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FORUM REVIEW ARTICLE

Stem Cell Therapies for the Treatment of Radiation-Induced Normal Tissue Side Effects

Marc Benderitter,¹ Fabio Caviggioli,² Alain Chapel,¹ Robert P. Coppes,³ Chandan Guha,⁴ Marco Klinger,² Olivier Malard,⁵ Fiona Stewart,⁶ Radia Tamarat,¹ Peter Van Luijk,³ and Charles L. Limoli⁷

Abstract

Significance: Targeted irradiation is an effective cancer therapy but damage inflicted to normal tissues surrounding the tumor may cause severe complications. While certain pharmacologic strategies can temper the adverse effects of irradiation, stem cell therapies provide unique opportunities for restoring functionality to the irradiated tissue bed. **Recent Advances:** Preclinical studies presented in this review provide encouraging proof of concept regarding the therapeutic potential of stem cells for treating the adverse side effects associated with radiotherapy in different organs. Early-stage clinical data for radiation-induced lung, bone, and skin complications are promising and highlight the importance of selecting the appropriate stem cell type to stimulate tissue regeneration. **Critical Issues:** While therapeutic efficacy has been demonstrated in a variety of animal models and human trials, a range of additional concerns regarding stem cell transplantation for ameliorating radiation-induced normal tissue sequelae remain. Safety issues regarding teratoma formation, disease progression, and genomic stability along with technical issues impacting disease targeting, immunorejection, and clinical scale-up are factors bearing on the eventual translation of stem cell therapies into routine clinical practice. **Future Directions:** Follow-up studies will need to identify the best possible stem cell types for the treatment of early and late radiation-induced normal tissue injury. Additional work should seek to optimize cellular dosing regimes, identify the best routes of administration, elucidate optimal transplantation windows for introducing cells into more receptive host tissues, and improve immune tolerance for longer-term engrafted cell survival into the irradiated microenvironment. *Antioxid. Redox Signal.* 21, 338–355.

Introduction

TARGETED RADIOTHERAPY is an effective treatment for cancer, but the amount of curative radiation that can be delivered to the tumor is limited by the sensitivity of normal tissues surrounding the lesion. While cancer therapies increasingly achieve cure and extend survival, they often result in chronic side effects in patients (29, 99, 142, 148, 149). Paradoxically, modern therapies threaten to increase the

burden of chronic toxicity, not reduce it (6). Acute reactions impacting normal tissue injury early after treatment are related to oxidative stress and inflammation that alter the microenvironment which includes sensitive stem cell niches (78). These changes prime the irradiated tissue bed for a wide-range of multifaceted late effects.

Recent research has identified a wealth of pharmacologic strategies to temper the adverse effects of radiation exposure (23, 163). Although pharmacologic interventions have only

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limited ability to mitigate severe side effects of radiotherapy, some studies have shown the potential of these treatments to inhibit the onset of tissue damage (163). While certain pharmacologic approaches are beneficial, none offer the potential of stem cell-based strategies, which afford the opportunity to functionally replace cells lost or damaged during irradiation. The use of stem cell therapy to promote recovery of normal tissues exposed to ionizing radiation aims at ameliorating the unintended side effects due to normal tissue damage. With the exception of bone marrow transplants, used for many years to reconstitute the hematopoietic compartment after ablative irradiation (83), the application of stem cell therapies for reducing other normal tissue sequelae remains a new but burgeoning area of research.

The potential benefits of stem cell therapy are certainly not limited to cell replacement, as significant evidence exists, showing that engrafted cells provide trophic support to the surrounding host tissue (123, 172, 196, 198). Regardless of the mechanism, protecting and/or restoring endogenous cell function will reduce normal tissue injury and hasten the recovery of patients who are subjected to irradiation. Mesenchymal stem cells (MSCs) were originally proposed for therapeutic purposes in regenerative medicine, based on their multipotent, proliferative, and anti-inflammatory properties. However, in recent years, therapeutic strategies are now evolving in which other stem/progenitor cell types are used alone or in co-transplantation with endothelial or epithelial progenitors to hasten the recovery and reconstitution of normal tissue.

The identification of stem cell populations and the capability to isolate and expand them for therapeutic uses has stimulated a wealth of research into regenerating injured tissue. Despite this promise, the past decade has also shown that translating the potential of stem cell therapy into actual practice is not easy, and many barriers, including immunorejection (22, 129), teratogenesis (106), regulatory (107) and ethical issues (46), still need to be overcome before such strategies become commonplace in the clinic. Thus, discussions of therapeutic efficacy to restore functionality to irradiated tissues are provided along with the caveats associated with such treatments. The present review will highlight recent advances in the application of various stem cell-based strategies to ameliorate radiation-induced normal tissue damage occurring within selected target organ sites.

Stem Cell Therapy to Ameliorate Radiation-Induced Cognitive Impairment

Worldwide, ~240,000 patients are diagnosed with brain tumors per year. Delayed adverse cognitive effects can occur in approximately 50% of irradiated patients, depending on radiation dose, fractionation schedule, irradiated volume, and location (29, 59, 82). Brain necrosis developing >6 months after radiotherapy is uncommon when total doses of 50 Gray (Gy) are delivered in fractions of 2 Gy or less; a tolerance dose of 57 Gy has been suggested. However, children who receive 30–35 Gy of whole brain irradiation frequently develop intellectual deficiencies over the next few years (84, 156, 180, 189).

Acute and early delayed effects are associated with short-term memory loss, fatigue, and somnolence (197). Acute responses involving oxidative stress and inflammation can elicit

apoptosis and signaling changes that contribute to disruption of the blood–brain barrier, hypoxia, transient demyelination, and more persistent injury (208). Late effects typified by demyelination, vascular breakdown leading to edema, and radionecrosis of the white matter are progressive and generally irreversible (181–183, 201). Current concepts of radiation injury now recognize that alterations to the microenvironment involving oxidative stress, inflammation, vascular dysfunction, and impaired neurogenesis contribute to central nervous system (CNS) pathology and disrupted cognitive processing (68, 69, 197, 208).

Some of the more promising interventions for ameliorating radiation-induced neurocognitive sequelae are agents that inhibit inflammatory processes (169, 170, 217). Agonists targeting the peroxisomal proliferator-activated receptor family can attenuate neuroinflammation, resulting in preserved hippocampal neurogenesis and cognitive ability after irradiation (169, 170, 216). Inhibiting the renin–angiotensin system also has shown promise at ameliorating late effects in the CNS after irradiation (41, 176).

One well-defined effect of cranial irradiation is its adverse effect on endogenous neurogenesis. Generation of CNS progenitor cells occurs in the subventricular (SVZ) and dentate subgranular zones (SGZ) (74, 202). Each of these processes contributes new glia and neurons to the brain. SVZ-derived neuroblasts migrate along the rostral migratory stream to repopulate the olfactory bulb, while SGZ-derived neural precursors repopulate the granule cell layer of the hippocampus (74). Irradiation depletes radiosensitive populations of multipotent precursors in the hippocampus, leading to an inhibition of neurogenesis and cognitive impairment (144, 167, 177). The growing evidence linking neural stem and precursor cell depletion to neurocognitive sequelae has stimulated efforts that are aimed at cell replacement strategies in the CNS.

