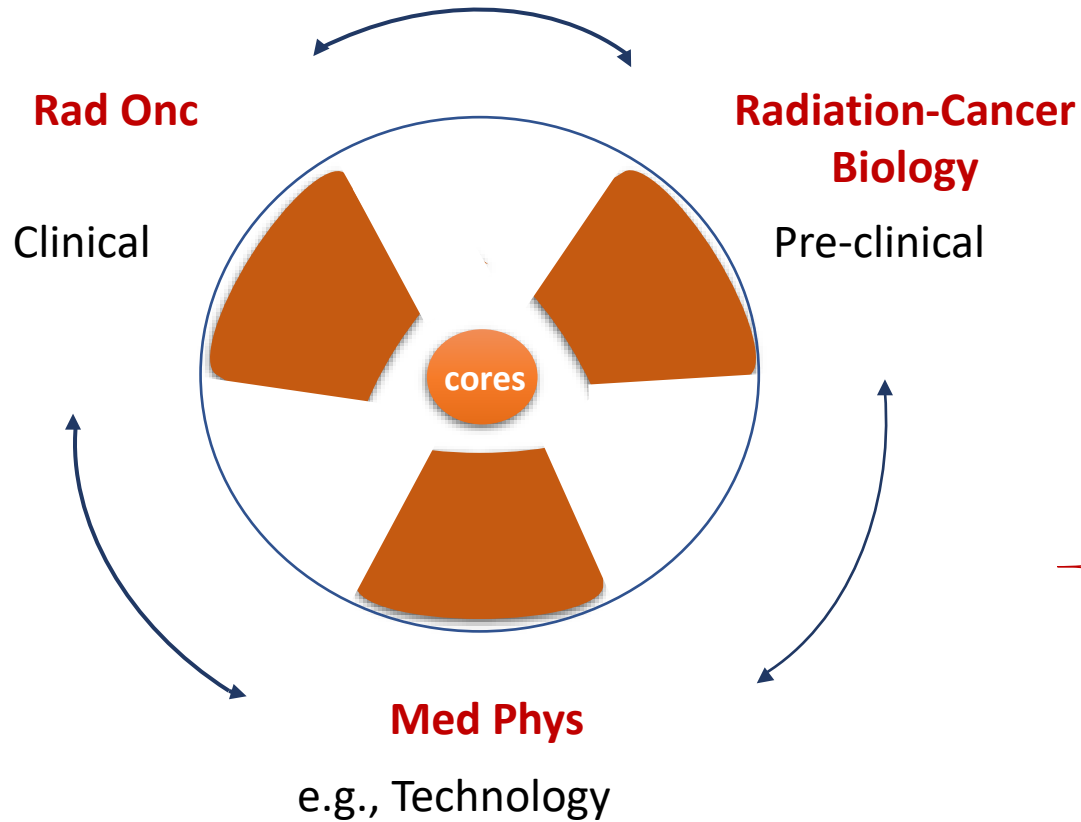
- ***Synergistic inter-disciplinary team expertise***
- ***Test a central hypothesis that defines the Center***
- ***Thematically-based U54 Centers (Priority areas)***

Targeted Priority Areas

consistent with CTAC Rad. Onc. WG recommendations:

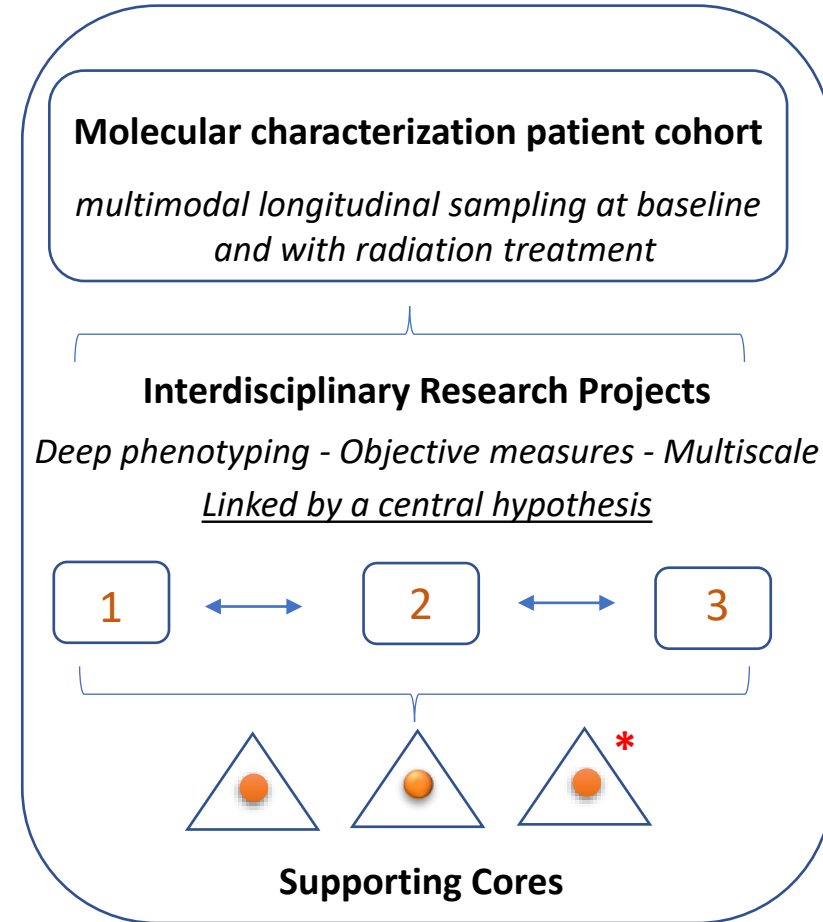
- Contextualized biological basis for RT responses;
 - Orthogonal approaches (-omics, imaging, sensors)
 - RT-inducible response signatures
- Heterogeneity of RT effects;
 - Longitudinal biological dosimetry
 - Late effects
- Multiscale biology and data science;
 - Holistic view of RT
 - Linking molecular, cellular, tissue, and patient scales;
- Workforce development;

