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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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Abstract

Background: 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 (RRP) and SBIR (Small Business Innovation Research) Development Center within the National Cancer Institute (NCI) issued four Requests for Proposals (RFPs) from 2010 to 2013. Twelve SBIR contract awards in total were made in response to the four 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: To assess the status of research and development efforts under the four RFPs on radiation-effect modulators, we searched PubMed for research articles, [google.com](https://www.google.com) for published abstracts, [clinicaltrials.gov](https://www.clinicaltrials.gov) for ongoing or completed clinical trials, and company websites for press releases and other news. All information obtained and reported here are publicly available and hence protect the intellectual property of the investigators and companies.

Results: Of the 12 SBIR projects funded, 5 (42%) transitioned successfully from Phase I to Phase II SBIR funding, and among the Fast-Track contracts, this rate was 100% (3/3). The internet search identified 3 abstracts and 6 publications related to the aims of the SBIR contracts. One-third of the companies (4/12) 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

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indication as a radioprotector and two drugs are under evaluation for their anti-cancer properties (an immunomodulator and a small molecule inhibitor).

Conclusions: NCI'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.

SUMMARY

With the intention of accelerating the translation of radiation-effect modulators, the Radiation Research Program at the National Cancer Institute collaborated with the SBIR Development Center to accelerate clinical translation of radiation-effect modulators. A summary of advances made through this collaboration has been previously described (Prasanna et al. Rad. Res. 2015). Here, we give an update on the SBIR funding for the development of radiation-effect modulators, which has resulted in multiple early phase clinical trials.

Keywords

Radioprotectors; Radiomitigators; Small Business Innovation Research

INTRODUCTION

Radiation therapy plays a prominent role in the treatment of cancer, with over half of all cancer patients receiving radiation during their cancer therapy. Radiation 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 (post-exposure) 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 SBIR (Small Business Innovation Research) Development Center previously issued four Requests for Proposals (RFPs) through 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 I contracts are for proof-of-concept and preliminary studies and are awarded a budget of up to \$300,000 for 9 months. Phase II contracts are awarded for up to \$2,000,000 over 2 years. Fast-Track contracts which include both phases allow applicants to immediately proceed to Phase II funding upon the completion of phase I milestones.

In a previous publication, we provided a summary of advances made with SBIR contract funding mechanism on development of radiation effect modulators, description of the application review process, a discussion on organ/site specific clinical needs for radiation

effect modulators, a generalized frame work for development, and a discussion on the value of the broader initiative with venture capital and pharma 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, in this article, we provide an update on the SBIR funded research contract topic on the development of radioprotectors and radiomitigators. Further, 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

National Institutes of Health (NIH) funding information is publicly available at: <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 I to Phase II funding. To assess the effectiveness of the contracts mechanism in stimulating research and focused development of radiation protectors and mitigators, we compared the numbers 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 has three regular receipt deadlines per year. We queried the NIH RePORTER database for NCI SBIR grants from 2009–2017 using the following search terms: radiation, mitigator, protector, modulator, radiomitigator, radioprotector, and radiomodulator.

Publicly available data on research progress was obtained using an internet search. 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 were related to the specific aims of the contracts were included. We searched www.clinicaltrials.gov (www.clinicaltrials.gov) using the company name and investigational agent to identify completed, active, recruiting, or withdrawn clinical 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 www.google.com search using the company name and investigational agent to capture any other information including abstracts presented at research conferences and news articles, as these are not often captured in the scientific literature databases.

RESULTS

Contract Solicitation and Phase I/II Funding Milestones

The contract solicitation for development of radioprotectors and radiomitigators resulted in the funding of 12 projects during a 4-year period compared to 11 grants over a 9-year period (Figure 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 I and II milestones for the SBIR funded research contracts that advanced to Phase II are summarized in Table 2.^{4–12} In the overall cohort of

SBIR contracts for protectors and mitigators, the rate of transitioning from Phase I to Phase II funding was 42% (5/12). All three submitted Fast-Track applications successfully completed Phase I milestones and transitioned to SBIR Phase II funding, while 22% (2/9) of the standard Phase I contracts advanced to Phase II funding.