Regenerative medicine targeted to the CNS took shape soon after the first isolation of neural stem cells from the rodent brain (173, 190). Application of stem cell therapies to ameliorate radiation-induced normal tissue injury soon followed, as neural stem cell transplants to the spinal cord were found to ameliorate radiation-induced myelopathy (174). While radionecrosis remains a complicating factor for spinal cord treatments (34), neurologic dysfunction is now considered the major dose-limiting factor for radiotherapy of the brain (56). The sensitivity of adult neurogenesis to irradiation has stimulated efforts to explore the use of stem cell transplantation for reversing cognitive dysfunction after cranial radiotherapy. Recent work has demonstrated the benefits of intrahippocampal transplantation of either human embryonic or human neural stem cells (hNSCs) to ameliorate radiation-induced impairment of cognition (1–3). In these studies, rats were cranially irradiated 2 days before bilateral intrahippocampal transplantation of human stem cells. At 1 and 4 months after irradiation and transplantation, significant survival of the transplanted cells was demonstrated. Engrafted cells migrated extensively throughout the septo-temporal axis of the hippocampus and differentiated along neuronal and astroglial lineages. Importantly, rats receiving stem cell transplants showed improved cognitive performance compared with irradiated rats receiving sham surgery (1–3). Key features of the foregoing experimental approach are depicted in Figure 1.

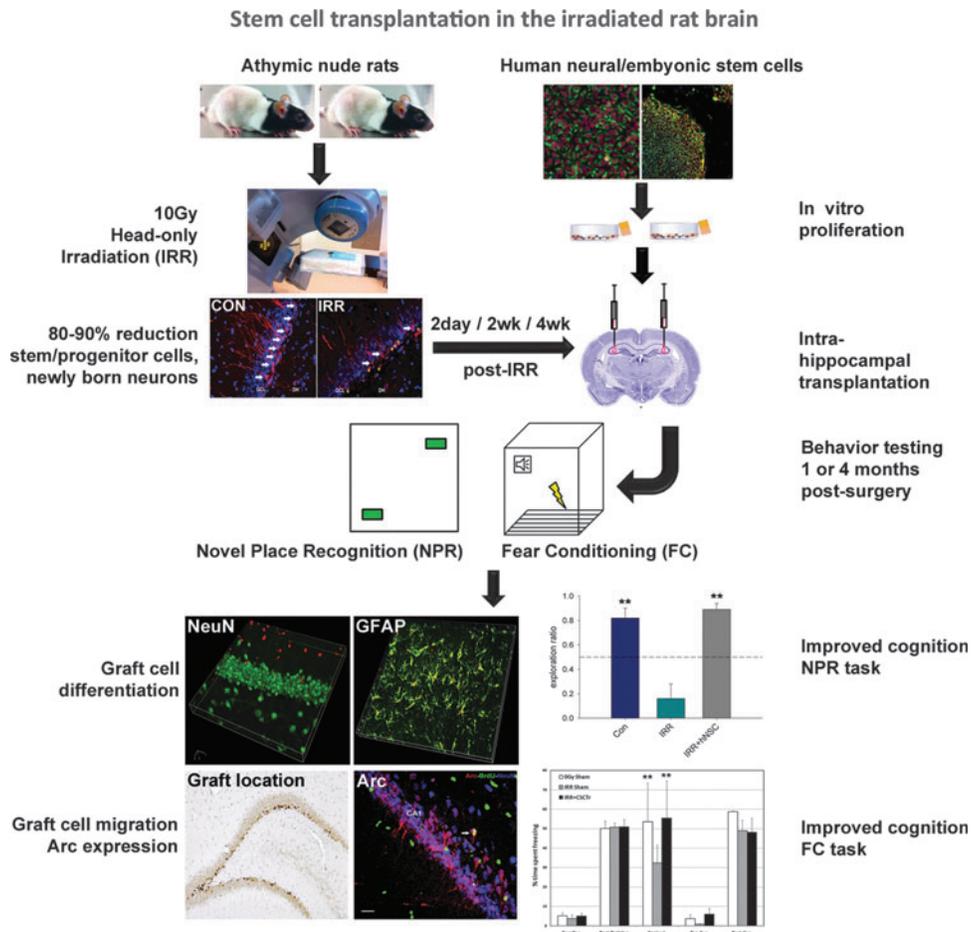


FIG. 1. Stem cell transplantation for ameliorating radiation-induced cognitive dysfunction. Immunocompromised athymic rats are subjected to cranial irradiation, while human stem cells are grown in parallel. At specified times (2 days, 2 or 4 weeks) after irradiation, animals are subjected to hippocampal transplantation with fixed numbers of human stem cells. At specific times (1 or 4 months) after irradiation, animals are then evaluated for cognitive performance using NPR and FC tasks. Irradiated animals transplanted with stem cells (IRR + hNSC) exhibit higher exploration ratios in NPR and increased time spent freezing in the context phase of FC, demonstrating improved hippocampal-dependent performance. After completion of cognitive testing, the brains of animals are analyzed for engrafted cell survival, migration, differentiated fate (NeuN-neuronal fate, GFAP-astroglial fate), and functional integration by the expression of the Arc. Asterisks represent significance ($p < 0.05$) compared to irradiated groups. Arc, activity-regulated cytoskeleton-associated protein; FC, fear conditioning; hNSC, human neural stem cell; NPR, novel place recognition.

The mechanisms of stem cell-based cognitive rescue after irradiation are definitely complex. The beneficial effects are likely to involve both the replacement of lost or damaged cells and increased trophic support to the brain by transplanted cells or endogenous stem cells homing to the site of radiation injury. Research by the group of Limoli has shown that transplanted cells express activity-regulated cytoskeleton-associated protein, suggesting their capability to functionally integrate into the hippocampus (2). Moreover, trophic factors such as glial cell line-derived neurotrophic factor and basic fibroblast growth factor (FGF) released from engrafted astroglial cells may support the functions of mature host neurons or foster neurogenesis and the maturing neuroblasts (35, 80, 101, 192). The release of brain-derived neurotrophic factor from transplanted hNSCs has been shown to provide some cognitive benefits in a mouse model of Alzheimer Disease (18). Moreover, bone marrow-derived stem cells may provide vascular support and help maintain the specialized vascular niche

for stem cell maintenance (54, 91, 150, 195, 220). They can be recruited directly to the site of radiation injury in the brain, where they appear to provide support to the microvasculature (28).

While regenerative medicine holds considerable promise, inherent limitations to the repair of neural tissue present practical limitations. The migration of engrafted cells toward damaged tissue is a critical step in stem cell therapy, and further work is required to elucidate the chemokine signaling networks that regulate this process (16, 31, 95). The risk of immunorejection also weighs heavily on any transplantation study (9). These issues impact the assessment of stem cell safety and efficacy in efforts to translate animal studies to the clinic (9). Clearly, there is much to learn, but despite these inherent shortcomings, the treatment of neurocognitive sequelae through stem cell therapy is a worthy pursuit, especially in the absence of any satisfactory, long-term interventions for this serious complication of cranial radiotherapy.

