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ORIGINAL ARTICLE

National Cancer Institute support for targeted alpha-emitter therapy

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Abstract

Background Radiopharmaceutical targeted therapy (RPT) has been studied for decades; however, recent clinical trials demonstrating efficacy have helped renewed interest in the modality.

Methods This article reviews National Cancer Institute (NCI)'s support of RPT through communication via workshops and interest groups, through funding extramural programs in academia and small business, and through intramural research, including preclinical and clinical studies.

Results NCI has co-organized workshops and organized interest groups on RPT and RPT dosimetry to encourage the community and facilitate rigorous preclinical and clinical studies. NCI has been supporting RPT research through various mechanisms. Research has been funded through peer-reviewed NCI Research and Program Grants (RPG) and NCI Small Business Innovation Research (SBIR) Development Center, which funds small business-initiated projects, some of which have led to clinical trials. The NCI Cancer Therapy Evaluation Program (CTEP)'s Radiopharmaceutical Development Initiative supports RPT in NCI-funded clinical trials, including Imaging and Radiation Oncology Core (IROC) expertise in imaging QA and dosimetry procedures. Preclinical targeted a-emitter therapy (TAT) research at the NCI's intramural program is ongoing, building on foundational work dating back to the 1980s. Ongoing "bench-to-bedside" efforts leverage the unique infrastructure of the National Institutes of Health's (NIH) Clinical Center.

Conclusion Given the great potential of RPT, our goal is to continue to encourage its development that will generate the high-quality evidence needed to bring this multidisciplinary treatment to patients.

Keywords Radiopharmaceutical targeted therapy · Targeted alpha-emitter therapy · National Cancer Institute

Introduction

The United States National Cancer Institute's (NCI) mission is to lead, conduct, and support cancer research across the nation. As such, NCI strives to advance scientific knowledge in an effort to help all people live longer, healthier lives [1]. The unique potential of radiopharmaceutical targeted therapy (RPT), and particularly targeted a-emitter therapy (TAT), will benefit from high-quality research ultimately enabling improved cancer patient care.

In the early 2000s, the United States Food and Drug Administration (FDA) approved two new RPT antibodies directed against the CD-20 B-cell antigen expressed on the surface of non-Hodgkin lymphoma cells, ^{90}Y-ibritumomab tiuxetan (Zevalin [2002]; Spectrum Pharmaceuticals, Inc.) and ^{131}I-tositumomab (Bexxar [2003]; GlaxoSmithKline) [2–4]. Despite high response rates and long duration of response compared to unconjugated anti-CD20 antibodies,

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Zevalin and Bexxar were not often prescribed for patients for whom it was indicated (non-Hodgkin lymphoma) in part due to medical, logistical, and financial issues [5]. Observing these market failures certainly gave pause to academic and industry scientists alike, and interest in development of new radiopharmaceuticals waned.

To consider the current status, challenges, and potential advances of RPT, NCI and Society for Nuclear Medicine and Molecular Imaging (SNMMI) collaborated on a joint workshop that met in 2013 [6] and again in 2014 [7]. These workshops built upon prior workshops and symposia focused on RPT and TAT led by individual efforts or by collaborations between the Department of Energy (DOE), various NIH institutes, National Academy of Sciences, and/or SNMMI [8–10]. More recently, the NCI-SNMMI workshops provided a forum for stakeholders representing different disciplines in academia, industry, and the government agencies to discuss not only the advances, but also the challenges of RPT and how to address them [11, 12].

Currently, review of available data [13, 14] strongly indicates that the safety and efficacy of RPT could be improved by implementing individualized treatment planning based on a 3D (voxel) dosimetry, similar to that used to optimize external beam radiotherapy. Robust evidence in support of this concept is necessary, which requires multidisciplinary collaboration. The NCI brought together experts in the fields of nuclear medicine, radiation oncology, and medical physics for a workshop in 2018 to address issues and strategies of dosimetry for future clinical trials [11]. This meeting resulted in several publications [15–17] and creation of the NCI IROC Focus Group to provide support for RPT dosimetry methodology and expertise for principal investigators of NCI-funded RPT clinical trials.

To stimulate US small business interest in RPT, contract topics were issued by the NCI SBIR program in three consecutive years starting 2015. This initiative resulted in several successful SBIR RPT projects [18], some of them leading to clinical trials as described below.

