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Radiation Oncology-Biology Integration Network (ROBIN): Bridging the gap between biological research and clinical practice

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Abstract

The Radiation Oncology-Biology Integration Network (ROBIN) initiative addresses critical gaps in radiation oncology by integrating advanced biological research, technological innovation, and clinical practice. ROBIN leverages "omics" technologies, data science, and integrative analyses to elucidate the mechanisms governing tumor and normal tissue responses to radiation therapy (RT). Through five specialized centers – OligoMET, ImmunoRad, GenRad, METEOR, and KIDSROBIN – the network covers a broad spectrum of cancer and radiation biology research. Each center conducts translational programs linked to clinical trials, targeting key domains including metastasis biology, RT-immune system interactions, and genomic determinants of treatment response. KIDSROBIN assures the invaluable inclusion of pediatric cancers to the consortium. By collecting clinically annotated human biospecimens and applying single-cell and spatially resolved omics, ROBIN enables mechanistic insights into radiation effects directly in patients. A central pillar of the initiative is its commitment to data standardization and sharing, using cloud-based platforms to generate accessible and interoperable datasets. ROBIN also prioritizes education and cross-disciplinary training to cultivate the next generation of scientists in radiation biology and oncology. This integrated approach positions ROBIN to drive transformative advances in radiation oncology and multimodal cancer therapy, informing personalized treatment strategies and improving patient outcomes.

This review provides an overview of the ROBIN program and its key strategies, research activities, and contributions to advancing radiation biology and oncology. The vision and leadership of Dr. Norman Coleman have been foundational to the development of the ROBIN initiative, inspiring a collaborative ecosystem that bridges science and clinical practice to drive meaningful impact in patient care.

Statement of Translational Relevance

Radiation therapy is a cornerstone of cancer treatment, yet the biological mechanisms governing tumor and normal tissue responses remain incompletely understood, limiting precision and therapeutic optimization. The Radiation Oncology–Biology Integration Network (ROBIN) addresses this gap by embedding comprehensive biological investigation within prospective clinical trials. Through longitudinal biospecimen collection, multi-omics and spatial profiling,

advanced imaging, and integrative data science, ROBIN generates mechanistic insights into radiation response, resistance, and toxicity directly in patients. Coordinated molecular characterization trials across multiple disease sites link laboratory discovery with clinical outcomes, accelerating biomarker development and informing rational combinations of radiation with immunotherapy, targeted agents, and other systemic treatments. ROBIN's emphasis on standardized data generation, sharing, and cross-disciplinary training ensures reproducibility, scalability, and broad scientific impact. Collectively, this framework reframes radiation therapy as a biologically informed and adaptable treatment modality, advancing precision oncology and improving outcomes for patients across cancer types.

Introduction

Approximately 50% of cancer patients are treated with radiation over the course of their disease [1]. Since its inception over one hundred years ago, radiation therapy (RT) has undergone a significant evolution, combining biology-driven insights, technology-focused approaches, and mathematical models to describe the complex biological [2] interactions between radiation and tissues and optimize cancer treatment. In the last two decades, significant advancements in human science have ushered in the era of omics and big data, transforming research approaches and paving the way for precision medicine. Omics technologies, including genomics, proteomics, metabolomics, and transcriptomics, have enabled a more comprehensive understanding of biological systems and diseases at multiple levels [3]. Nevertheless, these discoveries are relatively untapped in radiation oncology. Historically, most radiobiology research has been conducted either in cell lines or in preclinical model systems with limited data derived from intact human tumors. Modest interest from the pharmaceutical industry has contributed to a dichotomy in radiation oncology in which the technical precision of radiation delivery to tumors has continued to improve, but the biological determinants of how tumors and normal tissues respond and adapt to RT over time remains far less understood [4]. This gap underscores a severe unmet need to better characterize the effects of radiation treatment biologically to enhance the eradication of cancer cells while minimizing toxicity to normal tissues [5]. In this context, the Radiation Oncology-Biology Integration Network (ROBIN) U54 NIH/NCI program - the first of its kind - provides a unique opportunity to gather and apply new biological knowledge in the optimization of radiation treatment and its combination with systemic therapy.

According to the ROBIN mission, all research centers involved in this project provide highly focused research capabilities that:

- prioritize and support research to test translational hypotheses that advance understanding of mechanistic interactions and biologic consequences of radiation treatment
- generate highly granular and robust multi-omics data from clinical trials using radiation and radiation-supported therapies
- support longitudinal collection of clinically annotated research biospecimens prior to (e.g., baseline), during (e.g., on-treatment), and after RT

- apply modern cutting edge “omics” approaches to interrogate human specimens pre- and post-radiation
- develop a multidisciplinary workforce and engage stakeholders with the expertise to conduct studies in translational and preclinical research to best inform clinical radiation oncology studies, including leveraging data science and informatics approaches

Currently, the ROBIN program comprises five centers, including OligoMET, ImmunoRad, GenRad, METEOR, and KIDSROBIN (Table 1). Each ROBIN center conducts a program organized around clinical studies – Molecular Characterization Trials (MCT) – that allows each team to both test specific therapeutic approaches in the field of standard of care (SOC) or experimental therapies and to collect biological samples of human tumors and non-tumors within clinical outcomes and digital data. The biological samples are then utilized in translational research developed and performed at the bench. ROBIN also features a group dedicated to the collection and computerization of omics data derived from this analysis (Data Sharing and Integrative Analysis Core - DSIA) and a working group that promotes the dissemination of knowledge related to radiobiology and trains young scientists dedicated to this discipline (Cross Training Core - CTC).

Here, we summarize the main research efforts carried out by each ROBIN center, recognizing the visionary leadership and foundational work of Dr. Norman Coleman and his team, who conceived and launched the ROBIN initiative.

Dr. Norman Coleman: Visionary Leadership and Foundational Work

This article is dedicated to the memory of Norman Coleman, the motivational force behind ROBIN – a collaborative interdisciplinary effort to apply new biological knowledge to optimize radiation therapy in combination with systemic drugs, immunotherapy, and other agents (RFA-CA-21-040). Through an NCI U54 funding mechanism, ROBIN aims at developing research consortia that harness modern biotechnology tools to understand the complex effects of ionizing radiation on human cancer and normal tissues. To quote Dr. Coleman, “Radiation is a different ‘drug’ at different doses and fractionation, warranting more research.” Each of the programs described in this review address these fundamental questions. Moreover, most ROBIN investigators had the privilege of being encouraged and mentored by Dr. Coleman, experiencing his generous and selfless support.

Dr. Coleman was brilliant and courageous; he could always see the big picture and know where to stand. He was an example of rectitude and integrity. As the most senior governmental advisor on nuclear incidents, he played an important role to the country after 9/11 and in Fukushima, Japan [6]. As a physician scientist, he knew how to best integrate radiotherapy in a multidisciplinary approach to cancer and how to ensure it would remain a central tool in the management of our patients.

A strenuous advocate for health equality, Dr. Coleman remains a role model for innumerable investigators and colleagues. His dedication to the field included the vision of a central role for radiotherapy to address and reduce cancer care inequalities worldwide. Reaching the underserved was a constant theme in his career, and the inspiration behind the International Cancer Expert Corporation (ICEC), a non-profit organization he founded to provide mentorship in low- and middle-income countries and in regions with indigenous populations in upper income countries [6]. His passion and commitment to correcting inequalities were contagious. These qualities, along with his exemplary dedication to science, are Dr. Coleman's legacy to the many oncologists and biologists who were fortunate enough to meet him.