All but one company (11/12) applied for Phase II funding. Reasons that some Phase II applications were not successful included weak preliminary evidence of efficacy, poor rationale for Phase II specific aims, concerns regarding commercialization, and lack of evidence of outside funding, and clinical strategy. Companies that completed Phase II milestones also faced barriers to commercialization including unexpected safety concerns, poor marketability, and lack of outside funding.

Clinical Trials

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

BIO 300

BIO 300 is a synthetic genistein that was initially developed by the U.S. Armed Forces Radiobiology Research Institute (AFRRI) 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 cancer patients.¹³ Prior to 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 I SBIR contract was awarded in 2012 and funded pre-clinical efficacy studies in mice, and the phase II fast-track SBIR contract in 2014 funded the an IND application and a clinical study of BIO 300 in patients receiving radiotherapy.

Humanetics obtained FDA clearance on June 2, 2015 to proceed with a phase I/II 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 (NSCLC) 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 NSCLC 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 in order to determine the recommended dose. The trial also incorporates local control and survival endpoints, serum biomarkers, pulmonary function tests, 4D-CT ventilation scans to evaluate radiation lung fibrosis, and quality of life instruments.¹³

Additionally, on September 12, 2017, Humanetics Pharmaceuticals (Edina, MN) was awarded a US patent for BIO 300 for use in cancer patients with 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), National Aeronautics and Space Administration (NASA), Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD).

BMX-001

BioMimetix (Engelwood, CO) received funding to evaluate BMX-001, a metalloporphyrin antioxidant, as a radioprotector to prevent radiation mucositis in patients with head and neck cancer undergoing radiotherapy. In the Phase I SBIR contract, BioMimetix sought to establish optimum dose and schedule to reduce xerostomia, mucositis and inflammation in a mouse model and demonstrate BMX-001 does not interfere with the efficacy of cisplatin and radiation therapy *in vitro*. Phase II 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 I clinical trial is underway for patients with squamous cell head and neck cancer undergoing standard radiation treatment with cisplatin in collaboration with Duke University (<https://clinicaltrials.gov/>; NCT02990468). BMX-001 is given subcutaneously with a loading dose prior to the start of chemo-radiation followed by bi-weekly doses for the duration of radiation therapy plus an additional two 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 I and II SBIR grants for the development of BMX-001 as both a neuroprotector and a radiosensitizer for patients with gliomas. The Phase II SBIR grant supported an ongoing Phase I/II randomized clinical trial of patients with high grade glioma receiving radiation therapy and temozolimide, 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 I portion is to determine the MTD of BMX-001, and Phase II 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 I 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 radiation and concurrent 5-FU and mitomycin chemotherapy. Secondary objectives include toxicity measures, including rectal 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 signaling and has potential as a both a radiation countermeasure and a radioprotector for mucositis in cancer patients. 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 phase I 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 radiation therapy was registered but later withdrawn (<https://clinicaltrials.gov/NCT01728480>).

Cleveland Biolabs recently completed a Phase I trial (not supported by SBIR funding) of CBLB502 in patients with locally advanced or metastatic solid tumors that determined the MTD of 30 µg/day delivered subcutaneously on days 1, 4, 8, 11.¹⁵ A Phase II 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 (Hammelstown, PA) received a Phase I SBIR contract in 2014 to evaluate an oral sphingosine kinase-2 (SK2) inhibitor, ABC294640, as a therapy for gastrointestinal acute radiation syndrome (GI-ARS) in mouse. Through inhibition of SK2, ABC294640 blocks the formation of sphingosine 1-phosphate, a lipid signaling molecule that promotes cancer growth and pathologic inflammation; thus, ABC294640 may have both anti-neoplastic and anti-inflammatory effects. A prior Phase I 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 FDA Office of Orphan Products Development, and the Pennsylvania Department of Health.