To provide a forum for free discussion of ideas regarding the development and use of radionuclide therapies, the NCI Radiation Research Program (RRP) has helped convene an RPT Interest group. The roster of this group includes experts in radiochemistry, radiobiology, medical physics, nuclear medicine, and radiation and medical oncologists. Monthly presentations, each followed by discussion and question and answer sessions, allow for free-exchange of ideas and facilitate the establishment of best practices for clinical trials evaluating RPT. RRP is also involved in several RPT-related initiatives at the National Institute of Standards and Technology (NIST), Food and Drug Administration (FDA), Department of Defense (DOD), SNMMI, American Association of Physicists in Medicine (AAPM), and American Society for Radiation Oncology (ASTRO) to support RPT-related research and standards. In this article, we describe the NCI support for RPT, and particularly TAT, over the last decade.

Research and Program Grants (RPG)–funded projects

The NCI is the major supporter of RPT cancer research. Figure 1 surveys the portfolio landscape of NCI-funded RPT (including TAT) awards and respective award amounts in the period between 2010 and 2020. Figure 2 shows the mechanisms used to fund RPT and TAT projects. It is noteworthy that 13% of these grants were awarded to early-stage investigators, indicating their interest in this field. As shown in Fig. 3, institutions in 19 states received NCI funds for TAT-related research.

The funded projects cover a wide range of TAT-related research, from basic radiochemistry, radiobiology, and modeling of the effects of the radionuclide-emitted radiation on tumor and normal cells and tissues, through preclinical development of therapeutic radiopharmaceuticals to clinical trials. TAT projects currently funded by NCI are listed in Table 1, and have resulted in 330 publications. We encourage readers to visit the NIH RePORTER website [19] to learn more about these and other NIH-funded projects.

Cancer Therapy Evaluation Program Radiopharmaceutical Development Initiative

Most NCI-supported clinical trials are administered by the Cancer Therapy Evaluation Program (CTEP) [20], a part of NCI Division of Cancer Treatment and Diagnosis (DCTD) [21]. As part of CTEP drug development efforts, the Radiopharmaceutical Development Initiative (RDI) has been created for the clinical evaluation of novel theranostic radiopharmaceutical cancer therapies and diagnostics in collaboration with the pharmaceutical industry and academic investigators. Its goal is to complement industry development of these agents by supporting early-phase studies that test safety and possible signals of efficacy of radiopharmaceutical agents alone or in combination with other therapeutics that may add to their clinical benefit. This effort includes clinical trials in NCI-funded Clinical Trials Networks: Experimental Therapeutics Clinical Trials Network (ETCTN) and National Clinical Trials Network (NCTN). RPT trials conducted in these networks are supported by integrated centralized clinical and administrative services sponsored by NCI as presented in Fig. 4. Such services provide infrastructure to facilitate integration of molecular