ROBIN Centers

OligoMET (Grant Number U54 CA273956)

Metastasis is the primary cause of cancer mortality and is generally incurable once it occurs [7]. It remains a complex, multiscale systems problem requiring the integration of molecular, cellular, tissue, organ, and organism-level data [8]. Paradigm-shifting studies, including those led by the ROBIN OligoMET team (University of Maryland Baltimore, Weill Cornell Medicine, Thomas Jefferson University), have shown that metastatic capacity of cancers behaves along a spectrum of disease, including an oligometastatic state where metastases are limited in number and location. This concept has transformed the clinical approach to metastasis; however, a greater biologic understanding is needed to improve cure rates [9–11]. The OligoMET center aims to elucidate how radiation may modulate metastatic biologic processes, and to generate knowledge and strategies that could render metastatic disease curable [12], bringing a multidisciplinary perspective – clinical trial, molecular profiling, mouse modeling, and computational methods – to explore the impact of RT on tumor plasticity, metabolic reprogramming, and the tumor microenvironment in the metastatic setting [13,14]. The center conducts parallel mechanistic, hypothesis-driven co-clinical studies in men and mice to study radiation effects on oligometastasis [15,16], leverages partnership with biomarker companies for a broad and immediate clinical impact, and applies novel network methods to prioritize candidates for functional validation, sharing data across the ROBIN consortium to maximize impact. Additionally, OligoMET investigates molecular drivers of poorer outcomes in African American patients [17], with the goal of informing future trials and identifying therapeutic targets that reduce disparities beyond prostate cancer. Along with these purposes, the centerpiece of OligoMET's clinical effort is the MCT – a Phase II multi-institutional randomized study called TERPS (NCT05223803) – which tests the benefit of total tumor consolidation through metastasis-directed therapy (MDT) in oligometastatic prostate cancer. To date, over 80 patients have been screened, with 47 enrolled and randomized: 23 at University of Maryland Baltimore (UMB), 9 at University of Pittsburgh Medical Center (UPMC), and 5 each from University of California San Diego (UCSD), Virginia Bon Secours, and Thomas Jefferson. Enrollment continues to grow and is supported by active strategies, including site updates, regular meetings, and outreach via social media and newsletters. Correlative tissue, liquid biopsy, and imaging data are being collected for deep multi-scale profiling.

Translational work from OligoMET is elucidating radiation's effects in oligometastatic disease. Project 1 has developed and applied novel digital pathology multimodal AI approaches, plasma proteomic biomarkers, and T-cell receptor repertoire analyses in men with oligometastatic prostate cancer, yielding promising signatures associated with SABR benefit. Project 2 preclinical studies demonstrated that dietary interventions can modulate radiosensitivity; low-fat and calorie-restricted regimens enhanced radiation responses, whereas ketogenic diets unexpectedly promoted radio-resistance. Complementary efforts identified systemic metabolic signatures linked to SABR MDT, providing additional preliminary biomarkers to stratify patients most likely to derive durable benefits. In part, these data have already catalyzed the launch of the first integral-biomarker-designed randomized trial in this space (KNIGHTS, NCT06212583). Together, these wet-lab advances underscore how radiation may influence tumor cell plasticity, host metabolism, and immune contexture, while highlighting new opportunities for therapeutic radio-sensitization. Moreover, the OligoMET institutions – long recognized for their nationally attended didactic program in classical radiation physics and radiobiology [18,19] – are now leveraging this foundation to advance research in digital pathology, machine learning, and multi-modal bioinformatics model development, supported by a T32-funded curriculum at Weill Cornell Medicine [20].

Overall, the ROBIN OligoMET Center serves as a platform for the expansion of radiation oncology concepts, biomarkers, and technologies in the oligometastatic space (Figure 1). Its discoveries are expected to support the development of combined modality radiation trials through the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and the National Clinical Trials Network (NCTN).

ImmunoRad (Grant Number U54 CA274291)

The immune system plays a central role in modulating the in vivo response to RT. Stone et al. first demonstrated the role of immunity by showing that RT-induced TCD50 (dose to control 50% of tumors) varies with host immunocompetence, that also controls the tumor metastatic potential [21]. Since then, multiple mechanisms underlying the crosstalk between irradiated tissue and the host's immune system have emerged as significant determinants of RT response [22], explaining how rRT (local modality) can affect cancer survival when included in treatment regimens [23]. Both innate and adaptive immune effects of RT are currently being leveraged to enhance immunotherapy, translating preclinical evidence to clinical trials. However, despite the recognition of the immune system's contribution to cancer response to RT, successful translation to the clinic is lacking [24,25]. The ROBIN ImmunoRad Center was established to investigate interactions between RT and the immune system, focusing on how irradiated tumor tissue, surrounding normal tissue, the adjacent microbiome, and host immunity influence cancer outcomes. Rectal cancer serves as an ideal model to explore these mechanisms. Ten leading academic centers (Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center, University of Chicago, Rutgers University, Cedars-Sinai Medical Center, Institute of Cancer Research/Royal Marsden, University of Glasgow, University of Manchester, University of Leeds, and Gustave Roussy) are conducting a prospective MCT1 in rectal cancer (NCT05943210), aiming to enroll patients across the U.S. and Europe. Preoperative short-course radiotherapy (SCRT) was chosen as an optimal model to address these key scientific questions [26–29]. The MCT1 enables longitudinal collection of human biospecimen – tissue biopsies, blood, and stool at multiple timepoints – to support two major projects investigating radiation-induced biological and immune effects. It is providing unique human data on the effects of radiation as standalone modality. A parallel radiomics study integrates imaging with biological and clinical data. In-depth molecular analyses are being conducted to investigate the effects of RT on both the tumor and surrounding colorectal tissue, as well as on the host's immune system and microbiome. Artificial intelligence and machine learning are employed to develop models that predict interactions between patient characteristics, tumor attributes, and radiation parameters, informed by the data gathered from these studies (Figure 2).

A second prospective phase I-II MCT (MCT2; NCT05024097) is underway to evaluate a novel multimodal regimen combining SCRT (25 Gy/5 fractions) with etrumadenant (a dual antagonist of adenosine A2AR/A2BR receptors), zimberelimab (anti–PD-1), and FOLFOX chemotherapy in rectal cancer. The primary endpoint is the proportion of patients who achieve a complete response (CR). Part I is a modified 3+3 safety run-in for etrumadenant plus SCRT. Part II is an open label single arm Simon's 2-stage optimal design. With a sample size of 27 evaluable patients (stage 1 = 15 patients and stage 2 = 12 patients) the trial is powered to detect a CR rate of 25% or less versus the alternative, at least 45%. To date 21 patients have enrolled. In part I, a CR is observed in 1/5 (20%) evaluable patients. In part II, 11/15 accrued patients to stage 1 completed treatment and are assessed for response, reporting a CR rate of 82%. The trial is anticipated to proceed to stage 2 and accrue an additional twelve patients [30].