Stem Cell Therapy to Ameliorate Radiation-Induced Xerostomia

Worldwide, about 500,000 patients are diagnosed with head and neck cancer (HNC) per year. Of these, 70% are treated with radiotherapy alone or in combination with surgery and/or chemotherapy (94). Radiotherapy of HNC often involves co-irradiation of the salivary glands that may induce hyposalivation, an important factor in the development of xerostomia (58, 204). To avoid a long-term loss of salivary function, at least one parotid gland should be spared to a mean dose of less than 20 Gy to preserve function if the other is targeted with a higher dose. Alternatively, when both glands are irradiated, total doses need to be less than 25 Gy, whereas the submandibular gland needs to be spared to doses less than 35 Gy (25, 50, 116).

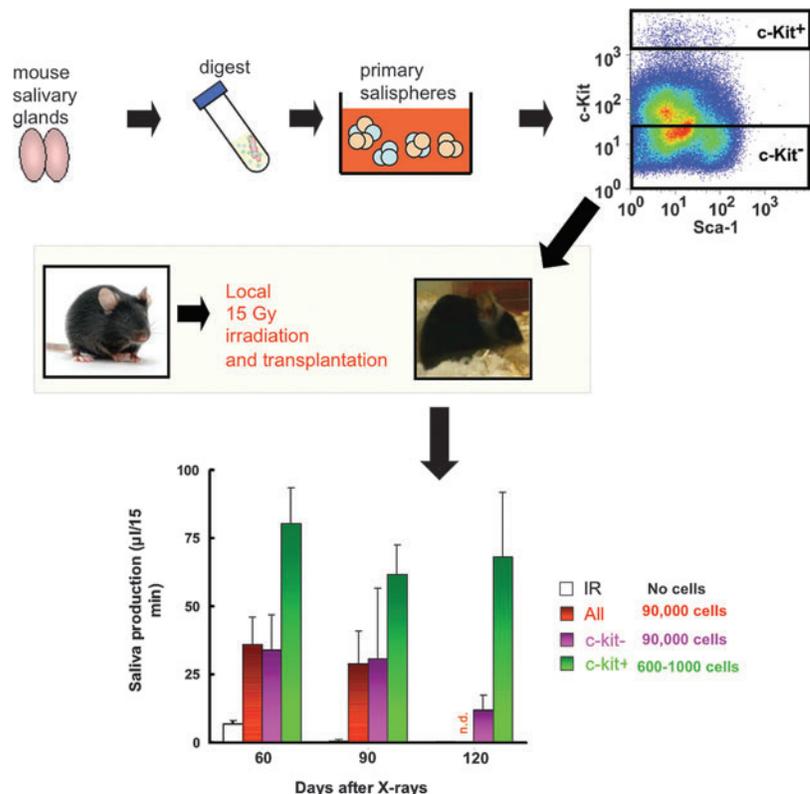
Current strategies that prevent radiation-induced salivary gland dysfunction include the use of protective medication, such as amifostine or pilocarpine (24, 27, 120), surgical relocation of the submandibular gland (215), and minimization of the radiation dose administered to the major salivary glands (43, 62, 153, 203, 206). Although intensity-modulated radiotherapy has provided a significant reduction of xerostomia, 40% of patients still develop life-long complaints (62). Radiation-induced damage to salivary glands mainly results from the inability of stem cells to produce a sufficient number of mature functional cells (110). Increasing the regenerative potential of salivary glands by stem cell therapy should help restore tissue homeostasis, and adult tissue stem cells have shown great clinical potential (43, 44, 55).

Interestingly, the non-functioning ducts mostly remain intact after irradiation (43), offering the opportunity for transplanted

stem cells to engraft to a proper niche and to regenerate the salivary gland. Indeed, the protective effect of prophylactic pilocarpine (26) and keratinocyte growth factor (KGF) (126) seems to be due to stimulated proliferation of ductal stem/progenitor cells. Ductal stem/progenitor cells can also be stimulated by factors which are secreted by bone marrow-derived cells (BMDCs) that home to damaged salivary glands after mobilization (125). Some studies controversially claim that salivary glands which are damaged by irradiation can be rescued by bone marrow stem cells that transdifferentiate or have adopted an acinar-like phenotype (121, 199). Similar observations have been made for MSCs (137). However, characterization of the most potent salivary gland stem cell is still ongoing.

Current research is largely focused on the characterization, isolation, and transplantation of tissue-derived stem cells. Both mouse (164) and human (67) salivary gland stem cells can be isolated from cultured salispheres. While identification of the bonafide salivary stem cell remains elusive, c-Kit⁺ cells exhibited a remarkable capability to ameliorate radiation damage, as shown in Figure 2 (124). Furthermore, CD24/CD29, CD49f, and CD133 expressing cells were able to differentiate into all salivary gland lineages (67, 124, 151, 164) and were able to regenerate the irradiated salivary gland (124, 151).

Despite these advances, several issues need to be addressed before these laboratory-based findings can be translated to the clinic (165). Evidence substantiating that functional recovery can be achieved through the preferential administration of transplanted cells via retrograde ductal injection needs to be obtained. Moreover, while several candidate salivary gland stem/progenitor cells have been suggested for human use (13, 42, 108, 127, 136, 157), safety issues need to be addressed experimentally before their clinical application (79).



Stem Cell Therapy to Ameliorate Osteoradionecrosis

Irradiation of bone may result in four major complications: osteoradionecrosis (ORN) (139), insufficiency fractures (40), severe alterations of bone growth, and radiation-induced neoplasms. Septic ORN typically occurs in HNC patients, combining superficial epithelial radionecrotic ulceration and deep exposed mandible, whereas aseptic ORN may affect the hip in pelvic cancer or the ribs in breast cancer. The estimated tolerance doses for mandibular bone are 60 and 72 Gy for 5% and 50% incidences of necrosis (63, 93).

ORN is a non-healing wound resulting from hypoxia, hypovascularization, and tissue hypocellularity followed by tissue breakdown (139). Early stages of bone atrophy are linked to the imbalance between bone formation and bone resorption (103). Irradiation leads to the inhibition of MSCs and osteogenic cell proliferation (179) and may promote the terminal differentiation of osteoblasts (48). During progression of the lesion, irradiated bone shows signs of osteoporosis characterized by atrophy and a disorganized trabecular structure, resulting from an imbalance in osteogenesis/osteolysis, defects in neovascularization, and fibrosis. After irradiation, the myofibroblasts appear at the initial inflammatory phase and persist during the constitutive fibrotic phase (14). Transforming growth factor- β 1 (TGF- β 1) is considered the main cytokine involved in this process, resulting in increased extracellular matrix secretion and decreased metalloproteinase excretion (51). TGF- β 1 plays an important role in establishing and maintaining vessel integrity by ameliorating damage to the arteries and veins surrounding the bone after irradiation (161). Vascular damage and ischemia appear before osteoblast alteration (60, 152).