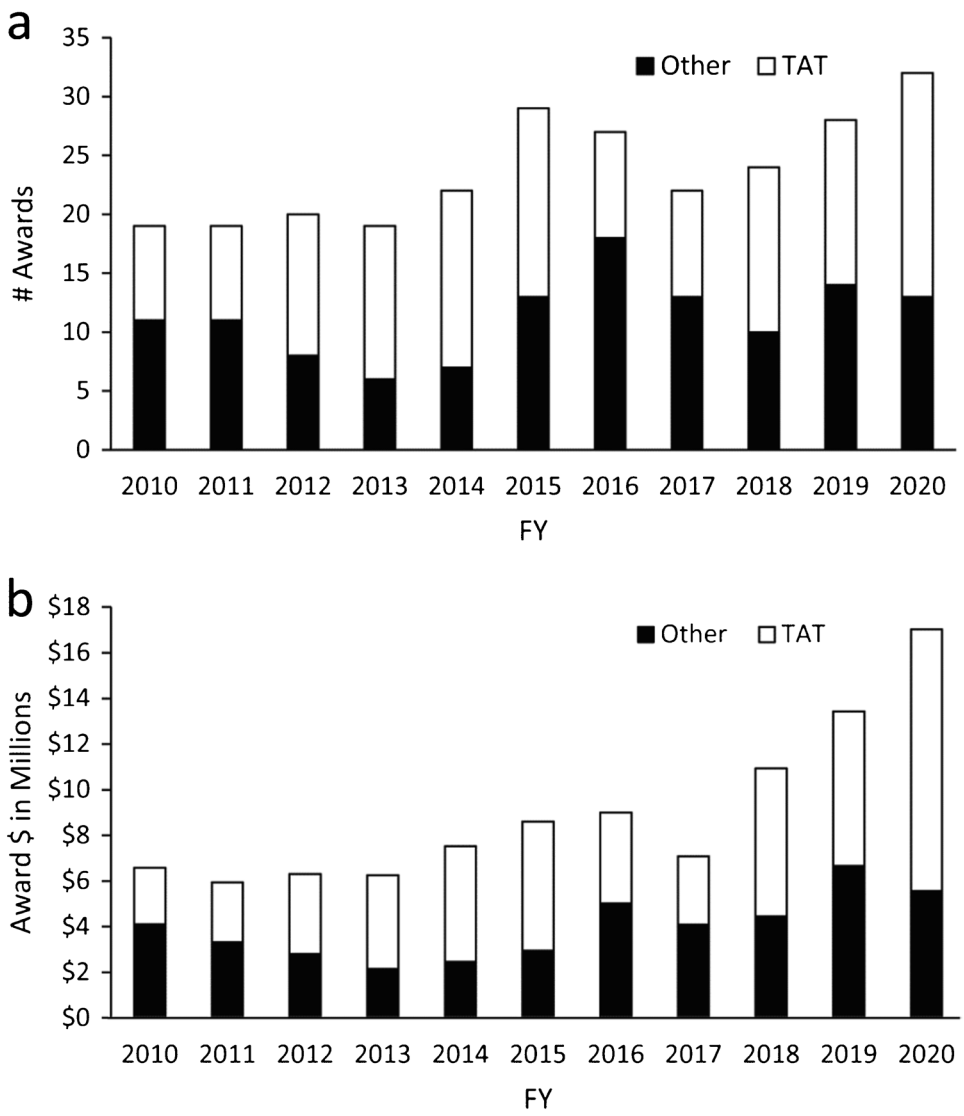

Fig. 1 Evolution of number (**a**) and funds (**b**) of active radiopharmaceutical targeted (RPT) grants over the last decade. FY, fiscal year; TAT, targeted alpha-emitter therapy

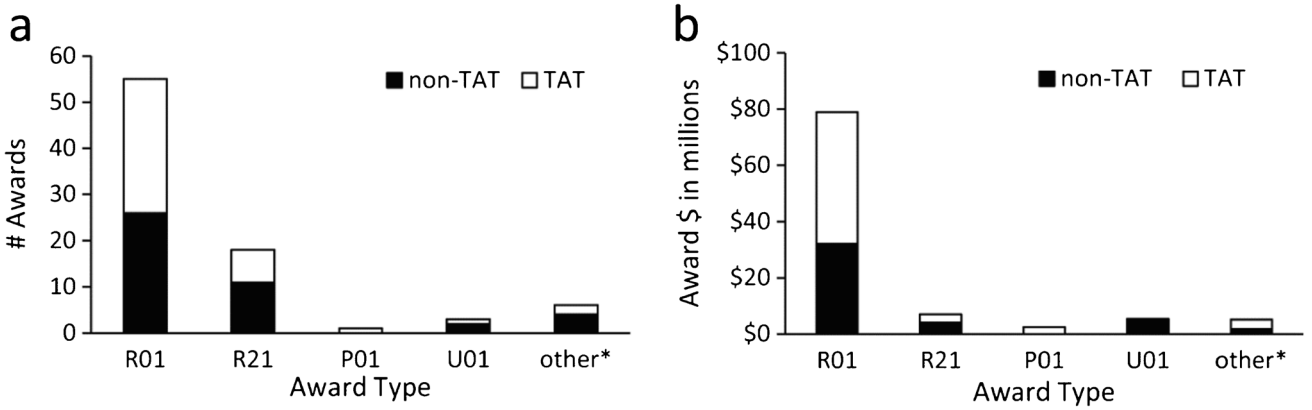

Fig. 2 Number (**a**) and funds (**b**) of radiopharmaceutical targeted (RPT) and targeted alpha-emitter therapy (TAT) grants awarded by different funding mechanisms (*other = R00, R03, R15, R37, U24)