Redhill Biopharma Ltd. (Tel Aviv, Israel) is currently pursuing the anti-cancer properties of ABC294640 (Yeliva®) and has initiated clinical trials in cholangiocarcinoma, hepatocellular carcinoma, and multiple myeloma (<https://clinicaltrials.gov/NCT03377179>; NCT02939807; NCT02757326). ABC294640 will be delivered orally as a mono-therapy in a Phase II trial for patients with advanced cholangiocarcinoma with a primary endpoint of response rate. A Phase trial of oral ABC294640 as second line mono-therapy 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 I/II trial of ABC294640 mono-therapy 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 due to 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 radiation therapy outcomes, both in terms of improving survival and post-treatment 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, RRP has been participating in many efforts geared to improve the outcome of radiation therapy. This specific contract topic was to translate promising therapies in the pre-clinical 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 publication in 2015.³ Progress on SBIR contracts should primarily be evaluated on the basis of transitioning from Phase I to II funding, Investigational New Drugs (INDs), patents, and clinical trials rather than publications; latter matrix may be more relevant for traditional R01 grants. We found that four companies (33%) have advanced their drugs into clinical trials, two as radioprotectors and two as anti-cancer therapies (an immunomodulator and a small molecule inhibitor). These outcomes illustrate the complex and varied paths towards launching clinical trials. Oftentimes, investigational agents have several potential properties (e.g., radiation protector and sensitizer), and small businesses obtain a mix of private and public funding, including SBIR funding from multiple government agencies (e.g., NCI, NIAID, etc). Then, the drugs progress forward to clinical trials for the indications that demonstrated the most promising pre-clinical 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; thus, the radiation-effect modulators currently in clinical trials are delivered with concurrent radiotherapy rather than after the completion of radiotherapy.

Three of the four drugs in active clinical trials (BIO 300, ABC294640, and CBLB502) were already fairly advanced in their development prior to receiving the SBIR contract. All three had received prior funding to investigate their potential as radiation countermeasures. Additionally, ABC294640 had been evaluated in a Phase I clinical trial in cancer patients 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 the company has progressed rather quickly into multiple clinical trials in cancer patients. The Phase I and II SBIR contracts in 2015 and 2016 funded pre-clinical efficacy and safety studies for BMX-001, which led to an IND and initiation of three clinical trials in 2016 and 2017.

We also found that the contract funding mechanism stimulated research into the development of radioprotectors, since the contracts mechanism funded more projects in less than half the time compared to the grants mechanism. Furthermore, since contract applications are accepted once per year but grant applications are accepted three 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 timeframe for the development of radiation-effect modulators can range from 10–15 years, which is a multi-step process and involves an acquisition of an agent from an academic laboratory for development and use in radiation oncology clinics after regulatory approval³. However, 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 timeframe could be significantly reduced to 5–10 years with funding from SBIR Development Center (Fig. 3). This was evident in the development of BIO 300 and ABC294640, which have received funding from other federal agencies.

This manuscript 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 excluding progress reports submitted to NCI progress 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, though we believe 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.

CONCLUSION

The RRP collaborated with the SBIR Development Center to issue four 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 enabling pre-clinical studies for novel therapeutics. The SBIR contract mechanism has led to several early phase clinical trials of radiation effect modulators in cancer patients 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 cancer patients.

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Figure 1.
Comparison of NCI SBIR contracts vs grants for the development of radioprotectors and radiomitigators by fiscal year. Contract solicitation occurred from 2011–2014.

Figure 2.
Flowchart of abstracts, publications, and clinical trials obtained from public internet search for progress on SBIR contracts for radioprotectors and radiomitigators.

Figure 3.
Generalized timeframe for the translation of radiation-effect modulator via SBIR pathway

Table 1.

Comparison of the Small Business Innovation Research (SBIR) grants and contracts with the R01 funding mechanism.

SBIR Grants	SBIR Contracts	R01 Grants
For-profit small businesses	For-profit small businesses	Non-profit 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 (FAR)	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: OMB: Office of Management and Budget; NIH: National Institutes of Health.

Table 2.

NCI's SBIR Funded Contracts for Radioprotectors and Radiomitigators that Advanced to Phase II. Specific aims involving humans are bolded.