Treatment of squamous cell carcinoma of the upper aerodigestive tract often requires large surgical bone removal and reconstruction with anastomosed free flaps (90). Irradiation reduces healing capacities and is associated with a higher risk of vascularized flap failure. The use of calcium phosphate biomaterials has been considered an alternative to autogenous bone grafts. However, calcium phosphate alone is not sufficient for bone substitution in irradiated areas (119), and it needs to be used in conjunction with total bone marrow (TBM) for more optimal stimulation of bone healing (Fig. 3). Biphasic calcium phosphate (BCP) associated with TBM provides better bone reconstruction after radiotherapy (131), whereas association of MSCs with calcium phosphate leads to better bone reconstruction in non-irradiated areas (12, 134, 211, 221). Studies in an irradiated mouse model also showed that TBM was superior to MSC for association with BCP for bone reconstruction in irradiated areas (64). These results highlight the potential benefits of stem cells used in conjunction with biomaterials for combined regenerative strategies proposed in clinical applications (64). A current phase I clinical trial for mandible ORN treatment (ClinicalTrials.gov, identifier: NCT01147315) will provide some of the first results in humans.

Stem Cell Therapy to Ameliorate Radiation-Induced Skin Fibro-Necrosis

Acute skin reactions that range from a mild rash to severe ulceration are one of the most common side effects of external radiotherapy. This pathological condition leads to pain, delays in treatment, and an overall decrease in quality of life

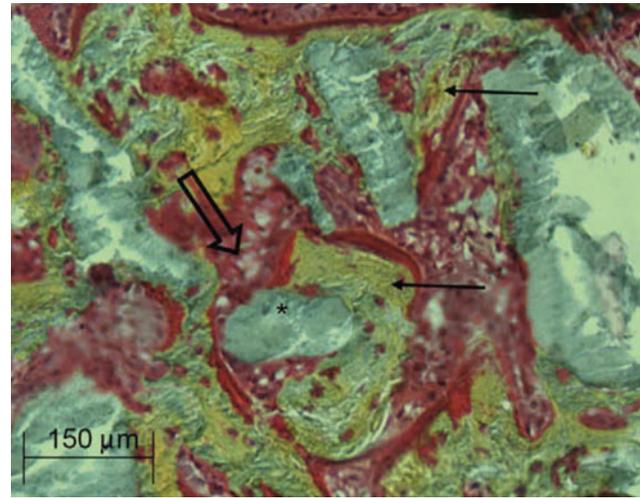


FIG. 3. Bone marrow grafts treated with BCP. Histologic section reveals healing of defective bone, shown as the BCP substitute associated with the bone marrow graft in the irradiated bone area. New bone formation (yellow, \leftarrow) in contact with the BCP (gray, $*$). Rich bone marrow (red, \Rightarrow) in contact with the BCP. BCP, biphasic calcium phosphate.

(130, 141). Radiation dermatitis may occur after a total dose of 55 Gy and usually manifests within 1–4 weeks. At later times, subcutaneous fibrosis and occasionally radionecrosis may develop (20). Acute reactions result from the loss of rapidly proliferating cells, combined with vascular and inflammatory responses. Late radiation effects manifest in the slowly proliferating cell populations, resulting in progressive TGF- β 1-mediated fibrosis and tissue hypoxia. Radiation-induced fibrosis and necrosis are usually considered intractable, manifesting as impaired healing and prone to recurrence even after minor trauma.

A current management strategy for skin fibrosis includes anti-inflammatory treatment with corticosteroids or interferon gamma, vascular therapy with pentoxifylline or hyperbaric oxygen, and antioxidant treatment with superoxide dismutase or tocopherol (52). Under certain circumstances, the radiolesion becomes refractory to treatment, leaving surgery as a final option, with increased risk of disability and morbidity. Such complications suggest the need to develop new therapeutic approaches using adult stem cells for the repair of radiation-induced tissue injury. Preclinical studies have identified MSCs as promising cell-based agents for the treatment of tissue necrosis. For clinical applications, MSCs can be expanded to mass culture, and they can be cryopreserved without loss of viability or stem cell potency (5, 118). Recent work has successfully demonstrated the preclinical benefit of systemic MSC injections for ulcerated skin and muscle restoration after high-dose irradiation (17). The beneficial effects rely on paracrine mechanisms, by which cytokines and growth factors that are released from engrafted cells favorably influence wound healing (73).

Recent studies have demonstrated a marked plasticity of adipose-derived stem cells (ADSC), mainly comprising mesenchymal cells. The harvest of adipose tissue is easy, generally involving minimally invasive lipoaspiration procedures. Topical administration of ADSC into full-thickness wounds normalizes defective wound healing in irradiated mice (61).

Interestingly, ADSC can differentiate into keratinocytes, and ADSC-derived KGF released at the site of injury may regulate the healing of the cutaneous wound. ADSC have also been shown to incorporate into vessels and differentiate into endothelial cells, leading to improved perfusion and vessel density (61). A schematic demonstrating the plasticity and capability of ADSC to facilitate wound healing is shown in Figure 4. Endothelial progenitor cells (EPC) similarly incorporated into vessels, differentiated into CD31-expressing endothelial cells, and increased perfusion and vessel density (102). An injection of EPC increased vascular permeability, suggesting that progenitor cell-induced nitric oxide-dependent vasodilatation and hyperpermeability were required for their proangiogenic effects (210, 212).

The group of Rigotti (175) demonstrated that lipoaspirate transplantation was clinically effective in the treatment of the side effects of skin radiation. Autologous fat grafts showed a generalized improvement of clinical symptoms in all 20 treated patients (104). Clinically purified autologous lipoaspirates were also proposed by the group of Akita (7) for the treatment of radiation-induced late skin complications. ADSC showed the capability to promote the growth of a microvascular bed that facilitated the subsequent correction of chronic ischemic damage. The group of Klinger also recently demonstrated (32) the efficacy of autologous fat grafts in the post-mastectomy pain syndrome (PMPS). The cohort was composed of 113 patients who were affected by PMPS and who underwent mastectomy with axillary dissection and radiotherapy. The reported pain control with a mean follow up of 13 months could be linked to inflammation reduction along with an improvement in tissue quality and scar softness with beneficial effects on nerve entrapment (115). Finally, adequate debridement combined with skin autograft and an injection of MSC showed significant therapeutic benefit for approximately 7 years in the medical management of severe skin and underlying muscle necrosis in eight patients (17).

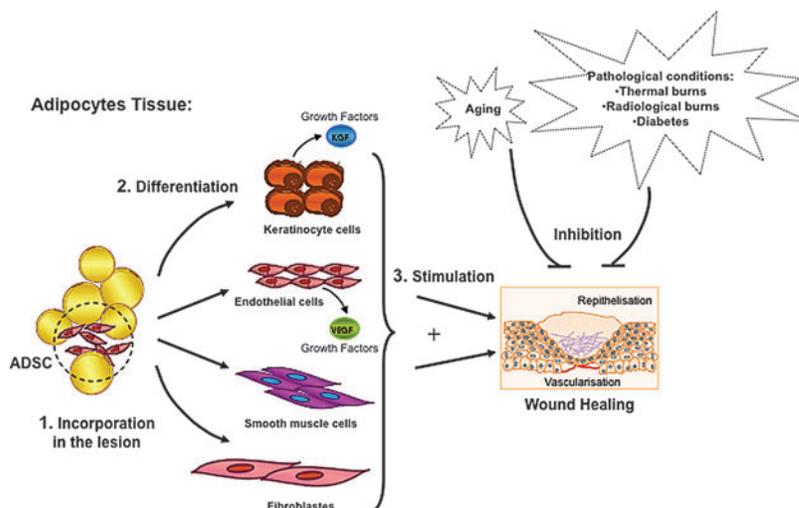
The foregoing pre-clinical and clinical studies have now demonstrated proof of concept for the use of stem cells in the therapeutic management of radiation-induced skin damage. Further innovations are now required to efficiently translate these findings into clinical protocols for minimizing the side effects associated with radiotherapy.

