

Biology Contribution

Decreasing the Toxicity of Radiation Therapy: Radioprotectors and Radiomitigators Being Developed by the National Cancer Institute Through Small Business Innovation Research Contracts



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Summary

The Radiation Research Program at the National Cancer Institute collaborated with the Small Business Innovation Research Development Center to accelerate clinical translation of radiation-effect modulators. A summary of advances made through this collaboration has been previously described by Prasanna and colleagues (*Radiation Research*, 2015). Here, we

Purpose: The use of radioprotectors and radiomitigators could improve the therapeutic index of radiation therapy. With the intention of accelerating translation of radiation-effect modulators (radioprotectors and mitigators), the Radiation Research Program and SBIR (Small Business Innovation Research) Development Center within the National Cancer Institute issued 4 Requests for Proposals (RFPs) from 2010 to 2013. Twelve SBIR contract awards in total were made in response to the 4 RFPs from September 2011 through September 2014. Here, we provide an update on the status of SBIR contract projects for the development of radiation-effect modulators.

Methods and Materials: To assess the status of research and development efforts under the 4 RFPs on radiation-effect modulators, we searched PubMed for research articles, google.com for published abstracts, clinicaltrials.gov for ongoing or completed clinical trials, and company websites for press releases and other news. All information obtained and reported here is publicly available and thus protects the intellectual property of the investigators and companies.

Results: Of the 12 SBIR projects funded, 5 (42%) transitioned successfully from phase 1 to phase 2 SBIR funding, and among the Fast-Track contracts, this rate was

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give an update on the Small Business Innovation Research funding for the development of radiation-effect modulators, which has resulted in multiple early-phase clinical trials.

100% (3 of 3). The Internet search identified 3 abstracts and 6 publications related to the aims of the SBIR contracts. One-third of the companies (4 of 12) have successfully launched a total of 8 clinical trials to demonstrate the safety and efficacy of their investigational agents. Two drugs are in clinical trials for their indication as a radioprotector, and 2 drugs are under evaluation for their anticancer properties (an immunomodulator and a small molecule inhibitor).

Conclusions: The National Cancer Institute's SBIR has provided pivotal funding to small businesses for the development of radioprotectors and radiomitigators, which resulted in multiple early-phase clinical trials. Longer follow-up is needed to determine the full impact of these novel therapeutics that enter clinical practice. Published by Elsevier Inc.

Introduction

Radiation therapy (RT) plays a prominent role in the treatment of cancer, with more than half of all patients with cancer receiving RT during their cancer therapy. Irradiation is effective in killing cancer cells, but collateral radiation exposure of normal tissues surrounding the target area is inevitable and often results in treatment-related adverse effects. Highly conformal advanced radiation technologies can reduce the radiation dose to normal tissues and the related treatment toxicity; however, there remains a substantial need to further reduce treatment-related toxicities. The search for radioprotectors to prevent (pre-exposure) or radiomitigators to mitigate (postexposure) adverse effects has long been a holy grail in radiation drug development.^{1,2}

With the objective of developing radiation-effect modulators, the National Cancer Institute (NCI), the Radiation Research Program (RRP), and the SBIR (Small Business Innovation Research) Development Center previously issued 4 Requests for Proposals from 2010 to 2013. We have previously described the SBIR funding process and the general framework for the development of radiation-effect modulators, including the generation of preclinical and clinical evidence for development leading to regulatory approval and the need for stronger academic–industry partnerships.³ SBIR phase 1 contracts are for proof-of-concept and preliminary studies and are awarded a budget of up to \$300,000 for 9 months. Phase 2 contracts are awarded for up to \$2,000,000 over 2 years. Fast-Track contracts that include both phases allow applicants to immediately proceed to phase 2 funding after the completion of phase 1 milestones.

In a previous publication, we provided a summary of advances made with the SBIR contract-funding mechanism on development of radiation-effect modulators, a description of the application review process, a discussion on organ- or site-specific clinical needs for radiation-effect modulators, and a generalized framework for development. We also included a discussion on the value of the broader initiative with venture capital and pharmaceutical companies to capitalize on the advances already made in this field through efforts for the development of medical

radiation countermeasures for use after radiological and nuclear emergencies.³

Here, we provide an update on the SBIR-funded research contract topic on the development of radioprotectors and radiomitigators. Furthermore, this update provides matrices of success for radiation-effect modulator development and discusses important challenges and potential remedies. These findings will inform efforts to improve the contract-funding mechanism for future applicants.