Indication	Company	Drug	Award Type	Year Started	Phase I Aims	Follow up	Phase II Aims	Follow up
Enteritis	RxBio Inc., Johnson City, TN	DFMO (α -difluoromethylornithine)	Phase I	2011	Evaluate radioprotecting/radiomitigating effect on gastrointestinal injury and evaluate the effect on cancer radiosensitivity in cell lines and mouse models of colon cancer.	No information publicly available.		
Lung injury		UTL-5g (TNF- α modulator); 21st Century Therapeutics Inc., Detroit, MI	Phase I	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.	Mice treated with UTL-5g and lung irradiation had lower plasma levels of TGF- β compared to mice treated with amifostine. ¹⁰		
Brain injury	ChrysalisBiotherapeutics, Galveston, TX	TP508 (biotherapeutic ic, 23 amino acid peptide)	Phase I and II	2011, 2013	Optimize dose and schedule for vascular protection. Demonstrate protection to brain tissue from radiotherapy damage. Determine whether the protection is selective to normal tissue without altering radiation cell killing of	No information publicly available.	Determine the following in mouse orthotopic xenograft models: 1. Whether the drug protects also cancer stem cells or whether its protective effects are specific to neuroprogenitor cells; 2. Whether the drug reduces radiotherapy-	TP508 stimulated endothelial cell sprouting from after irradiation and increased survival in mice. ¹²

Indication	Company	Drug	Award Type	Year Started	Phase I Aims	Follow up	Phase II Aims	Follow up
					cancer cells in mouse brains.		induced neuronal atrophy and cognitive impairment; and 3. How the drug affects neuroprogenitor cells and generation of new neurons.	
Mucositis	Buffalo Biolabs, Buffalo, NY	CBLB502 (TLR-5 agonist)	Phase I	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 radiotherapy.	CBLB502 reduced 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}		
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.	Mice treated with whole thorax lung irradiation and BIO 300 had improved survival with less airway damage, edema, congestion, and fibrosis compared to untreated controls. ¹¹	File IND for the use of BIO 300 in patients receiving radiotherapy for NSCLC. Conduct a clinical study to assess safety and efficacy of BIO 300 in improving the morbidity and mortality in patients receiving radiation therapy.	See text
Thrombocytopenia	Cellerant Therapeutics Inc., San Carlos, CA	CLT009, human allogenic megakaryocyte progenitors	Fast track	2012	Develop culture methods and assays for the expansion, characterization	No information publicly available.	Demonstrate large-scale manufacturing of megakaryocyte	No information publicly available.

Indication	Company	Drug	Award Type	Year Started	Phase I Aims	Follow up	Phase II Aims	Follow up
					and production of sufficient quantity 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 <i>ex vivo</i> cell culture expansion.		progenitor cells for clinical and to develop assays for product characterization.	
Mucositis	Terapio Inc., Austin, TX	RLIP76 (proteoliposo me)	Phase I	2013	Develop RLIP as a topical mouthwash. Test efficacy, systemic absorption and demonstrate no tumor protection in a hamster model.	No information publicly available.		
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.	Mice that received JVRSOD intraorally at the 3.0 or 30 mg 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.
Enteritis	Apogee Biotechnology Corp., Hummelstown, PA	ABC294640 (sphingosine kinase inhibitor)	Phase I	2014	Perform proof-of-concept studies to show that drug will reduce GI-ARS following abdominal or	Mice treated with ABC294640 and radiation had reduced histologic damage in the		

Indication	Company	Drug	Award Type	Year Started	Phase I Aims	Follow up	Phase II Aims	Follow up
Proctitis	Synedgen, Claremont, CA	PAAG-ployglucosa mine	Phase I	2014	Demonstrate efficacy in mitigation of radiation-induced proctitis in mice. Develop plans to demonstrate that PAAG does not protect cancer cells during radiotherapy.	Irradiated mice treated with PAAG has less proctitis. ⁵		
Brain injury	Luna Innovations Inc., Roanoke, VA	Fullerene-based radioprotectors	Phase I	2014	Perform preclinical studies to demonstrate safety. Perform preclinical studies to demonstrate effectiveness and improvement in therapeutic ratio in cell lines and animals.	No information publicly available.		
Mucositis	BioMimetix JV, Englewood, CO	BMX-001 (metalloprotein antioxidant)	Phase I and II	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.	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.	There were no adverse effects in mice and monkeys treated with BMX-001. ⁹