Currently, a total of 39/50 subjects have been enrolled to MCT1, with accrual continuing steadily. Over 140 tissue samples have been banked, extensively quality-controlled, and processed for spatial transcriptomic profiling using the 10x Genomics Visium HD platform. Preliminary integrative analysis reveals distinct transcriptional and spatial patterns across tumor and non-tumor tissues, with the analysis currently ongoing. Contributions from the University of Glasgow include samples from 10 patients, supporting multi-modal single-cell and spatial profiling. Early spatial transcriptomics analyses identified distinct alterations in immune and stromal cell phenotypes associated with RT response, including spatial reorganization of lymphocytes and altered distribution of macrophage-derived wound-healing signals. Preliminary analysis, using single-cell RNA sequencing of pre- and post-RT PBMC samples, identified dynamic transcriptional changes across immune subsets, including stress responses in B cells, wound healing, ECM remodeling and immune activation in monocytes, and MYC-driven activation in CD8+ T cells, suggesting that RT induces systemic immune reprogramming, aligning with the concept of trained immunity. In parallel, ImmunoRad investigates RT-induced changes in the microbiome. 16S/ITS sequencing of stool samples revealed shifts in bacterial and fungal populations – notably, increased Clostridiales and Trichocomaceae post-RT. These early findings underscore the interconnected impact of RT on immune and microbial ecosystems, informing future mechanistic studies.

Collectively, these efforts provide a robust molecular framework to dissect radiation-induced changes in the tumor microenvironment and to identify potential biomarkers of response and resistance. The findings are shared with the broader network of ROBIN investigators and the wider scientific community, creating a valuable resource for understanding the biological effects of RT on the immune system.

GenRad (Grant Number U54 CA274513)

The ROBIN GenRad center (Cleveland Clinic and Emory University) investigates the genomic and microenvironmental determinants, and temporal dynamics, driving the efficacy of radiation-based combination therapies (Figure 3). Despite the widespread use of RT-based combinations in oncology, mechanisms shaping response and resistance remain poorly known. The center's long-term goal is to understand these mechanisms to optimize therapy. Among the most promising new biologics currently being studied for use with RT are antibody-drug conjugates (ADC) and immune checkpoint inhibitors (ICI) [31–33]. The GenRad team employs an innovative MCT program, testing (a) radiation plus ADC in bladder cancer and (b) radiation plus ICI in head and neck squamous cell carcinoma (HNSCC) to characterize the mechanistic drivers underlying these RT-based approaches.

In bladder cancer, organ preservation therapy with RT+cisplatin is a standard-of-care (SOC) treatment option for locally advanced muscle invasive bladder cancer (MIBC). However, bladder dysfunction, recurrence, and poor overall survival remain significant challenges [34]. In this context, the RAD-SG trial (NCT05833867, MCT part A) evaluates the feasibility of combining RT with the ADC sacituzumab govitecan (SG) to enhance tumor control and reduce toxicity for bladder preservation therapy. The endpoint is to compare the outcomes and correlates of the study cohort with bladder cancer patients who receive immune checkpoint therapy alone or cisplatin plus radiation and determine the differential molecular effects from SOC RT+cisplatin versus RT+SG. The preliminary results show that RT+SG for definitive bladder cancer treatment is safe and feasible, with only grade 1 toxicities observed. Comprehensive genomics, serum proteomics, imaging, and ctDNA analysis are underway for the trial samples. A second MCT study examines HNSCC (NCT03521570) (MCT part 2), where both local and distant recurrence represent major challenges [35–37]. This investigation focuses on the differential mechanisms underlying the anti-tumor activities of RT+cisplatin compared to those of RT+ICI, aiming to uncover the unique genetic and immunologic factors that govern response to RT when combined with these two therapeutic classes. The trial is trial is completed, and the results have elucidated critical factors that drive treatment efficacy for chemotherapy plus radiation versus chemotherapy, radiation, and anti-PD1 [38]. In MCT part A, flow cytometry-based immune profiling is used to examine PBMC before, during, and at the end of treatment. The preliminary findings demonstrate an extensive accumulation of myeloid lineage cells during treatment, which suggests that ADC+RT reshapes systemic immune repertoires by increasing antigen presentation-competent immune cells. Strikingly, these effects are entirely distinct from the molecular drivers of efficacy in patients treated with just ICI. MCT part B showed that intensity-modulated re-irradiation in combination with PD-1 inhibition is not only tolerable but an effective therapeutic approach in patients with recurrent or second primary HNSCC [38] in some but not all patients. A shorter progression-free survival was associated with a 1.5-fold increase in PD1+Ki67+CD4+ T cells from baseline to week 2 or 4 of treatment, suggesting the need to further assess potential biomarkers in the tumor [38]. Analysis of our expansion cohort from the phase III Javelin HN100 trial with chemoradiation +/− avelumab revealed striking tumor mutations and microenvironmental factors that shaped efficacy and resistance. One notable finding is that intratumoral bacteria in HNSCC is a major source of resistance to therapy. The GenRad center is also working to improve the identification of patients who are sensitive or resistant to RT-based therapies based on new insights into transcriptional dynamics and temporal reprogramming during treatment. The team is leveraging longitudinal genomics and proteomic data from the MCTs treating MIBC or HNSCC patients with RT and chemotherapy versus RT and SG or ICI. This builds on recent experimental and clinical findings by GenRad research groups, which have identified highly refined gene expression programs associated with RT sensitivity and delta radiomics. These studies aim to establish a foundation for optimizing multimodal, radiation-based definitive treatment strategies.

Overall, knowledge gained through the program is deepening the understanding of biological processes driving sensitivity and resistance to RT-based therapies in combination with systemic agents, ultimately enabling more precise and effective treatments and improving cancer patient outcomes.

METEOR (Grant Number U54 CA274318)

The Washington University (WU) ROBIN Center, METEOR, is creating a resource for in-parallel single cell and spatially resolved omics to study how the immune system co-evolves with tumors during chemoradiation (CRT). The team investigates how SOC chemotherapy, radiation, and combined CRT remodels the TME and how this remodeling contributes to tumor relapse and radiation resistance (Figure 4). The METEOR-CRATR MCT collects longitudinal tumor, blood, and immune-relevant specimens from patients with locally advanced cervix and pancreas cancer (NCT05975593), two tumors where local control by RT is imperative for long-term outcomes [39–41]. Both cervical and pancreatic tumors are characterized by tumor permissive microenvironments and allow repeated sampling [42–46]. Preliminary single-cell and bulk RNA sequencing data implicate macrophages, dendritic cells, and T cells in the TME remodeling process. New technologies are being incorporated to study the impact of treatment-related changes in metabolism, DNA damage/ repair, and associated gene expression in tumor cells and TME. The team is also comparing the effects of treatment sequencing and modality and utilizing a new study of relapsed tumors. In addition to biospecimens collection, spatially and temporally resolved imaging and dosimetry are used to develop a granular understanding of the effects of SOC CRT on the TME. Through this work, new hypotheses and druggable targets are being generated to potentially improve local and systemic tumor control after CRT. Currently, METEOR has enrolled 26 cervical and 12 pancreatic cancer patients, obtaining 75 tumor samples (65 in the cervical arm and 10 in the pancreatic arm). Twenty-two cervical and 3 pancreatic patients have serial tumor samples. Blood is banked in both arms at the time of tumor biopsy; for the cervical arm, blood is also obtained during follow-up. A total of 126 radiotherapy plans have been archived in DICOM-RT format, and 11 cervical cancer patients underwent experimental MR imaging (DBSI).