Methods and Materials

National Institutes of Health (NIH) funding information is publicly available (<https://projectreporter.nih.gov/reporter.cfm>). The main differences between SBIR grants/contracts versus R01 funding mechanisms are provided in [Table 1](#). Using the NIH RePORTER website, we reviewed the proportion of SBIR contracts that progressed from phase 1 to phase 2 funding. To assess the effectiveness of the contracts mechanism in stimulating research and focused development of radiation protectors and mitigators, we compared the number of SBIR contracts and SBIR grants that were funded before, during, and after the period of contract solicitation (2011–2014). The SBIR grants funded under the NIH Omnibus SBIR grant solicitation have 3 regular receipt deadlines per year. We queried the NIH RePORTER database for NCI SBIR grants from 2009 to 2017 using the following search terms: radiation, mitigator, protector, modulator, radiomitigator, radioprotector, and radiomodulator.

Publicly available data on research progress were obtained using an Internet search. A PubMed search using the company name, investigational agent, and principal investigator of the SBIR contract was used to identify published research findings. Only research findings that were published after the award of the SBIR contract and that were related to the specific aims of the contracts were included. We searched clinicaltrials.gov (www.clinicaltrials.gov) using the company name and investigational agent to identify completed, active, recruiting, or withdrawn clinical

Table 1 Comparison of the SBIR grants and contracts with the R01 funding mechanism

SBIR grants	SBIR contracts	R01 grants
For-profit small businesses	For-profit small businesses	Nonprofit institutions, government agencies, and for-profit organizations
Researcher-initiated ideas are proposed via the Omnibus, or targeted grant solicitations are accepted	Targeted solicitation of research in areas specifically identified by the NIH awarding centers	Investigator-initiated ideas or can be solicited via a Request for Applications
Deliverables and milestones are identified by the applicant	Deliverables and milestones are recommended by NIH	Discrete, specified project in an area of an investigator's specific interest and based on the mission of the NIH
Governed by Federal Acquisition Regulations	Governed by the terms of the grant agreement (Code of Federal Regulations, OMB regulations, etc)	Governed by the terms of the grant agreement (Code of Federal Regulations, OMB regulations, etc)
Commercially focused product is mandatory	Commercially focused product is mandatory	Not necessarily product focused, emphasis on basic science

Abbreviations: NIH = National Institutes of Health; OMB = Office of Management and Budget; SBIR = Small Business Innovation Research.

trials. We also searched individual company websites for press releases or other news regarding progress in the development of the investigational agent. Finally, we performed a search on www.google.com by using the company name and investigational agent to capture any other information, including abstracts presented at research conferences and news articles, because these sources are not often captured in the scientific literature databases.

Results

Contract solicitation and phase 1/2 funding milestones

The contract solicitation for development of radioprotectors and radiomitigators resulted in the funding of 12 projects

during a 4-year period, compared with 11 grants over a 9-year period (Fig. 1). The public Internet search yielded 3 published abstracts and 6 manuscripts that were germane to the aims of the SBIR contracts, details of which are provided in Figure 1. Current progress and pertinent phase 1 and 2 milestones for the SBIR-funded research contracts that advanced to phase 2 are summarized in Table 2.^{4,12} In the overall cohort of SBIR contracts for protectors and mitigators, the rate of transitioning from phase 1 to phase 2 funding was 42% (5 of 12). All 3 groups that submitted Fast-Track applications successfully completed phase 1 milestones and transitioned to SBIR phase 2 funding, whereas 22% (2 of 9) of the standard phase 1 contracts advanced to phase 2 funding.