Stem Cell Therapy to Ameliorate Radiation-Induced Liver Disease

Whole liver cannot tolerate more than 35 Gy of radiation therapy (RT) in standard fractionation because of the induction of potentially lethal radiation-induced liver disease (RILD). RILD was recently analyzed in the Quantitative Assessment of Normal Tissue Effects in the Clinic project (63, 96, 158). Patients with classic RILD present with symptoms of fatigue, rapid weight gain, enlarged liver, ascites, and an isolated elevation in alkaline phosphatase, ~2 weeks to 4 months after liver RT (117). All other liver functions, including serum bilirubin and ammonia levels, are usually normal, unless the patients have radiation-induced reactivation of hepatitis B virus replication. Histopathologically, RILD is characterized as a hepatic central veno-occlusive disease with occlusion of the central vein lumina and hepatic sinusoids by reticulin and collagen fibers, resulting in vascular congestion and atrophy of centrilobular hepatocytes (66, 154, 171). Since radiation induces apoptosis of the liver sinusoidal endothelial cells (LSECs) in a dose-dependent manner, the clinical syndrome has also been named sinusoidal obstructive syndrome (53). Besides endothelial injury, regenerating hepatocytes are sensitive to radiation-induced mitotic catastrophe, as noted in patients with cirrhotic livers, who have elevated serum transaminases and ascites, indicating radiation-induced hepatocellular death (36).

Currently, there is no effective treatment for RILD (85). Since irradiation inhibits hepatocellular regeneration, it was hypothesized that intra-portal or intra-splenic transplantation of unirradiated hepatocytes would enable donor cells to efficiently engraft in irradiated liver lobes, and selectively proliferate in response to mitogenic growth factors as the irradiated host hepatocytes undergo cell cycle arrest and/or mitotic death. A model of RILD was developed in F344 rats after treatment with partial hepatectomy and hepatic irradiation (HIR) (88). Within 6 weeks after HIR, acute effects included perivenous steatosis and hepatocellular atrophy, while late effects manifested as severe bile duct proliferation and periportal fibrosis by 12 weeks. Mortality from RILD was 60–75%. Intrasplenic transplantation of 5×10^6 congenic hepatocytes ameliorated the acute and late effects of RILD and

FIG. 4. ADSC for the resolution of skin injury. ADSC exhibit marked plasticity toward keratinocyte and endothelial cells. Stem cells of the adipose lineage have the ability to differentiate into epithelial cells, acquire a functional keratinocyte phenotype, and differentiate into vascular cells. These cells can be used to facilitate the repair of radiation-induced skin injury as well as other pathological conditions of the skin. ADSC, adipose-derived stem cells.



significantly improved survival (88) with normal liver function. Immunohistochemical staining for donor hepatocytes revealed progressive proliferation with near-total replacement of the irradiated host hepatocytes by donor cells over 3 months. Such results are shown in Figure 5, where donor-derived repopulation of a liver lobe subjected to partial irradiation was demonstrated after hepatocyte transplantation (HT). Strikingly, proliferation of the donor hepatocytes occurred primarily in the irradiated liver lobes, evident in the lower power histomicrographs that highlight the efficiency of the preparative regime for replacing hepatocytes depleted during irradiation (Fig. 5).

Since classic RILD manifests as sinusoidal obstructive syndrome, it was reasoned that acute loss of LSEC in irradiated livers would require rapid restoration of the sinusoidal endothelium. Therefore, LSECs were transplanted via an intra-portal or intra-splenic injection after HIR and a recombinant adenovirus-expressing hepatocyte growth factor (HGF) was administered to provide mitogenic signals for donor cells. LSEC transplantation ameliorated radiation-induced sinusoidal obstructive syndrome with donor cells selectively engrafting and repopulating the irradiated hepatic sinusoidal endothelium by 8 weeks (100).

Orthotopic liver transplantation (OLT) is the only curative therapy for many patients with terminal liver diseases. However, due to shortage of donor livers, there is a long waiting list for OLT. HT is being explored as a therapeutic alternative. However, HT is limited because the number of cells that can be safely transplanted into the liver is inadequate to compensate for liver function. Encouraged by the massive repopulation of donor hepatocytes after HT for ameliorating RILD in rodents, focal liver irradiation was examined as a preparative regimen for HT in the treatment of metabolic liver diseases (85–87). Several investigators have demonstrated that preparative HIR in combination with hepatic mitogenic signals can enable selective engraftment (209) and proliferation of donor hepatocytes in irradiated host livers (37, 111, 132). Thus, preparative HIR has been used to correct liver function in murine and rodent models of inherited metabolic

diseases, such as primary hyperoxaluria (89, 97), Wilson's disease (133), and hypercholesterolemia (218).

A phase I clinical trial (NCT01345578) of preparative HIR to facilitate HT has been initiated in patients with metabolic liver diseases (70). Partial liver irradiation could be safely administered using stereotactic body RT via three dimensional conformal or intensity modulated radiotherapy followed by HT for the treatment of inherited liver diseases, liver failure, hepatic gene therapy, RILD, and for generating human-mouse liver chimera animal models.

Cardiac Damage and Stem Cell Replacement

Thoracic irradiation significantly increases the risk of cardiovascular disease in cancer survivors. Long-term survivors of Hodgkin's lymphoma and childhood cancers have 2 to >7-fold increased risks of cardiac death for total doses of 30–40 Gy (200). Increased cardiac morbidity and mortality also occur after irradiation for breast cancer, despite having a relatively small part of the heart included in the irradiation field. The Early Breast Cancer Trialists' Collaborative Group evaluated data from >30,000 women in randomized trials of radiotherapy versus no radiotherapy and showed a 27% excess of heart disease in the irradiated group (38, 140). The risk of cardiac death was related to the estimated mean cardiac dose, increasing by 3% per Gy (140).

Animal studies show that radiation-induced damage to the myocardium is primarily caused by damage to the microvasculature, leading to inflammatory and thrombotic changes and vascular leakage (184, 185). Progressive reduction in the number of capillaries led to reduced perfusion of the cardiac muscle, ischemia, myocardial cell death, and fibrosis (65, 138). Animal data are supported by clinical studies that demonstrate regional perfusion defects in non-symptomatic breast cancer patients at 6 months to 5 years after radiotherapy (4, 47). Radiation also predisposes to the formation of inflammatory, unstable atherosclerotic lesions, which are prone to rupture and may cause a fatal heart attack (155, 191).