METEOR leverages institutional expertise in genomics, proteomics, tumor metabolism and immunology to deeply investigate CRT-induced tumor and TME co-evolution. The overall hypothesis is that immunosuppressive CRT-associated changes in the immune TME can be targeted to improve systemic anti-tumor immune responses after RT. Although the preliminary data implicates macrophages and dendritic cells, METEOR's research is designed to explore CRT effects on multiple cell types and integrates new findings through pilot projects and data sharing. Considering that tumor cells and the TME are influenced by the tissue of tumor origin, it is important to study multiple tumor types to establish the common (and tumor-specific) mechanisms of CRT-related immunosuppression. Since the analysis focuses on small biopsies, new collaborators can also send them for analysis within the METEOR infrastructure.

The two research projects (Project 1: Cervix; Project 2: Pancreas) test the hypothesis that SOC CRT restricts durable anti-tumor immunity by increasing myeloid-derived cells with tumor permissive phenotypes in the TME. Each project tests its hypothesis using data generated in the Center's Shared Resource Cores for bioinformatics (METEOR-BLST) and for data management and sharing (METEOR-DST). Observations are validated through translational and functional genomics in vitro and in vivo. The ultimate goal is to identify myeloid-derived targets and test novel drug-RT combinations in mouse models to improve CRT outcomes. Preliminary results from Project 1 demonstrate that HPV genotype and gene expression drive cervix tumor biology, beyond histology. Furthermore, the pretreatment immune TME is diverse across patients, though CRT remodels the TME in consistent ways: inducing infiltration by novel populations of myeloid-derived cells and upregulating p53/MDM2 in human cervix tumor cells, while not significantly upregulating PDL-1 and PD-1 axes. Early findings from Project 2 reveal that SBRT impacts cCD1 infiltration in human and murine pancreatic tumors and that, following SBRT, cDCs have a poor APC phenotype with altered cCD1/cDR2 ratios in draining lymph nodes.

Together, METEOR is defining how CRT reshapes the TME, identifying key driven mechanisms of resistance, and generating translational targets to improve local control and systemic anti-tumor immunity.

KIDSROBIN (Grant Number U54 CA274516)

Responses to RT are notoriously variable, and this variability has served as the focal point of much clinical/translational research. Prior studies address inter-tumoral heterogeneity created by genetic modifiers that cause differential responses to RT within and among cancer types [47,48], as well as inter-patient heterogeneity – often highlighting patients' immune system contributions to RT response [25,49]. The KIDSROBIN team (Harvard University and University of California at San Francisco) focuses on the impact of new technology such as single-cell genomics and spatial transcriptomics to document intra-tumoral heterogeneity and uncover its influence on tumor architecture and RT outcomes [50–52]. The team's testable hypothesis is that variability in RT response is largely driven by intra-tumoral heterogeneity. Some of this heterogeneity is intrinsic to tumor cells and potentially actionable as adjuvants to RT. Other critical components might be cell-extrinsic and likewise druggable. An emerging new field in cancer biology is "Cancer Neuroscience", which explores tumor-nervous system interactions that may shape radiation responses, resistance, and even late neurocognitive effects [53]. To minimize confounding variables, KIDSROBIN focuses on two pediatric neuro-ectodermal cancers – diffuse midline glioma (DMG) and high-risk neuroblastoma (NBL). Intra-tumoral heterogeneity is a recently appreciated feature of adult and pediatric cancers in general [52,54–56], and neuroblastoma in particular [49,50]. With their relatively low mutational burden [57], these genetically simple pediatric cancers resonate with the iterative, “high C/low N” deep-dive approach of the broader ROBIN program. The team also notes that insights from infrequent pediatric cancers have historically proven to be generalizable to more common adult cancers.

The KIDSROBIN study plan leverages recent advances in cancer genetics and progenitor cell fate mapping of DMG and NBL, integrating single-cell genomics, epigenetics, and proteomics with modern computational biology. The MCT is developing two ongoing large cooperative group studies (PNOC023 and COG ANBL1531) to collect biospecimens and clinical data in a well-coordinated and harmonized fashion, aiming for 24-25 high-quality participants per cancer type, which is critical for rare pediatric cancers. To date, 33 patients have been accrued to arms A and B of PNOC023, and ANBL1531 has completed accrual. Through agreements providing access to additional institutional and cooperative group resources, KIDSROBIN has also secured 2,039 serial MRI scans from 253 patients for DMG radiomics studies, and 8,057 clinical notes from 99 patients with DMG and 7,597 clinical notes from 182 patients with NBL for natural language processing (NLP) studies. Analyses using biospecimens and imaging data from these correlative studies are underway while the clinical data are maturing. Following these developments, preliminary data have been obtained for single-cell spatial profiling experiments using the Xenium 10x Genomics platform. Frozen tissue from ANBL1531 baseline and post-treatment second-look surgical samples have also been obtained to identify distinct cell populations that are differentially depleted or enriched following ^{131}I-MIBG therapy. Using ctDNA samples obtained at baseline and following ^{131}I-MIBG therapy, nucleosome positioning studies have been performed to identify differential changes in transcription factor profiles in samples that showed a subsequent rise in ctDNA. Changes in serum miRNAs following ^{131}I-MIBG therapy have been profiled, identifying a number of differentially modulated miRNAs. Paired baseline ^{123}I-MIBG diagnostic scans and ^{131}I-MIBG scans with accompanying SPECT/CT images have been analyzed and were able to estimate the tumor-absorbed dose per unit of administered activity that can be used to understand differential outcomes after ^{131}I-MIBG. For radiomics studies, auto-segmentation, volumetric analysis, and feature abstraction are in process for paired pre-/post-induction MRI scans. Together, these projects are generating comprehensive, multimodal datasets to be analyzed by the Data Science Core, which will develop predictive computational models of intratumor heterogeneity and guide the design of optimal therapeutic interventions (Figure 5).

Overall, KIDSROBIN integrates cutting-edge genomics, imaging, and computational biology to elucidate how intra-tumoral heterogeneity drives variable RT responses in pediatric cancers, with the goal that discoveries made in this program will not only inform precision strategies for pediatric neuro-oncology, but also be more broadly translatable to adult cancers.

ROBIN Working Groups

Admin Core

The Administrative Working Group (Admin WG) is pivotal to the success of the ROBIN U54 project, providing the administrative framework required for this complex, multi-institutional initiative [58]. Its primary purpose is to coordinate across research cores and scientific projects, ensuring smooth operations, effective collaboration, and timely achievement of milestones. Key activities include managing day-to-day operations of the project, overseeing the budget, ensuring compliance with NIH guidelines, and maintaining fiscal accountability to safeguard the project's financial stability. Communication is another critical function. Given ROBIN's multi-site design, the Admin WG facilitates clear and consistent communication by organizing regular virtual and in-person meetings, workshops, symposiums and progress updates. It ensures the effective flow of information across each core, fostering alignment across all project components. The Admin WG also supports ROBIN's educational mission, coordinating efforts with the CTC core to provide interdisciplinary training for the next generation of radiation scientists necessary to advance the fields of radiation oncology and immunology knowledge and research. It helps to organize workshops, seminars, lectures and training sessions that bring together experts from different disciplines to share knowledge and mentor trainees. Finally, the Admin WG plays a key role in disseminating research findings, both within the scientific community and throughout a broader general audience, coordinating publications, conference presentations, and other outreach activities, including websites and social media content. These activities ensure that ROBIN-generated knowledge is widely shared and has a meaningful impact on radiation oncology and immunology.