All companies except one (11 of 12) applied for phase 2 funding. Reasons that some phase 2 applications were not successful included weak preliminary evidence of efficacy,

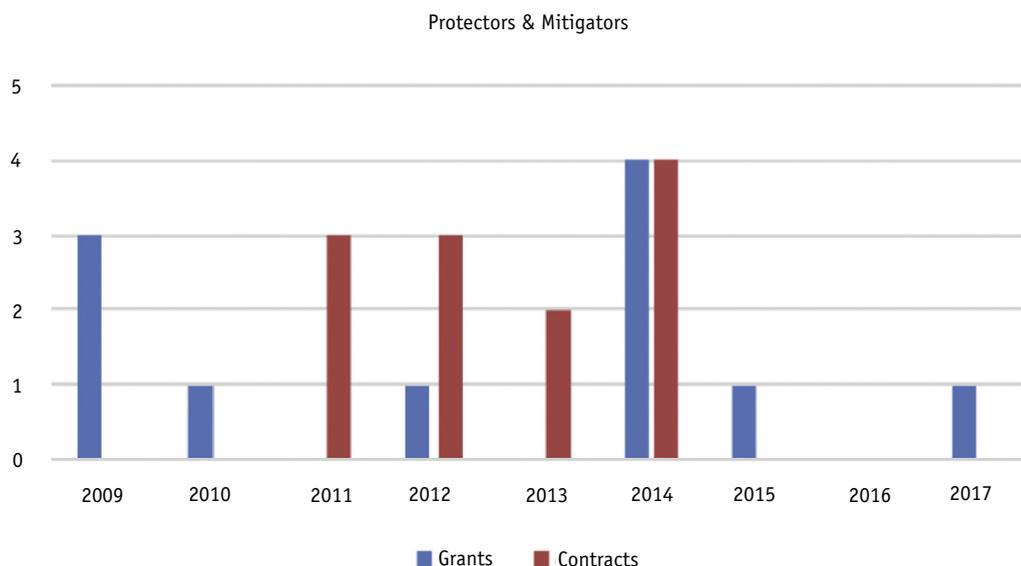


Fig. 1. Comparison of National Cancer Institute Small Business Innovation Research contracts versus grants for the development of radioprotectors and radiomitigators by fiscal year. Contract solicitation occurred from 2011 to 2014.

poor rationale for phase 2 specific aims, concerns regarding commercialization, and lack of evidence of outside funding and clinical strategy. Companies that completed phase 2 milestones also faced barriers to commercialization, including unexpected safety concerns, poor marketability, and lack of outside funding.

Clinical trials

One-third of companies (4 of 12) have successfully launched a total of 8 active (patients enrolled) or recruiting (seeking to enroll patients) clinical trials to demonstrate the safety and efficacy of their novel therapeutics funded by the SBIR contracts (Fig. 2). In 2 cases (BIO 300 and BMX-001), the drugs are being tested as radioprotectors, and 2 drugs (CBLB502 and ABC294640) are undergoing clinical testing for their anticancer properties (immunomodulator and small molecule inhibitor), rather than as a radioprotector or radiomitigator. Details of these compounds are given in the following sections.

BIO 300

BIO 300 is a synthetic genistein that was initially developed by the US Armed Forces Radiobiology Research Institute as a radiation countermeasure for soldiers and was later licensed by the Humanetics Corporation (Minneapolis, MN) and developed as a radiation countermeasure and also as a radiation-effect modulator for patients with cancer.¹³ Before the SBIR contract, Humanetics had successfully completed several efficacy and toxicology studies of BIO 300 in animal models, and a safety study in healthy human volunteers was initiated in 2007 (<https://clinicaltrials.gov/>; NCT00504335). The phase 1 SBIR contract was awarded in 2012 and funded preclinical efficacy studies in mice, and the phase 2 Fast-Track SBIR contract in 2014 funded the Investigational New Drug (IND) application and a clinical study of BIO 300 in patients receiving RT.

Humanetics obtained clearance from the US Food and Drug Administration on June 2, 2015, to proceed with a phase 1/2 clinical trial to evaluate the safety and efficacy of an oral suspension of BIO 300 in patients receiving chemoradiation for non-small cell lung cancer, with the goal of preventing radiation-induced pneumonitis and lung fibrosis.¹³ The trial is led by researchers at the Henry Ford Hospital (<https://clinicaltrials.gov/>; NCT02567799) and will assess dose-limiting toxicities and pharmacokinetics of BIO 300. Patients with stage II, III, or IV non-small cell lung cancer will receive BIO 300 with concurrent chemoradiation consisting of paclitaxel and carboplatin delivered over 6 weeks. The primary objective is to determine the adverse events associated with escalating doses of BIO 300 to determine the recommended dose. The trial also incorporates local control and survival endpoints, serum biomarkers, pulmonary function tests, 4-dimensional computed tomography ventilation scans to evaluate radiation lung fibrosis, and quality of life instruments.¹³

In addition, on September 12, 2017, Humanetics Pharmaceuticals (Edina, MN) was awarded a US patent for BIO 300 for use in patients with cancer who had solid tumors. Humanetics is also developing BIO 300 as a radiation countermeasure and a radioprotector for astronauts and has received funding from the National Institute of Allergy and Infectious Diseases (NIAID), the National Aeronautics and Space Administration, the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD).

