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Mesenchymal Stem Cells Beyond Regenerative Medicine

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Mesenchymal stem cells (MSCs) are competent suitors of cellular therapy due to their therapeutic impact on tissue degeneration and immune-based pathologies. Additionally, their homing and immunomodulatory properties can be exploited in cancer malignancies to transport pharmacological entities, produce anti-neoplastic agents, or induce anti-tumor immunity. Herein, we create a portfolio for MSC properties, showcasing their distinct multiple therapeutic utilities and successes/challenges thereof in both animal studies and clinical trials. We further highlight the promising potential of MSCs not only in cancer management but also in instigating tumor-specific immunity – i.e., cancer vaccination. Finally, we reflect on the possible reasons impeding the clinical advancement of MSC-based cancer vaccines to assist in contriving novel methodologies from which a therapeutic milestone might emanate.

Keywords: MSC, regeneration, autoimmunity, cancer, antigen, vaccine

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INTRODUCTION

Broadly distributed among tissues, MSCs are first generation adult stem cells of mesodermal non-hematopoietic origins. They were originally reported in bone marrow (BM) by Friedenstein et al. (1968, 1970) and later identified in adipose tissue, peripheral blood, cruciate ligaments, dental pulp, menses blood, amniotic fluid, fallopian tube, placenta, umbilical cord, and endometrial polyps (Caplan, 1991; Bianco et al., 2008; Ding et al., 2011; Sheng, 2015; Ullah et al., 2015). According to the International Society for Cellular Therapy (ISCT), MSCs are characterized by their (i) adherence to plastic, (ii) cell surface expression of CD73, CD90, and CD105 but not CD45, CD34, CD14, CD11b, CD79α, CD19, and HLA-DR (hematopoietic cell markers), and (iii) multipotency, the ability to differentiate into various mesodermal cell lineages such as osteoblasts, chondroblasts, and adipocytes (Dominici et al., 2006). However, the ISCT definition is no longer standardized

Abbreviations: ALS, amyotrophic lateral sclerosis; APC(s), antigen secreting cell(s); BM, bone marrow; CX3CL1, C-X3-C motif chemokine ligand 1; CXCR4, C-X-C Motif Chemokine Receptor 4; DC(s), dendritic cell(s); GMP, good manufacturing practice; GvHD, graft-versus-host disease; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; ISCT, International Society for Cellular Therapy; MAP, mitogen activated protein; MI, myocardial infarction; MIF, Migratory Inhibitory Factor; miRNA, microRNA; MSC(s), mesenchymal stem cell(s); NK, natural killer; NO, nitric oxide; PD-L1, programed death-ligand 1; SDF-1, stromal-derived factor-1; TLRs, toll-like receptors; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; T_{reg}, regulatory T cell; TSG6, tumor necrosis factor-inducible gene 6 protein.

as MSC identification criteria continue to change. Exemplifying this are the discovery that MSCs can also differentiate into cells of ectodermal and endodermal parentage (Wei et al., 2013) and the inclusion of novel surface markers to their identity (CD165, CD276, and CD82) (Al-Nbaheen et al., 2013). Several studies on MSC lineages have also identified distinctive molecular (Al-Nbaheen et al., 2013; Ullah et al., 2015; Wu et al., 2018), proliferation/differentiation (Kern et al., 2006), and functional properties (Keyser et al., 2007), accrediting the fact that their biology is still partially intelligible. The conventional notion, however, is that MSCs are (i) genomically stable, (ii) highly accessible, (iii) easy to isolate and expand, (iv) immune-privileged (low expression of MHC I/II and co-stimulatory molecules and – further explained in Section "Immunological Properties: A Paradigm" – immunomodulation), and – unlike other types of stem cells – (v) non-teratogenic and ethically conforming (Wei et al., 2013). Additionally, a number of reports showing that BM-MSCs from healthy donors perform better in proliferation/differentiation and secretion criteria compared to BM-MSCs from osteoarthritic (Murphy et al., 2002) and Gaucher disease patients (Campeau et al., 2009) corroborate that MSCs play a physiological role in homeostatic tissue maintenance, whereas their disturbance may foster disease pathogenesis. In this review article, we recapitulate a vast literature on MSC assets, demonstrating from preclinical and clinical perspectives how they render them fit candidates for cellular therapy. Finally, we discuss the trend of MSC utility against tumors to bridge to the highlight of this review – MSCs as cancer vaccines – pinpointing the flaws halting their clinical effectiveness while offering novel insight on how to overcome them.

