STEM CELLS TRANSLATIONAL MEDICINE®

LETTERS TO THE EDITOR

In Reply

In their letter to the editor [1], Raj et al. suggested that extreme caution should be taken prior to infusing mesenchymal stem cells (MSCs) as a cell-based drug delivery vector into patients with cancer due to the potential risk for promoting disease progression. Although we tested unmodified MSCs with no therapeutic potential [2], the approach used in this study was considered safe given that infusing allogeneic MSCs 4–6 days preprostatectomy is unlikely to alter the natural course of an individual's prostate cancer. It cannot be emphasized enough that caution should always be paramount when translating a new therapeutic platform into the clinic, and we acknowledge that tumor promotion is a theoretical concern. However, it is important to consider that this is not strongly supported by available clinical evidence that includes hundreds of clinical trials and thousands of patients, although it is also not clear that rigorous human studies in cancer patients have been conducted to assess this specific risk. We agree that MSCs have well-documented pro-tumorigenic properties, including pro-angiogenic and immunosuppressive potential as published by ourselves and many others in multiple preclinical animal models [3–8]; however, this does not necessarily preclude their use as a cell-based *drug delivery* vector in future studies for men with metastatic prostate cancer, assuming tumor homing efficiency can be improved upon and cells can be engineered to deliver a cytotoxic payload [2]. In addition, there is sparse evidence of long-term engraftment and the most consistent result from prior studies testing MSCs is that they are safe and well-tolerated in patients across a broad disease spectrum [9]. This includes no evidence of cellular transformation or tumor promotion in patients receiving large numbers of infused MSCs (i.e., 2×10^6 cells per kilogram up to 2×10^8 total); the first of whom were treated more than two decades ago [10–13]. For prostate cancer, the sheer incidence would argue that many of the men enrolled in these studies had diagnosed or occult disease, not to mention the thousands of patients that receive bone marrow transplants annually that also contain MSCs if an unselected product is used.

We would like to highlight that there is a distinct difference between the recruitment and/or expansion of endogenous (i.e., autologous) MSCs in tumors and the infusion of *allogeneic* MSCs as a cell-based drug delivery vector; the vast majority of which are entrapped in the lung and do not home to tumor tissue in robust numbers [14]. As stated above, there is no evidence of long-term MSC engraftment in any clinical study to date, at least in an allogeneic nonbone marrow transplant immunocompetent setting [11]. This is true of preclinical rodent and advanced primate models as well with limited persistence observed in vivo due to alloreactivity and death of the majority of cells <48 hours postinfusion [15–20]. Therefore, the direct effects of allogeneic MSCs are acute in nature; a point further documented by the weekly infusions required for the only clinical indication in which MSCs have demonstrated sufficient clinical efficacy to receive approval thus far—acute graft versus host disease. This observation does not argue that acute effects cannot promote long-term beneficial outcomes in damaged tissue—for example, by limiting acute fibrotic responses. Furthermore, if one believes that MSC recruitment is an ongoing process during malignant progression, as we have argued [6], and one assumes that infused allogeneic MSCs can supplant endogenously recruited ones that can promote disease progression, it would seem preferable to have those recruited cells carry with them a cytotoxic agent to counterbalance the pro-tumorigenic properties with a therapeutic effect [21].

In summary, although preclinical models have demonstrated that MSCs have pro-tumorigenic properties, primarily in syngeneic or immunocompromised coinoculation settings, clinical evidence does not support this being a significant risk in the context of allogeneic infusion for cell-based drug delivery. This is based on the collective experience of thousands of patients that have received MSCs in clinical trials worldwide for a variety of clinical indications with a well-tolerated safety profile and no evidence of ectopic tissue formation or tumor promotion [10–13]. It is also worth noting that there are three additional ongoing or completed phase I or I/II trials at independent institutions using genetically modified MSCs administered for therapeutic benefit in ovarian, lung, and gastrointestinal stromal tumor patients with no adverse events reported [14, 20, 22]. It is understood that these clinical observations are not definitive evidence of no risk and that more rigorous human studies with longer follow-up are required to be conclusive. However, they do support proceeding with clinical evaluation of these engineering cell platforms for tumors in organ sites that show high levels of entrapment or clearance postinfusion (e.g., lung, liver) or local delivery is an option (e.g., ovarian, glioblastoma), and potentially other tumor types if methods to enhance tumor tropism are developed or efficacy can be demonstrated at low levels of homing with transient engraftment. Future strategies that successfully enhance tumor tropism could also incorporate "suicide genes" or other approaches to eliminate the infused cells if necessary to further mitigate the potential for adverse outcomes. Despite the low perceived risk based on available evidence, continued development of these platforms should be predicated on careful monitoring of continued safety in treatment cohorts for unexpected sequelae. This is essential for further clinical translation and hopefully implementation of these innovative next-generation cell-based drug delivery strategies in a safe and effective manner.

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Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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