BMX-001

BioMimetix (Englewood, CO) received funding to evaluate BMX-001, a metalloporphyrin antioxidant, as a radioprotector to prevent radiation mucositis in patients with head and neck cancer who are undergoing RT. In the phase 1 SBIR contract, BioMimetix sought to establish optimum dose and schedule to reduce xerostomia, mucositis, and inflammation in a mouse model and demonstrate that BMX-001 does not interfere with the efficacy of cisplatin and RT in vitro. The phase 2 SBIR contract in 2016 was funded to complete safety/toxicology required for an IND and conduct clinical trials to establish proof of concept efficacy of BMX-001 in the treatment of head and neck cancer.

A phase 1 clinical trial is underway for patients with squamous cell head and neck cancer who are undergoing standard radiation treatment with cisplatin in collaboration with Duke University (<https://clinicaltrials.gov/>; NCT02990468). BMX-001 is given subcutaneously with a loading dose before the start of chemoradiation, followed by biweekly doses for the duration of RT plus an additional 2 weeks. The primary goal of the study is to determine the maximum tolerated dose (MTD) of BMX-001, and other objectives include measuring reductions in radiation-induced mucositis and xerostomia.

BioMimetix has also received phase 1 and 2 SBIR grants for the development of BMX-001 as both a neuroprotector and a radiosensitizer for patients with gliomas. The phase 2 SBIR grant supported an ongoing phase 1/2 randomized clinical trial of patients with high-grade glioma receiving RT and temozolomide, with the hope of protecting against cognitive deterioration and improving survival in collaboration with Duke University (<https://clinicaltrials.gov/>; NCT02655601). The goal of the phase 1 portion is to determine the MTD of BMX-001, and phase 2 will assess safety and efficacy in a randomized design of chemoradiation with or without BMX-001.

BMX-001 is also being investigated in a phase 1 clinical trial of patients with anal cancer receiving definitive chemoradiation in collaboration with the University of Nebraska (<https://clinicaltrials.gov/>; NCT03386500). The primary objective of this trial is to determine the MTD of BMX-001 in patients receiving irradiation and concurrent 5-fluorouracil and mitomycin chemotherapy. Secondary objectives include toxicity measures, including rectal

Table 2 NCI's SBIR-funded contracts for radioprotectors and radiomitigators that advanced to phase 2