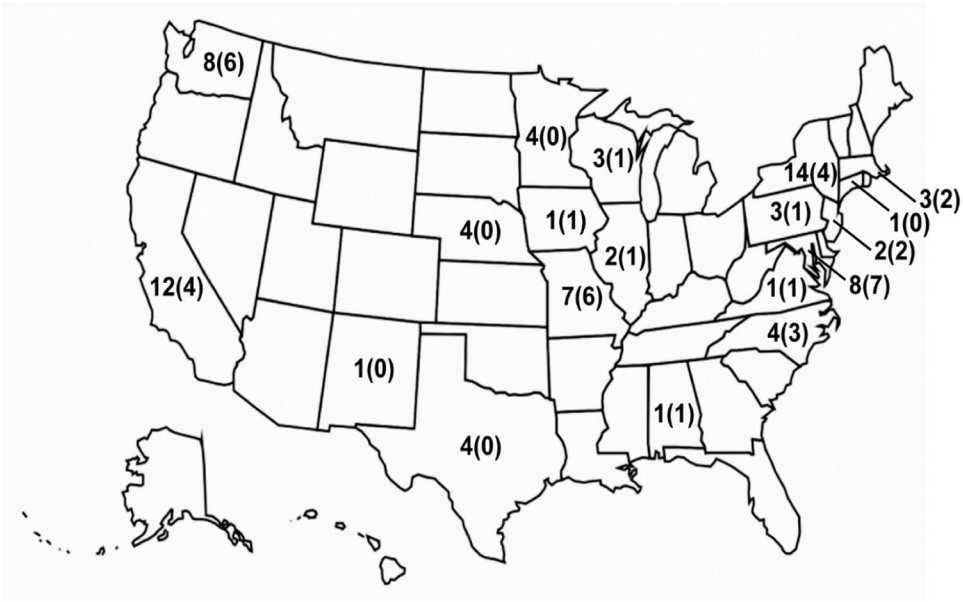

Fig. 3 Geographic distribution of radiopharmaceutical targeted (RPT) grants. Number in parentheses represent targeted alpha-emitter therapy (TAT) grants

Table 1 Currently funded TAT projects

Funding mechanism	Title
R21	Aptamer-Based Radiopharmaceuticals for the Targeted Alpha Particle Therapy of Prostate Cancer
R01	MIRDcell Version 3
R01	Small Molecule PSMA-Targeted Alpha Therapy
R01	Alpha-Particle Emitter Peptide Receptor Targeted Radionuclide Therapy for Neuroendocrine Tumors
R01	Astatine And Iodine Radiolabeled Monoclonal Antibodies
R01	Dose–Response in Radionuclide Therapy
R01	DOTA-based pre-targeting of alpha emitters
R01	Exploring the preclinical relevance of therapeutic radiolabeled daratumumab (anti-CD38) in combination with anti-CS1 CAR T cells as a novel combinatorial treatment for multiple myeloma
R01	Kallikrein-Targeted Alpha-Particle Therapy of Late-Stage Prostate Cancer
R01	Novel radioimmunoconjugates for targeted alpha-particle therapy of metastatic prostatic cancer
R01	Novel Reagents for Rapid and Stable Thiol-Based Bioconjugations
R01	Opening the Therapeutic Window for PSMA-Targeted Molecular Radiotherapy
R01	PARP-1 as a novel target for alpha-particle therapy in high-risk Neuroblastoma
R01	Pb-212 Peptide Receptor Targeted Prostate Cancer Therapy
U24	The TOPAS Tool for Particle Simulation, a Monte Carlo Simulation Tool for Physics, Biology and Clinical Research
R01	Combination Radiopharmaceutical Therapy and External Beam Radiotherapy
R01	The Radium-223 Combination Therapy Space; Improving Response and Clarifying Toxicities
P01	Molecular Targeted Radionuclide Therapy for Tumor Immunomodulation and Enhancing Immunotherapy Response
R37	Combining Targeted RIT and Synergistic Novel Agents to Eradicate AML

characterization, pharmacology, cancer biology, quantitative imaging, and radiation dosimetry into radiopharmaceutical-based clinical trials. Particularly important is the assistance provided by IROC to incorporate radiation dosimetry into RPT trials [22]. Research teams have the opportunity to add dosimetry to protocols, to ensure quality assurance, to acquire quantitative imaging, and to supplement data analyses through IROC.