Cross Training Core

The Cross Training Core Working Group (CTC WG) leads the ROBIN U54 network's educational and professional development initiatives, fostering knowledge exchange and multidisciplinary expertise in radiation oncology, medical physics, bioinformatics, cancer, and radiation biology. Each center's CTC coordinates seminars, workshops, and training opportunities accessible throughout the network, including the Young Scientific Exchange Program (YSEP), which offers "mini-sabbaticals" to promote collaboration and cross-pollination. The OligoMET CTC aims to clarify the radiobiology of oligometastatic cancer, and it has developed hands-on workshops to teach data science skills, supported by cloud-based infrastructure and multimodal data for hybrid training, including digital pathology. The ImmunoRad CTC trains the next generation of scientists dedicated to radiation oncology, biology, and immunology through an integrated curriculum of seminars, wet-lab and in-person training, YSEP mini-sabbaticals, and one-year seed grants to promote innovation and knowledge transfer. The GenRad CTC focuses on decoding the biological underpinnings of response in combination systemic therapy and RT; offers the "Luminary Lecture Series", featuring leaders in radiation oncology and biology; and supports YSEP, allowing trainees to rotate through partner laboratories according to their career goals. Finally, METEORITE and KIDSROBIN have expanded the thematic and educational reach of the ROBIN CTC WG activities by integrating emerging areas such as data science, artificial intelligence, innovative programming, intra-tumoral heterogeneity, and pediatric oncology. A core mission of the ROBIN CTC program is to empower participants – regardless of their current career stage – to explore disciplines beyond their own, gain new skills, and cultivate curiosity and passion for cross-disciplinary discovery.

Data Sharing and Integrative Analysis Core

The ROBIN network is assembling unique multimodal longitudinal datasets capturing biological and imaging signatures from baseline, through RT, and into follow up. The Data Sharing and Integrative Analysis Core Working Group (DSIA WG) aims to maximize the value of these datasets for testing ROBIN hypotheses, exploratory analyses, and, ultimately, for use by external investigators. While each ROBIN center collects and stores data locally, the long-term goal is to curate and migrate all datasets into accessible NIH/NCI repositories. The DSIA WG leverages open-source tools, cloud platforms, and the NCI Cancer Research Data Commons to make ROBIN datasets FAIR (findable, accessible, interoperable, and reusable) [59]. Given the variety and complexity of ROBIN data types, robust strategies for transparent and reproducible science are prioritized [60], including user-friendly guides, dataset description papers, and computational notebooks. This requires harmonized ontologies, standardized storage, computational representations, and supporting workflows [61]. Another priority is to adopt compatible image analysis data representations and workflows, including multi-modality imaging as well as RT planning-specific data. XNAT, an open-source imaging informatics platform [62], has been adopted for secure, multi-user, scriptable data management. Throughout the ROBIN network, each center is developing their own data processes and platforms. The DSIA WG is investigating cloud-based and automated workflows [63,64], along with open source, user-friendly notebook analysis [65], to guide the loading and processing of ROBIN data and other complex elements of the ROBIN patient-specific datasets. Code resources are shared via GitHub or containerized distributions, some hosted on persistent cloud platforms (e.g., Seven Bridges). Available tools include Wikis, Jupyter notebooks, R Studio environments, and integration with pyCERR – a Python-based evolution of the Computational Environment for Radiotherapy Research with AI auto-segmentation tools and radiomics capabilities. By integrating curated datasets, standardized workflows, and accessible tools, the DSIA WG supports transparent, rerunnable science, cross-disciplinary training, and biomarker discovery – advancing ROBIN’s mission and serving broader radiation oncology research and data-sharing needs.

Cone-Beam Computed Tomography Core

Cone-Beam Computed Tomography (CBCT) is a standard tool in modern RT for accurate patient positioning and target localization during each treatment fraction, generating rich imaging information with clinical and research applications [66]. Daily CBCT scans offer high-temporal resolution, longitudinal data that support adaptive RT, dose painting, patient-specific quality assurance, and treatment verification, while providing insights into treatment response [67]. However, quantitative CBCT use is limited by scatter, noise, and metal artifacts, restricting most applications to setup based on anatomy [68]. Daily/fraction CBCT-based delta radiomics is a promising research field [69–71]. The CBCT Working Group (WG) is formed within the ROBIN consortium [72] to address these limitations and leverage CBCT data to identify key factors influencing RT response. Its coordinated objectives include standardizing acquisition protocols, harmonizing datasets across institutions, and enabling seamless data sharing. The WG also investigates CBCT’s potential in assessing TME dynamics and normal tissue changes during RT. In collaboration with the DSIA WG, the team is establishing a centralized, multi-stakeholder repository, and developing solutions for artifact correction and inter-institution reproducibility [73]. Cutting-edge solutions under exploration include high-quality HyperSight CBCT [74], AI-driven image enhancement [66,67,75], and integration with MR, CT, PET, and genomic datasets to improve prediction of treatment response and normal tissue toxicity. By validating CBCT-derived metrics biologically and correlating them with longitudinal imaging and genomic data, the CBCT WG aims to uncover underlying mechanisms of response. Its mission is to advance adaptive RT, unify imaging standards, and fully unlock CBCT's potential to enhance precision and improve patient outcomes in radiation oncology.

Conclusion

The ROBIN consortium supports a transformative effort for radiation oncology and biology, bridging the gap between cutting-edge biological research and clinical practice. Rooted in Dr. Norman Coleman's vision of RT as a dynamic "drug" rather than a purely technical tool, the initiative seeks to harness its biological impact for innovation in cancer care. Guided by Dr. Coleman's lifelong commitment to science, equity, and mentorship, ROBIN brings together diverse expertise to advance biology-driven research, leverage emerging technologies, and foster multidisciplinary collaboration to shape the future of cancer treatment. By integrating omics data, technologies, computational modeling, and multidisciplinary collaboration, the ROBIN consortium is advancing the understanding of how tumors and normal tissues respond to RT. Each center within the consortium focuses on a specific aspect of radiation oncology and biology, from metastatic processes and intra-tumoral heterogeneity to immune system and normal tissue interactions, genomic and TME dynamics, and response to combined therapy. The work carried out by these centers is not only expanding our knowledge of radiation's biological effects but also paving the way for more personalized and effective treatment strategies – for both adult and pediatric cancers.

The preliminary findings across the ROBIN network demonstrate the unique strengths of this collective endeavor. OligoMET has provided translational evidence that radiation reshapes tumor plasticity, metabolism, and immune contexture in oligometastatic prostate disease, setting the stage for biomarker-driven clinical trials. ImmunoRad has begun to unravel the complex crosstalk between radiation, the immune system, normal tissue, and the microbiome in rectal cancer, revealing early molecular signatures of response and systemic immune reprogramming. GenRad has shown that novel radiation-based combinations with ADC or ICI are both feasible and biologically active in bladder cancer and HNSCC, generating insights into mechanisms of efficacy and resistance. METEOR is illuminating how chemoradiation remodels the tumor microenvironment in cervical and pancreatic cancers, identifying myeloid-driven immunosuppressive pathways as promising therapeutic targets. KIDSROBIN, by leveraging pediatric cancers as a model for intra-tumoral heterogeneity, has generated multi-modal datasets that capture the evolutionary dynamics of childhood tumors, with broad implications for both pediatric and adult oncology.