Indication	Company	Drug	Award type	Year started	Phase 1 aims
Enteritis	RxBio Inc, Johnson City, TN	DFMO	Phase 1	2011	Evaluate radioprotecting/radiomitigating effect on gastrointestinal injury and evaluate the effect on cancer radiosensitivity in cell lines and mouse models of colon cancer.
Lung injury	21st Century Therapeutics Inc, Detroit, MI	UTL-5g (TNF- α modulator)	Phase 1	2011	Examine whether the drug reduces tumor cell killing in vitro. Demonstrate efficacy in reducing radiation-induced lung injury in mice. Demonstrate that the drug does not affect tumor cell killing induced by radiation in mice.
Brain injury	Chrysalis Biotherapeutics, Galveston, TX	TP508 (biotherapeutic, 23 amino acid peptide)	Phases 1 and 2	2011, 2013	Optimize dose and schedule for vascular protection. Demonstrate protection to brain tissue from RT damage. Determine whether the protection is selective to normal tissue without altering radiation cell killing of cancer cells in mouse brains.
Mucositis	Buffalo BioLabs, Buffalo, NY	CBLB502 (TLR-5 agonist)	Phase 1	2012	Demonstrate protective effect to skin and oral mucosa after single- and fractionated multiple radiation dose regimens in mice. Demonstrate safety and efficacy of the drug in combination with RT.
Lung injury	Humanetics Pharmaceuticals, Minneapolis, MN	BIO 300 (synthetic genistein)*	Fast track	2012	Perform efficacy studies in mouse model to demonstrate inhibition of tumor growth and mitigation of radiation-induced lung damage.
Thrombocytopenia	Cellerant Therapeutics Inc, San Carlos, CA	CLT009, human allogenic MKP	Fast track	2012	Develop culture methods and assays for the expansion, characterization, and production of a sufficient quantity of MKP to initiate and complete IND enabling studies. Optimize media formulations, growth and culturing conditions, and scalability of production of MKP for preclinical efficacy, safety, and related IND studies using ex vivo cell culture expansion.
Mucositis	Terapio Inc, Austin, TX	RLIP76 (proteoliposome)	Phase 1	2013	Develop RLIP as a topical mouthwash. Test efficacy and systemic absorption and demonstrate no tumor protection in a hamster model.
Mucositis	Colby Pharmaceuticals, Menlo Park, CA	JVRSOD (gene therapeutic)	Fast track	2013	Perform dose- and schedule- optimization studies for protection from radiation-induced oral mucositis in mice. Identify and qualify a GMP manufacturing site.
Enteritis	Apogee Biotechnology Corp., Hummelstown, PA	ABC294640 (sphingosine kinase inhibitor)*	Phase 1	2014	Perform proof-of-concept studies to show that drug will reduce GI-ARS after abdominal or pelvic radiation in cell lines and mice.
Proctitis	Synedgen, Claremont, CA	PAAG-polyglucosamine	Phase 1	2014	Demonstrate efficacy in mitigation of radiation-induced proctitis in mice. Develop plans to demonstrate that PAAG does not protect cancer cells during RT.
Brain injury	Luna Innovations Inc, Roanoke, VA	Fullerene-based radioprotectors	Phase 1	2014	Perform preclinical studies to demonstrate safety. Perform preclinical studies to demonstrate effectiveness and improvement in therapeutic ratio in cell lines and animals.
Mucositis	BioMimetix JV, Englewood, CO	BMX-001 (metalloporphyrin antioxidant)*	Phases 1 and 2	2014, 2016	Establish optimum dose schedule to reduce xerostomia and mucositis in mice. Demonstrate that the drug does not interfere with standard of care in mice.

Abbreviations: DFMO = α -difluoromethylornithine; FDA = U.S. Food and Drug Administration; GI-ARS = gastrointestinal acute radiation syndrome; GMP = Good Manufacturing Practice; IND = Investigational New Drug; MKP = megakaryocyte progenitors; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; RT = radiation therapy; SBIR = Small Business Innovation Research; TGF- β = transforming growth factor beta; TLR-5 = toll-like receptor 5; TNF- α = tumor necrosis factor alpha.

* Advanced to clinical trials to improve radiation therapy outcomes through SBIR contracts.

Table 2 NCI's SBIR-funded contracts for radioprotectors and radiomitigators that advanced to phase 2 (*continued*)

Follow-up	Phase 2 aims	Follow-up
No information publicly available.		
Mice treated with UTL-5g and lung irradiation had lower plasma levels of TGF- β compared with mice treated with amifostine. ¹⁰		
No information publicly available.	Determine the following in mouse orthotopic xenograft models: (1) whether the drug also protects cancer stem cells or whether its protective effects are specific to neuroprogenitor cells; (2) whether the drug reduces RT-induced neuronal atrophy and cognitive impairment; and (3) how the drug affects neuroprogenitor cells and generation of new neurons.	TP508 stimulated endothelial cell sprouting from after irradiation and increased survival in mice. ¹²
CBLB502 reduced the severity of dermatitis and mucositis in mice that received single- and fractionated radiation regimens. ^{6,7} CBLB502 did not affect the radiosensitivity of orthotopically grown cancer in mice. ^{6,7}		
Mice treated with whole- thorax lung irradiation and BIO 300 had improved survival with less airway damage, edema, congestion, and fibrosis compared with untreated controls. ¹¹	File IND for the use of BIO 300 in patients receiving RT for NSCLC. Conduct a clinical study to assess safety and efficacy of BIO 300 in improving the morbidity and mortality in patients receiving RT.*	See text
No information publicly available.	Demonstrate large-scale manufacturing of MKP cells for clinical use and to develop assays for product characterization.	No information publicly available.
No information publicly available.		
Mice that received JVRSOD intraorally at the 3.0- or 30- μ g dose level had statistically significant improved survival. ⁸	Submit an IND application for JVRSOD. Perform safety and efficacy clinical trials in patients with head and neck cancer.*	No information publicly available.
Mice treated with ABC294640 and radiation had reduced histologic damage in the small intestine and improved survival. ⁴		
Irradiated mice treated with PAAG has less proctitis. ⁵		
No information publicly available.		
Systemic data were used to determine a FDA-approved safe starting dose for clinical study. ⁹	To complete safety/toxicology studies required for an IND and to support proof of concept clinical trials.*	No adverse effects occurred in mice and monkeys treated with BMX-001. ⁹