There is currently no specific pharmacological treatment for cancer therapy-related cardiomyopathy, although symptomatic

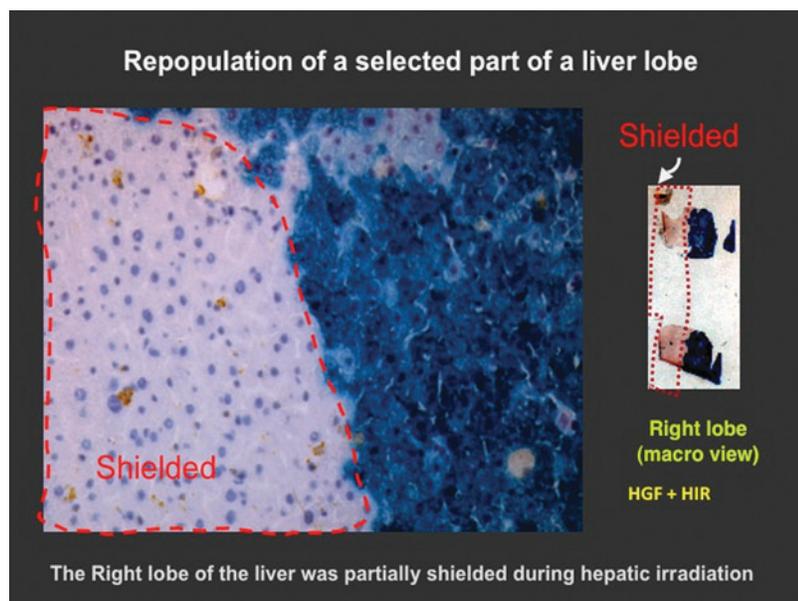


FIG. 5. Preparative liver irradiation for hepatocyte transplantation. The anterior half of the right lobe of liver was irradiated with a single fraction of 50 Gray in C57Bl/6 mice, followed by intrasplenic transplantation of 1×10^6 beta-galactosidase-proficient hepatocytes isolated from congenic Rosa mouse, 1 day after irradiation. Hepatic mitogenic signal was provided by intravenous administration of an adenovirus expressing recombinant human HGF within 1 h after liver irradiation. Animals were sacrificed 16 weeks after hepatocyte transplantation. Data show beta-galactosidase staining of a fresh frozen section of the right lobe of the liver 16 weeks after hepatocyte transplantation. Note preferential repopulation of the donor beta-galactosidase-positive hepatocytes (blue) in the irradiated liver lobe. HGF, hepatocyte growth factor.

patients may receive standard treatments for congestive heart failure, including angiotensin-converting-enzyme inhibitors. Animal studies have demonstrated some benefit from the radioprotector amifostine when administered before cardiac irradiation (112), or pentoxifylline, in combination with the antioxidant vitamin E (19, 122).

Recent studies have identified stem and progenitor cells that can generate myocytes, smooth muscle cells, and endothelial cells and participate in regeneration of the adult heart (11, 15, 30). Circulating BMDCs also migrate to sites of ischemic damage in the heart and can contribute to new vessel formation by fusion with resident cardiac cells and by secretion of pro-angiogenic and survival factors. Preclinical studies show that both mobilization and transplantation of BMDC improve the microvasculature and cardiac function after acute myocardial ischemia and in models of chronic cardiac fibrosis (39, 45, 49, 147). Since radiation is known to cause progressive microvascular damage and capillary loss (65, 138, 184, 185), this technology may also have potential for treating radiation-induced cardiac injury (Fig. 6), although this has not yet been tested.

Meta-analyses of randomized clinical trials demonstrate small, but significant, improvements in short-term cardiac function after BMDC therapy, with reduced benefit at later times (207, 214, 219). There was a positive correlation between the number of cells injected and an improvement in cardiac function, but there were no significant improvements in long-term survival (207). Preclinical studies indicate that only 1–3% of injected BMDC are found at infarcted areas of the heart, although *ex-vivo* enrichment of specific cell populations, for example, CD34+ cells, can considerably increase this engraftment. Cardiomyocyte progenitor cells (CPC) and embryonic stem cells (ESC) have greater capacity for stable engraftment and proliferation, and they can differentiate into cardiomyocytes. There are several ongoing phase 1 trials using CPC isolated from a biopsy of the patient's own heart and expanded *ex-vivo* (92, 166). Preliminary results seem promising, but the numbers of patients included are very small (21). Challenges for the future in applying stem cell therapy for radiation injury to the heart include the identification and

expansion of optimal cell types, the number of cells, the route of administration, and the timing of therapy.

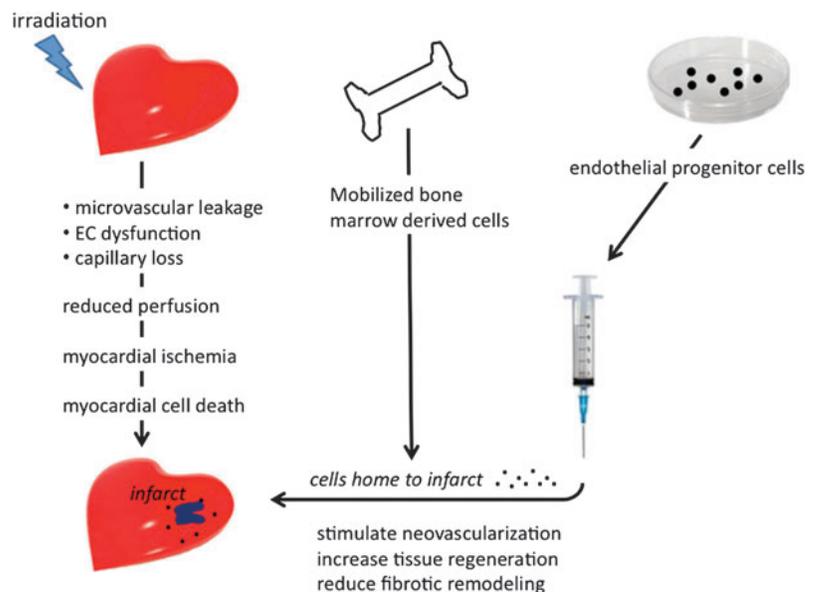
Stem Cell Therapy to Ameliorate Radiation-Induced Proctitis

Approximately 500,000 patients per year undergo abdominal or pelvic radiotherapy worldwide. Of these, 5–10% will develop pelvic radiation disease (PRD) within 10 years (10). Acute radiation responses, including abdominal pain, diarrhea/constipation, and malabsorption, may interrupt or delay the radiotherapy protocol. Late radiation responses, including fibro-necrosis, fistulae, hemorrhage, and occlusion, can result in significant morbidity and mortality.

Acute epithelial ulceration, mucosal and submucosal inflammation, and chronic radiation enteropathy are characterized by excessive extracellular matrix deposition, vascular sclerosis, and muscular dystrophy. The cellular and molecular mechanisms of PRD include oxidative stress, stem cell death with compromised epithelial renewal (162), microvascular damage with endothelial cell death, and pro-inflammatory and pro-thrombotic changes (77, 143, 159). A current management strategy for PRD includes anti-inflammatory treatment with sulfasalazine, vascular therapy with hyperbaric oxygen or argon plasma coagulation, and pharmacological modulation of fibrosis. The management of severe radionecrosis requires surgical intervention.