Together, these efforts underscore ROBIN's global impact: advancing biological understanding of radiation responses, addressing health disparities, and creating scalable resources – from multimodal datasets to harmonized informatics platforms – that will serve the entire scientific community and humanity. Equally vital is the network's commitment to cultivating the next generation of scientists and clinicians through robust cross-training initiatives, ensuring that Dr. Coleman's legacy of mentorship continues to inspire future leaders in the field.

In summary, ROBIN is ushering in a new era of radiation oncology, where integrative biology, advanced technology, and clinical innovation converge to improve outcomes for patients worldwide. By bridging science and practice, and by fostering collaboration across institutions and borders, ROBIN is laying the foundation for precision, equity, and transformative progress in cancer care.

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Conflicts of Interest

F.G., C.LP., M.D., J.St., D.C., C.D.S., K.H., J.C., D.S.Y., N.S., A.S., J.Sc., C.R., D.HK., C.VB., J.N., Y.H., J.Y., L.R., L.M., G.H., R.B., J.L.N., J.L., X.Y., have no conflicts of interest.

T.C. is a co-founder of Gritstone Oncology and holds equity. T.C. acknowledges grant funding from Bristol-Myers Squibb, AstraZeneca, Illumina, Pfizer, An2H, and Eisai. T.C. has served as an advisor for Bristol-Myers, MedImmune, Squibb, Illumina, Eisai, AstraZeneca, and An2H. T.C. is an inventor on intellectual property and a patent held by MSKCC on using tumor mutation burden to predict immunotherapy response, which has been licensed to PGDx.

P.T. declares in the past 36 months: Grants/Contracts with NIH/NCI (R01CA271540 and U54CA273956), Department of Defense (W81XWH-21-1-0296), Royalties/Licenses: patent "Compounds and Methods of Use in Ablative Radiotherapy" (patent#: 9114158) licensed with royalties from Natsar Pharmaceuticals, consulting fees received from RefleXion Medical, Natsar Pharmaceuticals, Bayer Healthcare, Janssen, Pfizer, Lantheus, Novartis, Pfizer and Regeneron; patent "Compounds and Methods of Use in Ablative Radiotherapy" (patent #: 9114158) licensed with royalties from Natsar Pharmaceuticals, Leadership/Fiduciary role with NRG Oncology, ASTRO & AACR.

F.M. is a co-founder of and has equity in Harbinger Health, has equity in Zephyr AI, and serves as a consultant for both companies. She is also on the board of directors of Recursion Pharmaceuticals. F.M. declares that none of these relationships are directly or indirectly related to the content of this manuscript.

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Data Availability Statements:

No new data were generated or analyzed for this review.

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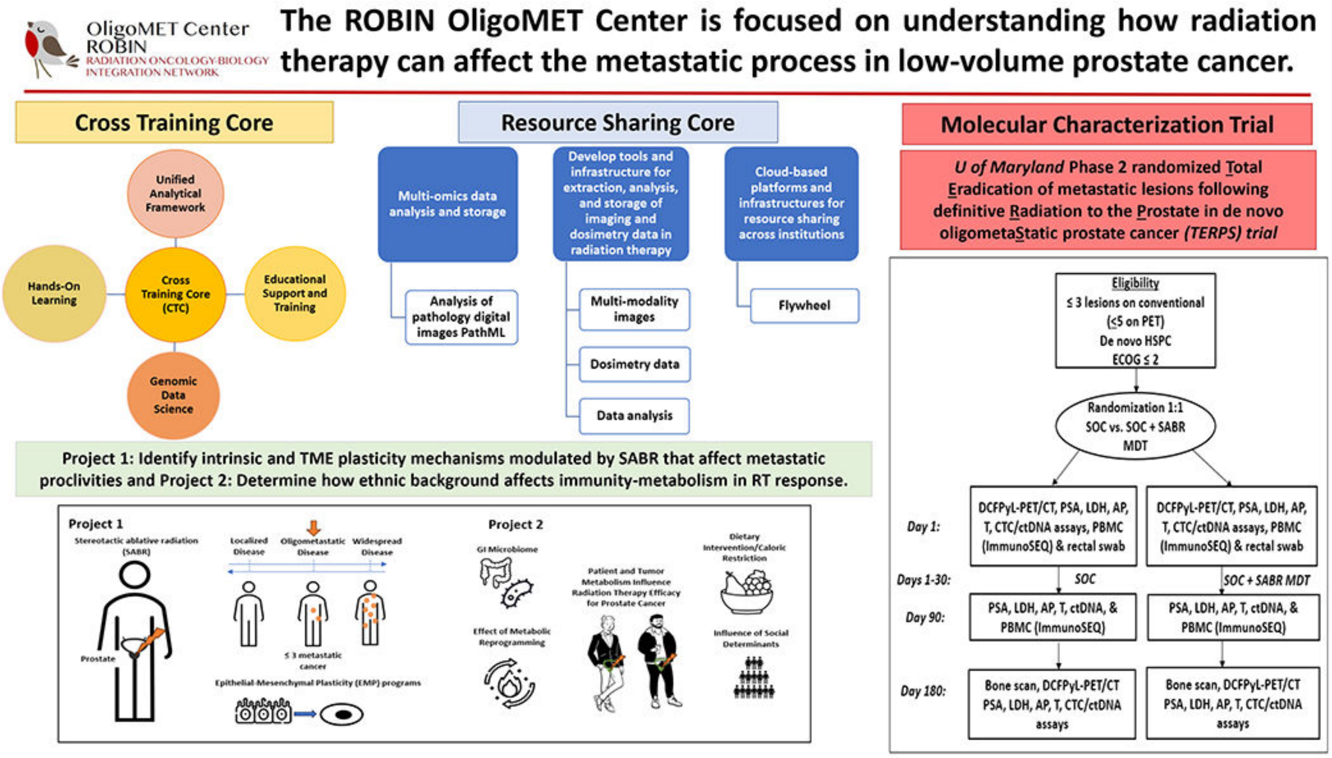


Figure 1.