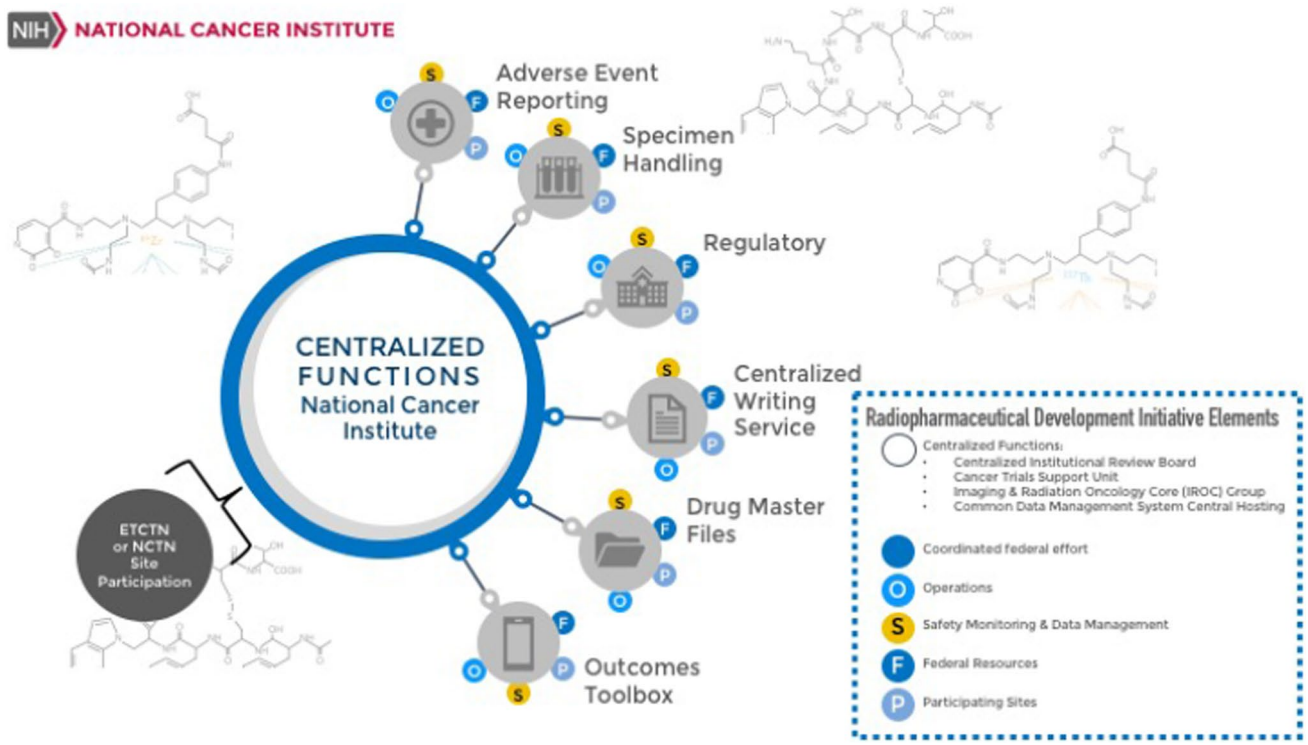

Fig. 4 Infrastructure created to support participants of NCI Clinical Trials Networks (https://www.cancer.gov/research/infrastructure/clinical-trials/nctn). Abbreviations: ETCTN, Experimental Therapeutics Clinical Trials Network; NCTN, National Clinical Trials Network

Table 2 RPT trials carried out at NCI Clinical Trials Networks: Experimental Therapeutics Clinical Trials Network (ETCTN) and National Clinical Trials Network (NCTN)