Stem cell therapy may offer a novel strategy to treat PRD. In abdominally irradiated mice, MSCs injected via the tail vein engraft to the enteric mucosa (213), enhance structural recovery, and delay death (186). The implantation of MSCs into the wall of the irradiated intestine facilitates repair of radiation-induced damage by inhibiting ulceration (113). Lorenzi *et al.* (128) reported that MSCs improved muscle regeneration and increased contractile function of anal sphincters after injury. Engrafted MSCs might regulate epithelial stem cell niches that provide and maintain an optimal microenvironment for stem cell function by releasing cytokines and growth factors such as interleukin-11, HGF, FGF-2, and

FIG. 6. Radiation-induced myocardial damage and stem cell treatments. Irradiation causes microvascular damage and capillary loss, which leads to inadequate perfusion of the tissue and may result in myocardial infarct. Bone marrow progenitor cells can either be mobilized to the blood using growth factors, or extracted and cultured *in vitro* to enrich populations of endothelial progenitor cells. Mobilized or injected progenitor cells home to the infarct area and stimulate surviving cells to proliferate and regenerate damaged tissue.



insulin growth factor-I (187). Interestingly, repeated infusion of MSC-derived bioactive components after abdominal irradiation increased survival, decreased diarrhea, and improved the small intestinal structural integrity of irradiated mice (75). Mitigation of lethal radiation-induced intestinal injury can also be achieved by the transplantation of bone marrow-derived adipose stromal cells (BMASCs). Transplantation of BMASC increased blood levels of intestinal growth factors and induced the regeneration of intestinal villi, thereby accelerating functional recovery of the intestine (178). A summary of pre-clinical data regarding the treatment of radiation pelvic disease with MSCs is provided in Table 1.

In 2006, the radiation oncology accident at the public hospital in Épinal-France affected 425 patients who were under treatment for prostate cancer. Patients were overdosed by approximately 10–20%. Clinical consequences were severe, and sequelae classified from grade 2 to 5 on the common terminology criteria for adverse events 3.0 scale were noted (135, 160). Three patients received intravenous infusions of MSCs (5×10^6 /kg) from allogeneic bone marrow derived from family donors for the treatment of hemorrhagic refractory radiation-induced fistulizing colitis. Clinical parameters, including pain, hemorrhage, and fistulization, were evaluated (magnetic resonance imaging, colonoscopy) before and after (1 and 6 months) MSC therapy. Two patients showed a substantial clinical response for pain and hemorrhage after MSC

therapy with no adverse events. One patient experienced a relapse in pain after 6 months and was responsive to a second infusion of MSCs. In another patient, early fistulization was stopped by MSC treatment, with stable remission since then observed over a 3-year follow up. These positive clinical responses suggest that MSC therapy may represent a safe and effective intervention for patients developing rectitis and/or cystitis of varying severity (205).

Conclusions

Allogeneic hematopoietic stem cell transplantation has been successfully used over the past 4 decades for patients with hematologic diseases (81). Conventional myeloablative transplantation includes conditioning with high-dose radiotherapy and chemotherapy to eradicate residual disease and recipient (host) immunity in preparation for healthy donor-derived hematopoietic stem cells (graft). This has been the first and most robust demonstration of the efficacy of stem cell therapies to completely reconstitute a sterilized tissue after high-dose radiotherapy, thereby opening new avenues for the treatment of other radiation-induced normal tissue sequelae.

After more than a decade of intense activity, the science of stem cells seems to be catching up with its promise. Clinical trials have established techniques for cell delivery and

TABLE 1. PRE-CLINICAL MODEL OF MESENCHYMAL STEM CELL TO TREAT PELVIC RADIATION DISEASE

<i>Configuration</i>	<i>Main results Non human primate</i>	<i>References</i>
Total body irradiation	Engraft in gut	72
	<i>Mice</i>	
Abdominal	MSC when infused to mice that received either extended or localized irradiation, migrate to almost all tissues (including gut) where they engraft transiently usually at very low levels of detection	72, 145
	Engraft into enteric mucosa	113
	Repair radiation-induced intestinal damage by inhibiting ulceration	186
	Favor reestablishment of cellular homeostasis by both increasing endogenous proliferation processes and inhibiting apoptosis of radiation induced of small epithelial stem cells	187
	MSC release cytokine and growth factors such as IL-11, hepatocyte growth factor, fibroblast growth factor-2, and insulin growth factor-1 that prevent intestinal radiation injury. Repeated infusion of MSC-derived bioactive components increased survival rate, decreased diarrhea occurrence, and improved small intestine structural integrity	75
	Improved muscle regeneration, increased contractile function of anal sphincters after injury (without radiation)	128
	Mitigation of radiation-induced lethal intestinal injury can similarly be achieved by transplantation of BMASC. BMASC increases blood levels of intestinal growth factors and induces regeneration of intestinal villi, thereby accelerating functional recovery of the intestine	178
	Rescue epithelial integrity.	71
	Limit radiation effect on the small intestine in an interleukine-6-dependent manner by reducing the levels of pro-inflammatory cytokines, while inducing anti-inflammatory cytokines, MSC dampen the systemic inflammatory response in radiation-induced syndrome	
	Improve liver function and modulate hepatocellular death.	146
	Regenerate the small intestine epithelium, which, in turn, restored the enterohepatic recirculation pathway initially damaged by irradiation. The consequence was a distant hepatic protection without engraftment of MSC in the liver	

BMASC, bone marrow-derived adipose stromal cell; IL-11, interleukin-11; MSCs, mesenchymal stem cells.