bleeding, pain, bowel movements, dysuria, hematuria, and dermatitis.

CBLB502

Buffalo BioLabs (Buffalo, NY) received funding to develop CBLB502, a toll-like receptor 5 agonist that activates NF- κ B (nuclear factor kappa B) signaling and has potential as a both a radiation countermeasure and a radioprotector for mucositis in patients with cancer. CBLB502 is also thought to have immunotherapeutic effects via activation of innate and adaptive immune responses. Most notably, Cleveland BioLabs (Buffalo, NY; formerly Buffalo BioLabs) received a DoD award of \$45 million to develop CBLB502 as a radiation countermeasure.¹⁴ In a phase 1 SBIR contract, Buffalo BioLabs demonstrated a protective effect of CBLB502 against radiation-induced damage to the normal mouth epithelium and improved recovery. A clinical trial of CBLB502 for patients with squamous cell head and neck cancer receiving cisplatin and RT was registered but later withdrawn (<https://clinicaltrials.gov/>; NCT01728480).

Cleveland BioLabs recently completed a phase 1 trial¹⁵ (not supported by SBIR funding) of CBLB502 in patients with locally advanced or metastatic solid tumors that determined the MTD of 30 μ g/d delivered subcutaneously on days 1, 4, 8, and 11. A phase 2 randomized placebo-controlled trial was initiated in the Russian Federation with CBLB502 as neoadjuvant therapy in treatment-naïve patients with primary colorectal cancer who are recommended for surgery (<https://clinicaltrials.gov/>;

NCT02715882). The primary objective is to determine the safety and tolerability of CBLB502, and secondary outcomes measures include assessment of immune cell changes in tumors and levels of cytokines in the blood.

ABC294640

Apogee Biotechnology (Hummelstown, PA) received a phase 1 SBIR contract in 2014 to evaluate an oral sphingosine kinase-2 inhibitor, ABC294640, as a therapy for gastrointestinal acute radiation syndrome in the mouse. Through inhibition of sphingosine kinase-2 inhibitor, ABC294640 blocks the formation of sphingosine 1-phosphate, a lipid-signaling molecule that promotes cancer growth and pathologic inflammation; thus, ABC294640 may have both antineoplastic and anti-inflammatory effects. A prior phase 1 clinical trial initiated in 2011 determined that ABC294640 was safe and well tolerated in patients with solid tumors.¹⁶ On March 31, 2015, RedHill Biopharma Ltd. acquired ABC294640 from Apogee for an upfront price of \$1.5 million, plus \$4 million in milestone payments, and tiered royalties starting in the low double-digits.¹⁷ Up to that point, Apogee had received cumulative funding in excess of \$14 million for the support of ABC294640, including grants and contracts from the NCI, BARDA, DoD, the US Food and Drug Administration Office of Orphan Products Development, and the Pennsylvania Department of Health.

RedHill Biopharma Ltd. (Tel Aviv, Israel) is currently pursuing the anticancer properties of ABC294640 (Yeliva) and has initiated clinical trials in cholangiocarcinoma,