Title	Tumor origin	Network	NCT number
Olaparib and Radium-223 Dichloride in Treating Men with Metastatic Castration-Resistant Prostate Cancer that has Spread to the Bone	Prostate	ETCTN	NCT03317392
Radiation Medication (Radium-223 Dichloride) Versus Radium-223 Dichloride Plus Radiation Enhancing Medication (M3814) Versus Radium-223 Dichloride Plus M3814 Plus Avelumab (a Type of Immunotherapy) for Advanced Prostate Cancer Not Responsive to Hormonal Therapy	Prostate	ETCTN	NCT04071236
Testing the Addition of Radium Therapy (Radium-223 Dichloride) to the Usual Chemotherapy Treatment (Paclitaxel) for Advanced Breast Cancer Spread to the Bones	Breast	ETCTN	NCT04090398
Testing the Addition of an Anti-cancer Drug, Triapine, to the Usual Radiation-Based Treatment (Lutetium Lu-177 Dotatate) for Neuroendocrine Tumors	Neuroendocrine	ETCTN	NCT04234568
Testing the Addition of a New Anti-cancer Drug, Radium-223 Dichloride, to the Usual Treatment (Cabozantinib) for Advanced Renal Cell Cancer That Has Spread to the Bone (RadiCal)	Kidney	NCTN	NCT04071223

NCI-supported trials involve both early-phase and late-phase clinical studies of cancer treatments in high priority areas of unmet medical needs. RPT trials currently active, or approved and about to be open within the NCI Clinical Trials Networks, are listed in Table 2. More are in different stages of programmatic development and administrative review.

SBIR-supported projects

There is great potential for innovative, sophisticated, and mostly affordable technology to provide clinical benefit to patients. In addition to the RPG pool, NCI also supports the innovative biotechnology small businesses for research and development. Small businesses play an important role in translating technology from the lab to the clinic.

The NCI SBIR Development Center is the NCI's engine for accelerating technology translation, providing funding, mentoring, and networking assistance for small businesses with next-generation cancer technologies. The SBIR and Small Business Technology Transfer (SBIR/STTR) programs are focused by design: Phase I awards support shorter term (e.g., 1 year) feasibility or proof of concept projects, and phase II awards support longer (e.g., 2–3 years) research and development (R&D) efforts. According to the 1998–2018 National Economics Impacts report commissioned by NCI SBIR, the NCI investment in small businesses yielded $9.1B in total sales of products and services resulting from NCI SBIR/STTR phase II awards [23, 24].

Through SBIR/STTR programs, the United States Congress has mandated that Federal funds be set aside to strengthen the role of innovative small businesses in Federally funded research or research and development (R/R&D). Specifically, SBIR/STTR programs are called to (1) stimulate technological innovation; (2) use small business to meet Federal R/R&D needs; (3) foster and encourage participation by socially and economically disadvantaged SBCs (SDBs), and by women-owned SBCs (WOSBs), in technological innovation; and (4) increase private sector commercialization of innovations derived from Federal R/R&D, thereby increasing competition, productivity, and economic growth [25].

In FY2020, the NCI budget set aside for SBIR/STTR was $179 M. An analysis of the NIH RePORTER database indicated 1530 NCI SBIR/STTR phase I and II projects which were awarded across fiscal years 2010 and 2020, comprising a portfolio cutting across therapeutics, devices for cancer therapy, imaging, in vitro diagnostics, cancer biology, cancer control and epidemiology, and digital tool technologies. An analysis of abstract text for the terms "radiopharmaceutical" or "targeted alpha" returned a combination of 17 SBIR/STTR phase I and II projects supported by both grants and R&D contracts. Of these, TAT projects account for 17% of RPT projects funded by SBIR/STTR (Table 3). We expect that the recent positive outcomes from clinical trials of RPT will lead to increased interest by small businesses in TAT and more successful applications for SBIR support.