Proposed U54 *ROBIN* Center Structure



- *Synergistic inter-disciplinary team expertise*
- *Test a central hypothesis that defines the Center*
- *Thematically-based U54 Centers (Priority areas)*

U54 Center

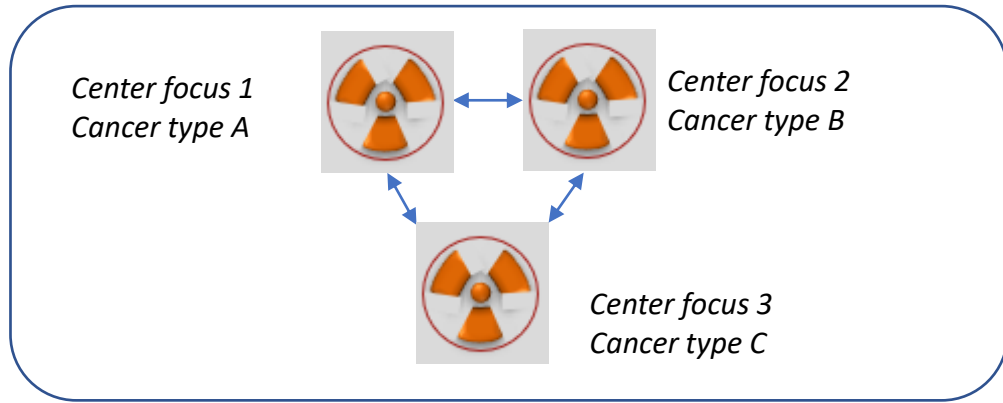


Examples of Cores:

- Imaging & Dosimetry, -Omics, Biospecimen, Data Sciences (dedicated data manager)
- Administrative, Cross-training core*

Proposed U54 *ROBIN* Program Structure

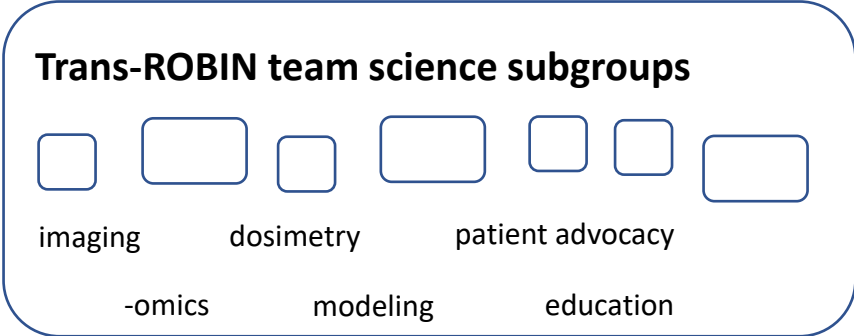
A Landscape view of *ROBIN* network composed of 3 U54 Centers






B \longleftrightarrow = **Restricted Fund for collaborative trans-*ROBIN* projects**
(e.g., 15% of Center budget)

C

Steering Comm.
U54 Center PI
& NCI staff representation



D Broader Community Affiliate “Spokes”

- Connection with existing NCI infrastructure;
 - CSBC, CRDC, CCG, CPTAC, ITCR, HTAN...
 - CCT T32 - R25 training programs
- Alliance with DOE & NASA Labs
 - Supercomputers/JDACS4C, data- sensors
 - NASA- normal tissue, sensors
- Inform basis for future ETCTN & NCTN trials at the end of the award period

Proposed Initiative: NCI U54 *ROBIN* Program

- Our SPL **RFA set-aside** allocation guidance is \$6M x 5 years = \$ 30M (projected FY22 20% RFA policy cut not included)

Program *pending approval	Average Award TC/yr.	# of Funded Centers	Program Budget x 1 yr	Program Budget x 5 yr
Human Tumor Atlas Network U2C	\$4.3M	10	\$43M	\$215M
Cancer Systems Biology Consortium U54	\$2.0M	12	\$24M	\$118M
Drug Response Sensitivity Network U54	\$2.5M	5	\$12.5M	\$62M
Radiation Oncology-Biology Integration Network U54*	\$2.0M *	3 *	\$6M	\$30M

- Based on comps to similar network programs, propose each **U54** be sized to a maximum of **\$2.0M in Total Costs**
- Anticipate to **build a Network of 3 U54 Centers: \$ 6M Total Costs (projected FY22 20% RFA policy cut not included)**
 - one to two receipt dates
 - request exemption waiver to not exceed the projected for FY22 20% RFA policy cut
- Program staff will work with DEA to facilitate broad interdisciplinary expertise to review applications at these intersections;
- Receipt September 2021; review March 2022; May 2022 Council; Active in FY22 – FY27

Measures of success for the NCI U54 *ROBIN* Program

- Develop a robust and enabling **molecular characterization** knowledge base of RT responses that describe the trajectories of individual patients undergoing treatment (longitudinal-dynamic);
- Testing of **new hypotheses** that relate the **underlying biological responses** to the physical dose delivered;
- Serve as a nucleation point for the field through deposition of **curated multi-scale data** into the NCI cancer data ecosystem;
- Workforce development: develop the **next generation of interdisciplinary radiation scientists**, ripple effect on K awards, T32 training grants focused on radiation sciences.