TABLE 2. CLINICAL TRIALS AND PRE-CLINICAL STUDIES TO TREAT THE ADVERSE CONSEQUENCES OF RADIOTHERAPY

Organ system	Radiation dose (Gy)	Normal tissue endpoint	Paradigm	Stem cell type administration (preclinical studies)	Stem cell type administration (clinical trial)	Follow up time
Bone marrow	12	Bone marrow aplasia	Hematopoietic stem cell/progenitor depletion and stem cell "niche" destruction	BM, HSC, MSC	BM (81)	30 years
Brain	>57	Brain radionecrosis, cognitive dysfunction	Inflammation, vascular breakdown, disruption of BBB, CNS progenitor depletion, stem cell "niche" destruction (74, 144, 167, 177, 202), hypoxia, demyelination, necrosis (197, 208)	hESC (1, 3), hNSC (2, 3)	No	—
Salivary glands	>35	Xerostomia (58, 62, 204), salivary flow	Stem cell/progenitor depletion (110)	BM (121, 199), MSC (37), salivary gland stem cell (13, 42, 67, 124, 127, 151, 165)	No	—
Bone	>60	Bone growth alteration, bone weakening, and osteo radionecrosis (139)	Hypocellularity (48, 179), hypovascularization, hypoxia (139), and fibro-necrosis (14, 51, 60, 152, 161)	BM, MSC (64)	BM associated to biomaterial (Phase I) (64, 131)	Few months
Skin	>50	Skin radionecrosis (20), pain (130, 141)	Chronic inflammation, damage to the microvasculature, epidermis stem cell/progenitor depletion, ischemia, fibroblast death, and fibro-necrosis	MSC (17, 73), ADSC (61), EPC (102)	MSC (local injection, 2×10^6 /kg, repetitive injections, curative strategy) (companional treatment) (17) and lipoaspirate (Phase I) (7, 32, 104, 115, 175)	8 years and 13 months
Liver	>35	Radiation-induced liver disease (96, 158), sinusoidal obstructive syndrome (36, 53, 66, 154, 171)	Vascular (sinusoidal) breakdown, hepatocyte cell death, and inhibition of hepatocellular regeneration	Hepatocyte	Hepatocyte (intrasplenic transplantation, 6.10^6) (Phase I) (70)	—
Heart	>30–40	Atherosclerosis (155, 191), cardiac attack (38, 191)	Inflammation, damage to the microvasculature (184, 185), ischemia, myocardial cell death, and fibro-necrosis (4, 47, 65, 138)	—	No	—
Colon-rectum	>35 Gy	Pelvic radiation disease (10), colo-rectal ulceration, rectitis, cystitis, and fistulae	Chronic inflammation, damage to the microvasculature (77, 143, 159), epithelial stem cell/progenitor depletion (162), ischemia, myofibroblast death, and fibro-necrosis	MSC (33, 75, 113, 128, 186, 187, 213)	MSC (i.v. injection, 2×10^6 /kg, repetitive injections) (compassional treatment)	4 years

ADSC, adipose-derived stem cell; BBB, blood brain barrier; BM, bone marrow; CNS, central nervous system; EPC, endothelial progenitor cells; GFAP, glial fibrillary acidic protein; hESC, human embryonic stem cell; HSC, human stem cell; hNSC, human neural stem cell; IRR, irradiation.

protocols for establishing feasibility, safety, and early-stage efficacy in humans. The first clinical trials for pathologies, including diabetes (98), cardiac infarct (57), Crohn's disease (76), or Graft versus Host disease (118), have demonstrated safety with trends of efficacy.

Preclinical studies presented in this review provide encouraging proof of concept regarding the therapeutic potential of stem cells for treating the side effects associated with radiotherapy at different organ sites, including brain, salivary glands, bone, skin, heart, liver, and gut. Initial clinical data for radiation-induced lung (114), bone (ClinicalTrials.gov, identifier: NCT01147315), and skin (17, 32) injury indicate that certain complications may be amenable to stem cell-based approaches. However, successful translation to the clinic still faces many hurdles. Subsequent work will be critical in determining if/how and when to incorporate stem cell interventions into clinical trials. By gaining a further understanding of the molecular interactions between donor stem cells and host tissue, and how such interactions are modulated by host immunity (109), we could discover ways to expedite the use of stem cells in the clinic. While data demonstrating the efficacy of stem cells in the clinic remain sparse, additional evidence demonstrating long-term safety is also needed; transplanted stem cells should not form teratomas or undergo transformation and they should not promote tumor recurrence, even after complete tumor sterilization. Many of these issues are likely to be resolved by the appropriate selection of stem cell types for transplantation, but requires further preclinical testing.

Lessons from clinical trials should also be taken into account; since the first reported trial in 1995, cultured MSCs have been used in 125 registered clinical trials (registered at <http://clinicaltrials.gov/>) without any reported confounding side effects related to the cell therapy. The resistance to transformation of MSCs produced in four clinical-grade cell therapy facilities was investigated, and data demonstrated that MSCs with or without chromosomal alterations showed progressive growth arrest and entered senescence without evidence of transformation either *in vitro* or *in vivo* (194). The long-term genomic stability of cultured adult stem cells may minimize certain concerns regarding their oncogenic potential (188).

While current clinical data support the long-term safety of MSCs, concerns do persist, and some are related to the potential of transplanted MSCs to adversely impact tumor growth and metastasis after radiotherapy. A variety of experimental tumor models involving the exogenous addition of MSCs have led to conflicting findings regarding their capability to promote or suppress tumor growth (105). Depending on the model, mechanisms put forth have included the inhibition or promotion of apoptosis, angiogenesis, or immunity and related interactions within the tumor microenvironment. Understanding the mechanisms in which adult somatic stem cells modulate tumor growth will be essential for the safe and efficient advancement of stem cell therapies that counteract radiation injury. A summary of data regarding stem cell therapies that are specific to the organ site from selected clinical trials and pre-clinical studies are provided in Table 2.

Pluripotent stem cells represent attractive sources of starting material for cell-based therapies, largely due to their self-renewing properties and their capability to differentiate into

tissue from all three germ layers (8). The use of pluripotent ESC is still fraught with ethical controversy and concerns of genetic instability and immune tolerance (46, 106, 129). The group of Yamanaka (193) has recently developed a technique for *in-vitro* reprogramming of terminally differentiated cells, such as skin fibroblast, into pluripotent cells that closely resemble ESC. These induced pluripotent stem cells (iPS) could be used for transplantation, with theoretical reductions in the risk of immune rejection. Such a technology also provides the capability to generate cell banks for future uses. Despite these potential benefits, several issues with iPS technology still need to be resolved before clinical use is possible. Viral integration strategies used for cellular reprogramming add an element of oncogenic risk, and reprogrammed somatic cells may harbor underlying mutations of unknown consequence (168).

Regenerative therapy for radiation injury is at an important juncture. Breaking down traditional barriers between specialized fields will be challenging, but necessary, if we are to move stem cell biology beyond basic science and toward the development of truly beneficial regenerative therapies. To foster this sort of multidisciplinary collaboration, a parallel effort needs to bring academic science in closer contact with clinicians. The fate of future stem cell physician-scientists and patients suffering from the adverse side effects of radiotherapy will certainly depend on the outcome.

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Abbreviations Used

ADSC = adipose derived stem cells
Arc = activity-regulated cytoskeleton-associated protein
BCP = biphasic calcium phosphate
BMASCs = bone marrow-derived adipose stromal cells
BMDC = bone marrow-derived cell
CNS = central nervous system
CPC = cardiomyocyte progenitor cells
EPC = endothelial progenitor cells
ESC = embryonic stem cells
FC = fear conditioning
FGF-2 = fibroblast growth factor-2
Gy = Gray
hESC = human embryonic stem cell
HGF = hepatocyte growth factor
HIR = hepatic irradiation
HNC = head and neck cancer
hNSC = human neural stem cell
HT = hepatocyte transplantation
IL-11 = interleukin-11
iPS = induced pluripotent stem cell
KGF = keratinocyte growth factor
LSECs = liver sinusoidal endothelial cells
MSCs = mesenchymal stem cells
NPR = novel place recognition
OLT = orthotopic liver transplantation
ORN = osteoradionecrosis
PMPS = post mastectomy pain syndrome
PRD = pelvic radiation disease
RILD = radiation-induced liver disease
RT = radiation therapy
SGZ = subgranular zone
SVZ = subventricular zone
TBM = total bone marrow
TGF- β 1 = transforming growth factor- β 1