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Response to *Nature* commentary "Clear up this stem-cell mess"

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In a Comment entitled "Clear up this stem-cell mess" published in the September 27, 2018 issue of *Nature*, Sipp *et al.* argue that "confusion about mesenchymal stem cells is making it easier for people to sell unproven treatments" [1]. The authors discuss the explosive growth of stem cell medical tourism clinics worldwide where legitimate scientific advancements and the vernacular of science are misappropriated as part of marketing strategies to promote the sales of unproven cellular therapies branded as stem cells. We applaud the Commentary's effort and are grateful for the visibility afforded to the vexing issue of stem cell tourism. The International Society for Cellular Therapy (ISCT) as well as other scholarly societies toiling in the stem cell discovery and cell therapy space have long been at the forefront of advocacy, education and lobbying against the unethical and illegal selling of unproven stem-cell therapies of all ilk and mesenchymal stromal cells (MSCs) in particular. The authors further propose that MSC terminology facilitates deceit by medical tourism outfits by specifically appropriating the key word "stem" as a means to obfuscate the public. The authors propose as a remedy that discovery and translational science self-identified as MSC-centric should be excluded at scientific forums, proscribed by scholarly publications and rendered ineligible for peer-reviewed "stem cell" public funding. This is where we diverge with the Commentary and its conclusions.

Clearly, stem-cell medical tourism outfits routinely appropriate scientific terminology – like MSCs – to give the illusion of legitimacy. We further agree that publicly curated websites such as clinicaltrials.gov can be coopted by unscrupulous medical tourism operations for a wide array of cell therapy interventions outside the Food and Drug Administration (FDA) jurisdiction including, but not limited to, MSCs.

Although various acronyms have been used in the past to describe MSCs, it is now widely recognized that culture-adapted progeny derived from tissue resident mesenchymal progenitors are not to be conflated with endogenous mesenchymal stem cells. The cell biological properties of culture-expanded MSCs may well share some imprinted functional similarities with the endogenous native progenitors that may or may not be relevant in their use as an experimental cellular pharmaceutical. Although the designation of MSCs was as stem-cells at their inception in 1991, their further re-designation as "stromal" accurately reflects the meaningful differences between endogenous and culture-adapted MSC products.

To reflect this distinction the ISCT issued in 2006 guidelines recommending the term "multipotent mesenchymal stromal cells" as a more accurate moniker, and these guidelines have gained wide acceptance by the scientific community [2]. The ISCT is also engaged in educating scientific and business communities as well as the public in the potential abuse of cell therapies including the unethical distribution for profit of unproven cell therapies outside of institutional review board (IRB)–sanctioned and regulated clinical trials [3]. Furthermore, an array of learned societies, including the World Health Organization (WHO), International Council for Commonality in Blood Banking Automation (ICCBBA) and the International Standards Organization (ISO), strive to adapt MSC etymology to keep apace of requirements of consensus terminology.

Sipp *et al.* appropriately state that clinical studies using MSCs (or any stem cells for that matter) must

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adhere to the same standards of research design and oversight that apply to any responsible clinical trial before the cells are administered to human participants. We feel that the editorial thread pursued conflates the activities of medical tourism outfits with legitimate IRB-sanctioned and regulator-licensed clinical trials conducted by ethically minded industrial and academic entities, including the National Institutes of Health (NIH), in the conduct of clinical trials. The discussion would have been enriched by acknowledgement of recent European Union (EU) approval of Alofisel (darvadstrocel; allogeneic Adipose Stromal Cells (ASCs) for Crohn's fistular disease) by the EU that followed publication of an adequately powered and designed industry-sponsored clinical trial required for marketing approval of MSCs. Importantly, a number of rigorously peer-reviewed publicly and privately funded regulator-compliant trials are underway in the US, Europe and Asia to determine the utility of MSCs for therapeutic use.

A rich scientific literature of MSC discovery and well-designed clinical trials of MSCs for therapeutic use speak to the impact of the field on human therapeutics [4]. The implication that studies nominally examining MSCs should be disqualified from publication or funding is an ill-considered posture that runs counter to the interests of the scientific community and public. The ISCT will continue to maintain its support for evidence-based translation of MSC therapies to improve patients' lives.

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