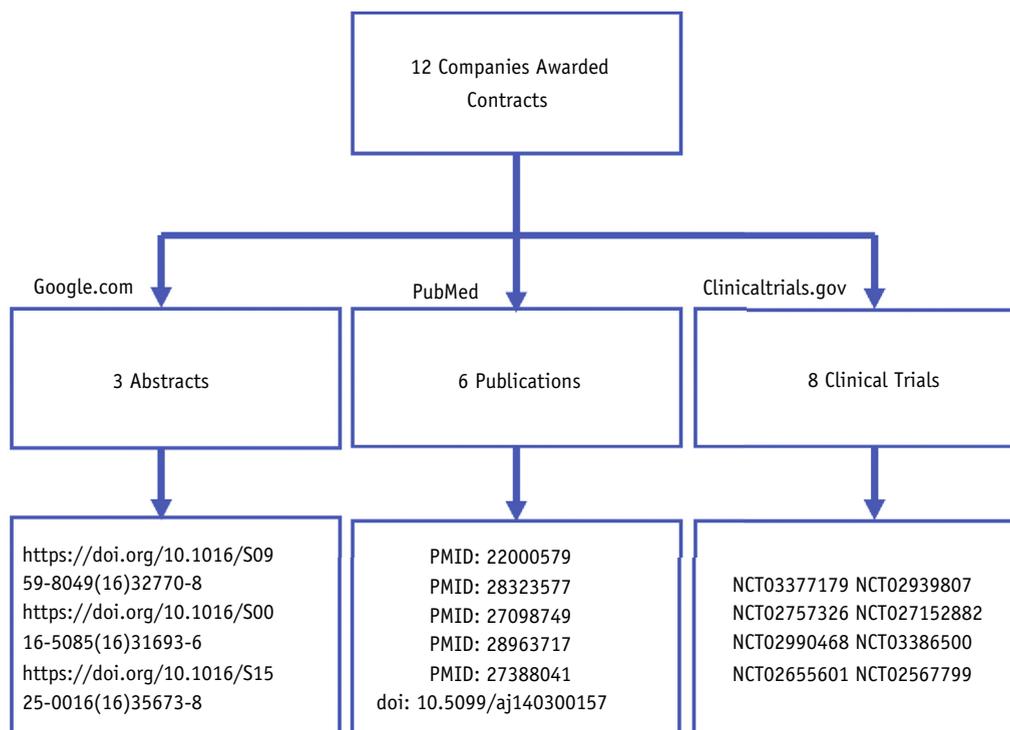


Fig. 2. Flowchart of abstracts, publications, and clinical trials obtained from public Internet search for progress on Small Business Innovation Research contracts for radioprotectors and radiomitigators.

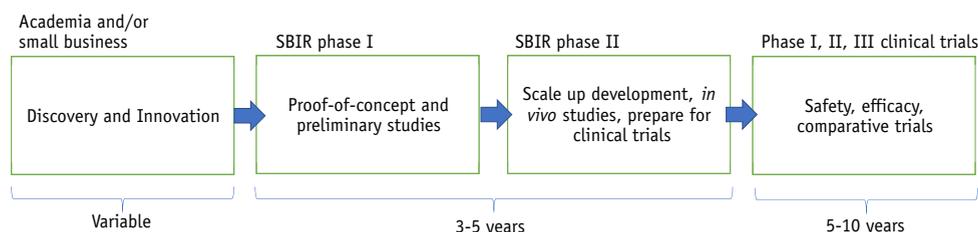


Fig. 3. Generalized time frame for the translation of radiation-effect modulator via SBIR pathway. *Abbreviation:* SBIR = Small Business Innovation Research.

hepatocellular carcinoma, and multiple myeloma (<https://clinicaltrials.gov/>; NCT03377179; NCT02939807; NCT02757326). ABC294640 will be delivered orally as a monotherapy in a phase 2 trial for patients with advanced cholangiocarcinoma, with a primary endpoint of response rate. A phase 2 trial of oral ABC294640 as second-line monotherapy for patients with advanced hepatocellular carcinoma also has a primary endpoint of response rate. For patients with refractory or relapsed multiple myeloma, RedHill has initiated a phase 1/2 trial of ABC294640 monotherapy with the goals of determining the MTD, response rate, and survival.

Discussion

The search for radioprotectors and radiomitigators has long remained an elusive goal in radiation oncology because of the fundamental challenge of developing a drug that selectively protects normal tissue without affecting tumor control.² This specific topic, development of radiation-effect modulators, issued via NCI SBIR contract initiative, was not only to develop radiation-effect modulators but also to encourage academic–industry partnerships in radiation oncology, with the ultimate overarching goal of improving RT outcomes, both in improving survival and posttreatment health-related quality of life. The mission of the SBIR program is to stimulate technological innovation, increase private-sector commercialization of federal research and development, increase small business participation in federally funded research and development, and foster participation by disadvantaged persons and companies in technological innovation. Serving these objectives of the NCI SBIR program, the RRP has been participating in many efforts geared to improve the outcome of RT. This specific contract topic was to translate promising therapies in the preclinical stage of development into clinical practice, which serves the public good.

