Subverting misconceptions about radiation therapy

To the Editor:

More than a century after the discovery of ionizing radiation, its pleomorphic effects on living organisms continue to puzzle and inspire investigations on how to optimize this powerful therapeutic tool. The recent publication by Price *et al.* investigates the effect of whole-body irradiation on radiation-resistant Langerhans cells (LCs) and their migration to lymph nodes to elicit the generation of regulatory T cells (T_{reg} cells)[1]. The authors ascribe the radiation resistance of LCs to heightened activation of the cyclin-dependent kinase inhibitor CDKN1A (p21), a stalwart mechanism of protection from radiation in many normal and malignant cells. Cell-cycle arrest mediated by p21 extends the opportunity for a cell to execute the DNA-damage response and repair and thereby avoid deletion by apoptosis.

The mechanism described builds on pre-existing evidence of diminished immunosurveillance of irradiated normal skin[2] and introduces an immunological dimension to the role of radiation as a carcinogen[3]. The authors speculate that the peculiar resistance of LCs to radiation and their induction of T_{reg} cells might have evolved as a mechanism to preclude autoimmunity toward the skin, an organ constantly exposed to damage from ultraviolet radiation. Interestingly, among atomic-bomb survivors exposed to total-body radiation, the excess relative risk of skin cancer was 15, 5.7 or 1.3 as a function of age with exposure at an age of 0–9, 10–19 or 20–39 years, respectively[4]. This age-dependent effect is intriguing from an immunological point of view, since an opposite trend would be expected on the basis of diminishing immunocompetence with age.

However, the generalization of these findings to clinical radiotherapy is invalid.

Experimental mice received total-body irradiation (TBI) in large doses (6 or 12 Gy, near and exceeding, respectively, the dose lethal to 50% of C57BL/6 mice) before being challenged by subcutaneous injections of B16 melanoma tumor cells. Irradiated mice developed larger tumors than their unirradiated control counterparts did shortly after TBI treatment (within 12–24 h), but the effect was abolished when mice were inoculated 5 weeks after TBI.

As Price *et al.* acknowledge in the discussion of their findings[1], the use of TBI in these experiments has little in common with the usual clinical practice of radiotherapy, in which localized radiation is delivered to established tumors, in a highly targeted fashion, with much effort expended to avoid normal tissue through the strategic use of fractions of much lower dose administered over time. Extensive experience in treating skin cancer with single-modality radiotherapy has demonstrated lasting tumor control in approximately 90% of basal cell carcinomas and 80% of squamous cell carcinomas[5]. Radiation therapy has maintained its solid role in the therapeutic arsenal for the treatment skin cancer since the 1900s[6], a fact difficult to reconcile with the conclusions of Price *et al.*[1]. Unfortunately, misinterpretation of this paper as evidence for a general immunosuppressive action of radiotherapy is already being delivered to the public (http://medicalxpress.com/news/2015-09-doctors-caution-radiotherapy-skin-cancer.html).

Thus, the work of Price *et al.*[1] needs to be considered in the context of current research delineating how localized radiotherapy of cancer can have both pro-immunogenic effects and immunosuppressive effects. The identification of critical cross-talk between radiation-induced signals and the immune system of cancer carriers offers the opportunity to both optimize the clinical use of radiotherapy and enhance the effects of cancer immunotherapies[7]. This rationale has inspired ongoing therapeutic investigations that combine immunotherapy agents to correct the immunosuppressive effects of radiation and/or enhance its immune system–promoting effects. For example, clinical radiotherapy can be successfully combined with blockade of immunological checkpoints that counteracts a radiation-induced increase in T_{reg} cells[8]. Moreover, evidence is emerging that local radiation therapy can convert a tumor into an individualized cancer vaccine in a setting of otherwise ineffective immunotherapy and can work in concert with immunotherapy to control the primary tumor and metastasis outside the radiation field[9,10].

COMPETING FINANCIAL INTERESTS
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Price, Idoyaga and Merad reply:

A recent article from our group reported on an underlying mechanism of resistance to depletion by ionizing irradiation that is used by LCs, a unique population of dendritic cells that reside in the epidermis[1]. Formenti *et al.* raise one major objection to our report: that our mouse model system bears little resemblance to clinical radiotherapy. In our tumor-challenge experiments, we administered TBI at a dose of 6 Gy to mice that we subsequently challenged subcutaneously with B16 cells. As stated in our initial report, our goal was two-fold. First, we sought to determine the effect of conditioning-radiation therapy on the local