To the Editor:

In a recent Perspective, Bianco *et al.*[1] addressed a number of misconceptions regarding the biological nature and function of bone marrow–derived mesenchymal stem cells (MSCs) and their impact on current efforts to achieve clinically successful MSC-based therapies. The MSC committee of the International Society of Cell Therapy (ISCT) applauds this endeavor and strongly supports a number of opinions articulated in the Perspective. For example, the committee agrees that the widespread use of qualitative metrics to evaluate multipotency *in vitro* has led to the erroneous conclusion that virtually all adherent cells derived from connective tissues represent functionally equivalent MSC populations that are equally potent from a clinical perspective. Indeed, Bianco *et al.*[1] correctly point out that the use of organ-specific stem cells to treat organ-specific diseases provides the greatest probability of successfully translating stem cell science into clinical therapies.

Nevertheless, the committee feels that criticisms levied against efforts to exploit nonprogenitor MSC functions to treat diseases outside of the skeletal system were biased and in some regards unfairly critical. For example, Bianco *et al.*[1] state that the nonprogenitor effects of MSCs, such as immune modulation, remain unknown and unverified and have escaped conclusive validation in defined *in vivo* model systems. The committee advocates a more balanced view on this topic. Although stromal cells from different connective tissues have lineage-specific properties and therefore do not all fall under the narrow definition of 'skeletal stem cells', the prevailing literature indicates that these cells share some nonprogenitor functions[2] and may therefore be therapeutically effective for treating specific clinical indications outside of the skeletal system. We submit that some claims about the therapeutic potency of MSCs are exaggerated. However, Bianco *et al.*[1] did not acknowledge the rapidly expanding body of literature exploring nonprogenitor MSC functions, which in some cases have provided a solid foundation for moving forward with MSC-based clinical therapies. For example, rapid progress in dissecting the immune-modulatory functions of MSCs was achieved in part because many proteins that have been shown to contribute to this activity, such as Toll-like receptors, inducible nitric oxide synthase (iNOS), indoleamine 2,3-dioxygenase (IDO), prostaglandin E receptor 2 (PGE_2), B7 homolog 1 (B7-H1) and human leukocyte antigen G (HLA-G), have well-described functions in the immune system. Moreover, several studies published in high-impact journals, including *Nature Medicine*, have demonstrated that MSC-mediated immune modulation yields a therapeutic benefit in experimental animal models of sepsis[3], graft-versus-host disease (GvHD)[4] and asthma[5]. These studies used molecular and genetics-based approaches to examine the underlying mechanisms of action. Although it is true that the precise mechanisms of MSC-based therapies in human patients are largely inferred, completed phase 1 and 2 clinical trials have reported statistically significant benefits in patients with steroid-resistant GvHD[6], severe systemic lupus erythematosus[7] and complex perianal fistulas[8]. Clinical trial data also exist indicating that MSC-based therapies may benefit patients with cardiac disease[9]. It is important to note that not all MSC-based clinical trials have met their primary endpoint of efficacy, including an industry-sponsored phase 3 trial of mass-produced, random-donor MSCs for the treatment of GvHD[10]. However, negative clinical trial results are also valuable in informing the translational development of a cellular product.

Although the field of regenerative medicine is rife with unsubstantiated claims of benefit and is often biased by strong commercial interests, it is important that the legitimate scientific enterprise does not allow this noise to overshadow meaningful advances in the field. By providing a skeletal system–centric view of MSCs, the Perspective by Bianco *et al.*[1] relegates the rapidly growing body of literature dedicated to exploring nonprogenitor functions of MSCs, including immunomodulation, to obscurity and undermines the efforts of legitimate and dedicated scientists to understand these functions and exploit them to achieve a therapeutic benefit in human patients. Indeed, our committee believes that the existing scientific data are sufficiently mature to warrant MSC-based clinical trials for disease indications beyond the skeletal system. However, we acknowledge that the sound establishment of MSC-based therapies requires controlled, randomized, prospective clinical trials that incorporate mechanistic-based studies to fully assess the pharmaceutical underpinnings of such therapy.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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To the Editor:

In their recent Perspective, Bianco *et al.* indicated that uncertainties regarding the nature, identity, function, mode of isolation and handling of mesenchymal stem cells (MSCs) have a major impact on their envisioned therapeutic use[1]. Although there is merit in this work, we would like to highlight some limitations in the definition of therapeutic reagents and debate the basic principles that characterize experimental medicine.

The authors clearly summarize the evidence underlying the identification of specific skeletal self-renewing stem cells and progenitors and indicate that these are system defined and are therefore both structurally and functionally different from nonprogenitor connective tissue cells—sometimes referred to as MSCs—that can be found in almost every organ. We fully endorse the need to keep these two cellular entities separate to avoid confusion between stem and progenitor functions and the regulation of tissue homeostasis. This distinction is fundamental in understanding the rationale behind the current therapeutic applications of mesenchymal 'stromal' cells. The definition of stromal cells has undergone a paradigm shift in recent years. In addition to the traditional view of stromal cells supporting and organizing a parenchymal framework, numerous studies have unveiled their important role in modulating tis-