OligoMET U54-ROBIN

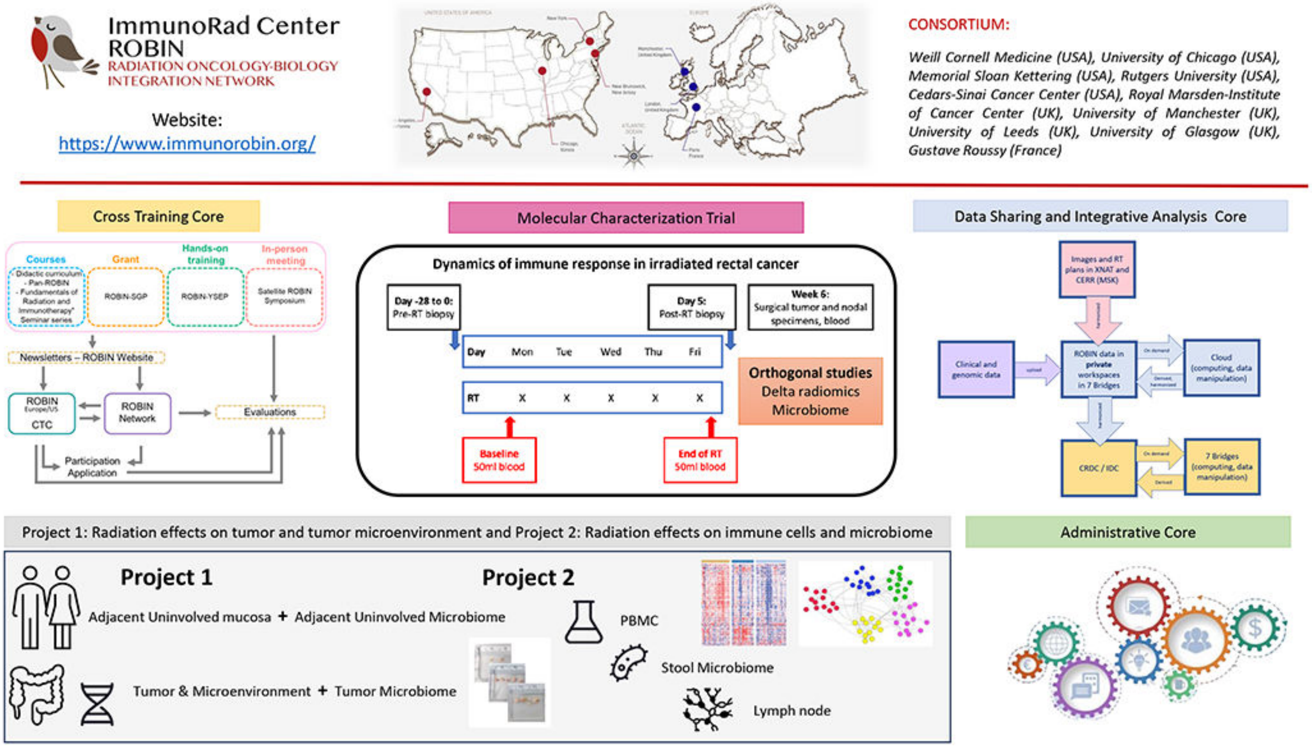


Figure 2.

ImmunoRad U54-ROBIN

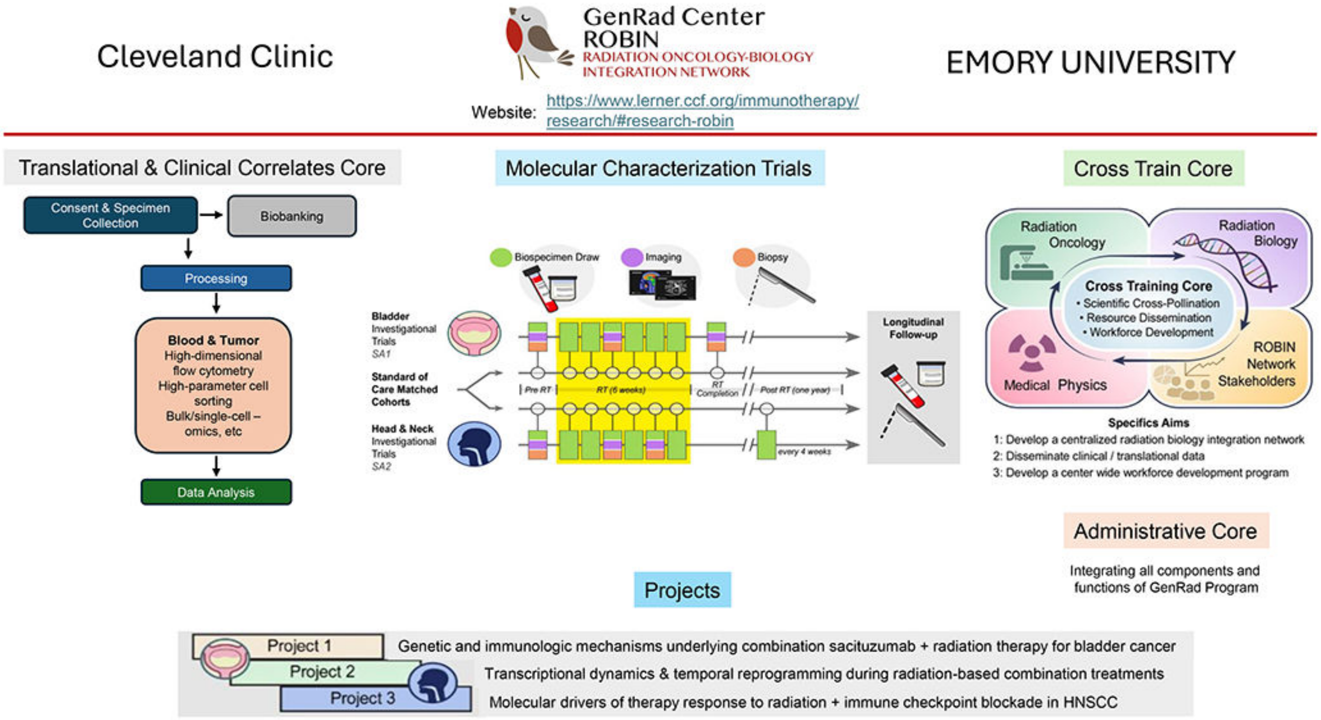
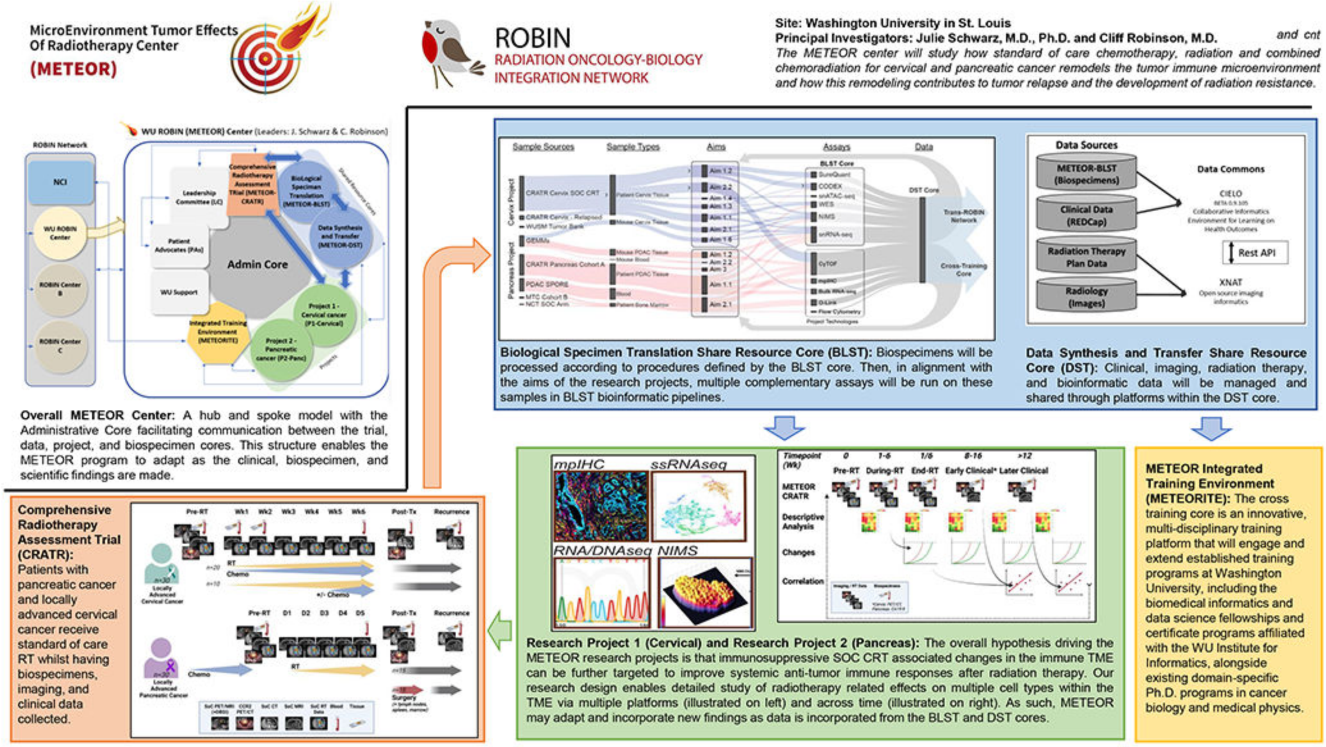