TAT at the NCI Intramural Program

Current preclinical TAT efforts at the NCI complement the Center for Cancer Research (CCR) Liver Cancer Program, which aims to improve diagnosis and treatment of patients with this disease. Hepatocellular carcinoma (HCC), the most common type of liver cancer, has radiosensitivity comparable to other epithelial tumors and both external and intra-arterially administered radiotherapy represent standard of care treatments for patients with locally advanced HCC [26]. The Laboratory of Molecular Radiotherapy is systematically assessing a range of biomolecule categories (e.g., antibodies and antibody derivatives, peptides, and small molecules) specific to tumor-selective targets for molecular radiotherapy in general and TAT specifically using HCC as a model system [27–29]. Biomolecules are being rigorously screened using in vitro (e.g., target binding in cell-free and isogenic cell-based assays, functionalization, radiolabeling, serum stability) and in vivo studies (e.g., pharmacokinetics, biodistribution, imaging characteristics, and dosimetry) prior to undergoing therapeutic studies (e.g., tumor control, survival, and dosimetry). This approach has the benefit of yielding promising HCC-selective imaging agents, which could be used in identifying recurrent disease after local ablative therapies, which remains a clinical diagnostic challenge. Having access to a platform where diverse biomolecules can be identified, validated, and systematically tested for TAT has the potential to help improve outcomes for patients with HCC. Furthermore, such an approach could be applied

Table 3 NCI SBIR and STTR projects on TAT awarded from FY2010 through FY2020

Award mechanism	Funding mechanism	Project title
SBIR R&D Contracts	R43	Targeted Radiopharmaceuticals for Uveal and Metastatic Melanoma
	R44	Targeted Ac-225-Radiopharmaceutical for Metastatic Uveal Melanoma
SBIR grants	R43	Targeted Theranostics for Metastatic Melanoma
	R43	Image Guided Therapy for Metastatic Melanoma
	R43	Production of Image-Guided Metastatic Melanoma Therapy Radiopharmaceuticals
	R44	Preclinical pharmacology, toxicology, biodistribution and dosimetry, and radionuclide production CMC validation for Pb-212 receptor targeted alpha-particle therapy for neuroendocrine tumors
	R44	GMP peptide manufacturing, pharmacology/toxicology, and scaled radionuclide production and validation for Pb-212 receptor targeted alpha-particle therapy clinical trials for metastatic melanoma

R43, SBIR phase I; *R44*, SBIR phase II

to other malignancies as well. Importantly, because these efforts are keenly focused on clinical translation, collaboration with medical, surgical, and radiation oncologists as well as nuclear medicine physicians occurs early in the developmental pipeline.

Much of the work being performed by the Laboratory of Molecular Radiotherapy builds on early foundational work by investigators at NCI. The radiochemistry and preclinical studies performed in the NCI Radiation Oncology Branch pioneered the development of chelating agents for radiometals, including alpha-emitters [30], specifically the CHX-A″ DTPA that was provided for the first in human clinical trial with ^{213}Bi at Memorial Sloan-Kettering. The chelating agent for ^{212}Pb (^{203}Pb for SPECT imaging), TCMC (1,4,7,10-tetraaza-1,4,7,10-tetra(2-carbamoylmethyl)cyclododecane), was also developed by this group and used in a large number of very large preclinical studies treating disseminated peritoneal malignancies to define optimal dose level and response, administration timing, combination strategies with chemotherapeutics, and mechanistic studies of actual in vivo tumor response to all of these therapies. These studies provided the support for the first in human clinical trial with ^{212}Pb at University of Alabama in Birmingham to treat patients with HER2-positive ovarian cancer [31]. Lastly, with all of these truly comparative studies performed, actual per unit dose therapeutic index value of ^{213}Bi, ^{212}Pb, ^{211}At, and ^{227}Th could be determined to optimize the appropriate choice of radionuclide, targeting agent in use in a specific preclinical model. These studies clearly established the need to define optimal choices of radionuclide and targeting agent (size and type), as both then apply to the disease presentation in scale and scope. However, while a-emitting radiopharmaceutical research has been an active area of preclinical research by NIH investigators since the 1980s [32, 33], clinical investigations using TAT did not start at the NIH Clinical Center (CC) until much more recently and benefitted from the boost given to the field by the FDA approval in 2013 of the first clinical α-emitting radiopharmaceutical, $^{223}RaCl_2$.

Collaborative efforts of diverse groups within the NIH including nuclear medicine, NCI radiochemistry, and other researchers such as Jeffrey Schlom and Thomas Waldmann resulted in important preclinical and clinical work that moved the field of radiopharmaceutical imaging and therapy with β^--emitters using chemistry developed by this same group. Early clinical work in the 1980s by prominent then-NIH intramural investigators such as Steve Larson and Jorge Carrasquillo focused on diagnostic [34] or primarily β^--emitting therapeutic agents [35, 36], studying issues such as route of administration [37] and the use of intact versus fragmented antibodies [38] as ligands for radiopharmaceutical therapy.