In this article, we provide the current status and progress on development of radiation-effect modulators via congressionally mandated available funding from the SBIR Development Center since our last publication³ in 2015. Progress on SBIR contracts should primarily be evaluated on the basis of transitioning from phase 1 to 2 funding and on INDs, patents, and clinical trials rather than

publications; the latter matrix may be more relevant for traditional R01 grants. We found that 4 companies (33%) have advanced their drugs into clinical trials, 2 as radioprotectors and 2 as anticancer therapies (an immunomodulator and a small molecule inhibitor).

These outcomes illustrate the complex and varied paths toward launching clinical trials. Oftentimes, investigational agents have several potential properties (eg, radiation protector and sensitizer), and small businesses obtain a mix of private and public funding, including SBIR funding from multiple government agencies (eg, NCI or NIAID). Then, the drugs progress to clinical trials for the indications that demonstrated the most promising preclinical findings. None of the drugs in current clinical trials are being tested as radiomitigators, likely because some drugs are thought to have potential for both protection and sensitization. Therefore, the radiation-effect modulators currently in clinical trials are delivered with concurrent RT rather than after the completion of RT.

Three of the 4 drugs in active clinical trials (BIO 300, ABC294640, and CBLB502) were already fairly advanced in their development before receiving the SBIR contract. All 3 had received prior funding to investigate their potential as radiation countermeasures. In addition, ABC294640 had been evaluated in a phase 1 clinical trial in patients with cancer, and both BIO 300 and CBLB502 had already been studied in healthy human volunteers as part of their development as radiation countermeasures. However, BMX-001 was in an earlier stage of development at the time of the SBIR contract, and its company has progressed quickly into multiple clinical trials in patients with cancer. The phase 1 and 2 SBIR contracts in 2015 and 2016 funded preclinical efficacy and safety studies for BMX-001, which led to an IND and the initiation of 3 clinical trials in 2016 and 2017.

We also found that the contract-funding mechanism stimulated research into the development of radioprotectors because the contracts mechanism funded more projects in less than half the time compared with the grants mechanism. Furthermore, because contract applications are accepted once per year but grant applications are accepted 3 times per year, some companies might have missed the window to apply for the contract and instead applied for grant. Therefore, these results may even underestimate the influence of contract topics for stimulating research into a target area.

In general, the time frame for the development of radiation-effect modulators can range from 10 to 15 years, which is a multistep process and involves an acquisition of an agent from an academic laboratory for development and use in radiation oncology clinics after regulatory approval.³ However, with acquisition of a radiation-effect modulator from the available pipelines, such as from the radiation countermeasures development programs at NIAID or BARDA, and its focused development for use as radiation-effect modulator, this time frame could be significantly reduced to 5 to 10 years with funding from SBIR Development Center (Fig. 3). This result was evident in the development of BIO 300 and ABC294640, which have received funding from other federal agencies.

This article provides a useful benchmark for understanding the research progress for a cohort of SBIR contracts funded to develop radiation-effect modulators. The Internet search used was comprehensive and identified all pertinent publicly available information. However, this analysis also has some important limitations. We have only presented publicly available information and have excluded progress reports submitted to NCI and company data containing confidential/commercially sensitive information. It is possible that some research and development progress has been made on some drugs but remains confidential. However, we believe that substantial achievements are unlikely without any abstracts, publications, or clinical trials in the public domain. Given the considerable time and investment required for drug development, it may also be too early to determine research outcomes for some companies. Finally, this is a small cohort of radiation-effect modulator contracts, and it would be interesting to compare these results with other cohorts of NCI SBIR contracts and grants.

Conclusions

The RRP collaborated with the SBIR Development Center to issue 4 SBIR contract-funding solicitations for the development of novel radioprotectors and radiomitigators. NCI SBIR has provided small businesses with vital funding to complete the IND application, enabling preclinical studies for novel therapeutics. The SBIR contract mechanism has led to several early-phase clinical trials of radiation-effect modulators in patients with cancer and has facilitated collaboration between industry and academic medical centers. These efforts have provided a pipeline for novel innovations to be translated from the bench to the clinic, which can ultimately improve outcomes for patients with cancer.

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