Figure 3.

GenRad U54-ROBIN



Site: Washington University in St. Louis
Principal Investigators: Julie Schwarz, M.D., Ph.D. and Cliff Robinson, M.D.
The METEOR center will study how standard of care chemotherapy, radiation and combined chemoradiation for cervical and pancreatic cancer remodels the tumor immune microenvironment and how this remodeling contributes to tumor relapse and the development of radiation resistance.

Overall METEOR Center: A hub and spoke model with the Administrative Core facilitating communication between the trial, data, project, and biospecimen cores. This structure enables the METEOR program to adapt as the clinical, biospecimen, and scientific findings are made.

Biological Specimen Translation Share Resource Core (BLST): Biospecimens will be processed according to procedures defined by the BLST core. Then, in alignment with the aims of the research projects, multiple complementary assays will be run on these samples in BLST bioinformatic pipelines.

Data Synthesis and Transfer Share Resource Core (DST): Clinical, imaging, radiation therapy, and bioinformatic data will be managed and shared through platforms within the DST core.

Comprehensive Radiotherapy Assessment Trial (CRATR): Patients with pancreatic cancer and locally advanced cervical cancer receive standard of care RT whilst having biospecimens, imaging, and clinical data collected.

Research Project 1 (Cervical) and Research Project 2 (Pancreas): The overall hypothesis driving the METEOR research projects is that immunosuppressive SOC CRT associated changes in the immune TME can be further targeted to improve systemic anti-tumor immune responses after radiation therapy. Our research design enables detailed study of radiotherapy related effects on multiple cell types within the TME via multiple platforms (illustrated on left) and across time (illustrated on right). As such, METEOR may adapt and incorporate new findings as data is incorporated from the BLST and DST cores.

METEOR Integrated Training Environment (METEORITE): The cross training core is an innovative, multi-disciplinary training platform that will engage and extend established training programs at Washington University, including the biomedical informatics and data science fellowships and certificate programs affiliated with the WU Institute for Informatics, alongside existing domain-specific Ph.D. programs in cancer biology and medical physics.

Figure 4.

METEOR U54-ROBIN (Created in BioRender. [Caruthers, D.]. [https://app.biorender.com/citation/697a49483c5096d22c8894fc] [https://app.biorender.com/citation/697a489a70aea632395491af])

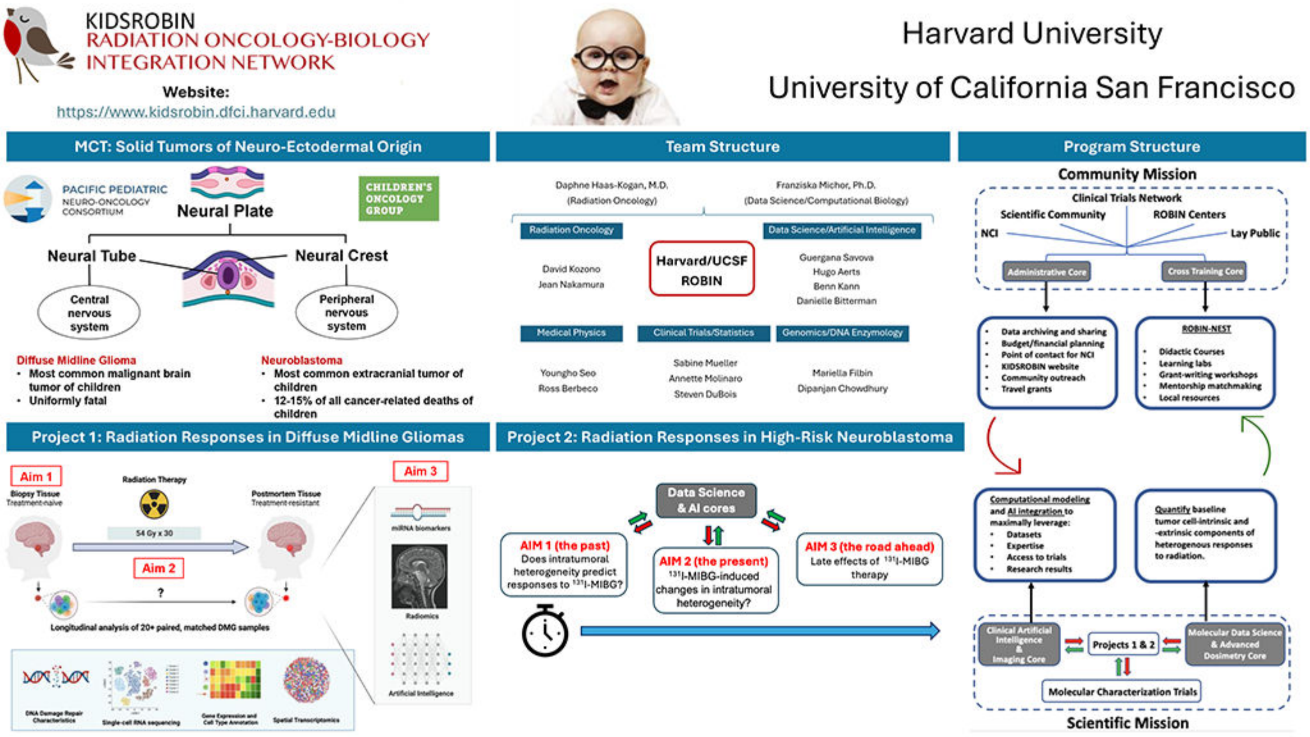


Figure 5.

KIDSROBIN U54-ROBIN (Created in BioRender. [Filbin, M.]. [https://app.biorender.com/citation/6983a09651b5b705811315be] [https://app.biorender.com/citation/6983a040d8559ee5b802e5e9])

Table 1.

ROBIN Centers and Websites

ROBIN Centers	**Website**
OligoMET	https://www.medschool.umaryland.edu/radonc/divisions/division-of-translational-radiation-sciences/robin-oligomet-center/
ImmunoRad	https://www.immunorobin.org/
GenRad	https://www.lerner.ccf.org/immunotherapy/research/#research-robin
METEOR	https://sites.wustl.edu/translationalradiation/meteor-center/
KIDSROBIN	https://kidsrobin.dfci.harvard.edu/