While there are many components to NCI's Intramural Program spread out over many locations, the majority of NCI's clinical research occurs at the NIH CC located on its main campus in Bethesda, MD. The NIH CC opened in 1953 and is one of the only hospitals in the world where the entirety of its operations is focused on clinical research. The CC has 200 inpatient beds and has been a strong proponent of the "bench-to-bedside" model, acting as the clinical testing ground for the many excellent ideas and hypotheses generated from the work of NCI's intramural preclinical investigators. In 2019, the NIH CC was home to 1534 active clinical protocols, of which 775 are interventional clinical trials, and recruited over 9000 new patients with over 95,000 outpatient visits and 42,000 inpatient days to these trials [39].

For the support of clinical trials related to either diagnostic or therapeutic radiopharmaceuticals, the NIH CC houses in total five positron-emission tomography/computed tomography (PET/CT) scanners, three single-photon emission computed tomography (SPECT) gamma-cameras, and two separate locations for radiolabeling compounds for human use including a good manufacturing practice (GMP) radiopharmacy with three medical cyclotrons for PET diagnostic agents. In addition to standard radioactive injection rooms located in several strategic areas throughout the hospital for outpatient radiopharmaceutical administrations, the NIH CC has two shielded hospital suites with staff trained for handling and taking care of radioactive patients. Having an area of the hospital dedicated to radiopharmaceutical treatment such as this allows for more intensive study of radioactive agents and makes possible investigations requiring labor/time-intensive pharmacokinetic or elimination studies, or administration levels high enough to require inpatient stays.

In 2018, the NIH CC administered a dose of a thorium (^{227}Th) TAT to a mesothelioma patient (NCT03507452), becoming the first in the USA to use a human ^{227}Th dose. Currently, there are a number of additional ongoing or planned clinical trials in the NCI Intramural Program using TATs based on ^{223}Ra, ^{225}Ac, and ^{212}Pb in a variety of malignancies including prostate cancer, neuroendocrine tumors, and hepatocellular carcinoma. Furthermore, as is true to the NIH bench-to-bedside paradigm, ongoing preclinical work with TAT by NCI investigators will fuel future clinical TAT investigations at the NIH CC [29, 40, 41].

Conclusions

Several radiopharmaceuticals have been approved for treatment of thyroid cancer, hepatic malignancies, bone metastases, neuroendocrine tumors, and adrenergic

receptor-expressing tumors. Recent positive reports from clinical trials of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive metastatic castration-resistant prostate cancers indicate high probability of imminent approval of this radiopharmaceutical to treat millions of patients all over the world [42]. Several other therapeutic radiopharmaceuticals are being developed by academia and industry, which may yield many more such agents to treat patients with various malignancies.

The NCI has had and continues to have a critical role throughout research and development of RPT by supporting, through peer review funding, extramural programs in academia and small businesses including preclinical and clinical studies. In addition, intramural research programs such as the Laboratory of Molecular Radiotherapy and the Targeted Radionuclide Therapy Section on the NIH campus are direct progeny of the early foundational work on TAT at the NIH.

Encouraged by the progress, there are areas in RPT where more research will accelerate clinical implementation. Defining how dose-rate and pharmacologic features influence therapy and differences between RPT-mediated tumor cell death and that of external beam radiotherapy, identifying targetable vulnerabilities to RPT that could yield therapeutic index gains especially when combined with rational inhibition of DNA repair pathway enzymes, and determining how the tumor microenvironment affects the aforementioned all can help better guide how, when, and if to deploy this modality.

Radiopharmaceuticals are already transforming how we use and think about radiation. Their unique features that merge clinical pharmacology, nuclear medicine, radiation, and medical oncology are a strength. Oncology is de facto multidisciplinary and RPTs fit at that interface. It is only through rigorous preclinical and clinical study that the existing agents have become available to patients in the clinic. The NCI recognizes the remarkable progress and future potential of these ongoing research and development efforts and the role RPT and TAT can play in fulfilling the mission to lead, conduct, and support cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives.

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Code availability Not applicable.

Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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