MSC FITNESS FOR CELLULAR THERAPY

Regenerative Properties

Numerous studies illustrate the regenerative potential of MSCs based on their homing, engraftment, (trans)differentiation, and ability to replace apoptotic/necrotic tissue or dissipate paracrine signaling to boost injured tissue function (Prockop, 1997). *In vitro*-cultured systemically-infused MSCs home *via* their chemokine and toll-like receptors (TLRs) into several organs including BM, heart, and liver in which they can persist for prolonged periods of time (Devine et al., 2001; Allers et al., 2004; Lüttichau et al., 2005; Tomchuck et al., 2008). Factors in favor of homing are young recipient age, irradiation, decreased cell passage number, cytokines/inflammation, as well as increased chemokine receptor and TLR expression (Horwitz et al., 2002; François et al., 2006; Shi et al., 2007; Kyriakou et al., 2008; Tomchuck et al., 2008). Besides the former receptors, MSCs express a variety of adhesion molecules, endopeptidases, and growth factors in addition to their cognate receptors, which facilitate MSC tethering, endothelial rolling, and transmigration to tissues (De Becker and Van Riet, 2016). MSCs might mobilize as well under several stimuli such as growth factors (Asahara et al., 1999) and xenobiotics (Llevadot et al., 2001) before engrafting into tissues where they either (trans)differentiate to the constituent cells (Prockop et al., 2010) or secrete various humoral factors in the extracellular space such as cytokines, chemokines, and mRNA/microRNA (miRNA)-containing microvesicles to modulate tissue function (Wei et al., 2013). Factors influencing tissue engraftment efficiency are cell death, immune rejection, and first-pass lung entrapment which can be overcome by optimizing delivery methods, ameliorating target tissue receptivity, and schooling MSCs to resist tissue hostility (Kean et al., 2013; Ezquer et al., 2017).

Following adherence to plastic *in vitro* or tissue engraftment *in vivo*, MSCs form colonies and (trans)differentiate into a myriad of cell lineages (Kuznetsov et al., 1997; Li H. et al., 2006; Wang et al., 2012; Vonk et al., 2018). For this to occur, their microenvironment must contain multiple mitogenic or stimulating factors (Tontonoz et al., 1994; Sekiya et al., 2002; Lucarelli et al., 2003; Solchaga et al., 2005; Fontaine et al., 2008; Inada et al., 2008; Pavlova et al., 2012); be subjected to hypoxic conditions (Mohyeldin et al., 2010; Zhang et al., 2019); or scaffolded to closely mimic organ architecture or function (Ouyang et al., 2003; Ohgushi et al., 2005). However, a newer understanding of the regenerative abilities of MSCs *in vivo* later emerged, linking tissue regrowth not to MSC (trans)differentiation exclusively but rather to autocrine and paracrine signaling transduced through their communication with local stimuli (Crisostomo et al., 2008), growth factors (Hahn et al., 2008), and inflammatory mediators (Haynesworth et al., 1996). This creates a rich nutritive milieu to which cells in the vicinity also contribute (Caplan and Dennis, 2006). Within the trophic environment are factors dictating angiogenesis (Min et al., 2002), hindrance of apoptosis (Xu et al., 2007), inhibition of fibrosis, mitosis in local tissue (Takahashi et al., 1999), and formation of a structural niche with other resident stem cells (Méndez-Ferrer et al., 2010). In addition, MSCs secrete microvesicles and exosomes which contain pro-angiogenic growth factors and miRNA as a means to establish cell-to-cell communication (Gong et al., 2017; Phinney and Pittenger, 2017). On the other hand, multiple factors can still hamper MSC regenerative functions such as temperature, media type (Kubrova et al., 2019), interference of plastic adherence with cellular function (Mabuchi et al., 2012), chromosomal abnormalities, transformation, and tumor growth especially in MSCs of murine sources. Having said that, isolation and culture protocols recently developed for human MSCs derived from healthy subjects appear as promising endeavors to overcome those hurdles (Bernardo et al., 2007; Law and Chaudhuri, 2013; Conforti et al., 2016). For example, transformation and persistence were addressed in a protocol that uses skin tissue of patients undergoing any relevant medical intervention. To obtain MSCs, the tissues are disinfected and enzymatically digested in good manufacturing practice (GMP). Cell yields are then sorted with antibody-coupled magnetic beads, and cultured MSCs are validated according to ISCT criteria. Finally, several tests are performed to assess *in vivo* toxicity, tumorigenicity, and biodistribution/persistence (Tappenbeck et al., 2019). The data of another clinical study, which warranted its authors an "orphan designation" in Germany for graft-versus-host disease (GvHD) treatment using MSCs, authenticate the effectiveness of such

protocol. Indeed, generating the MSCs entailed the enrichment of BM aspirates of several donors using an automated cell separation unit and processing system followed by the expansion of MSCs in culture over 14 days. From this bank, clinical-grade MSCs are obtained and cultured in platelet lysate serum-free media whose utility eliminates the risks associated with the use of fetal bovine serum such as immunogenicity and pathogenicity (Kuçi et al., 2016; Bader et al., 2018).

Immunological Properties: A Paradigm

In addition to its tissue repair characteristics, the secretome of MSCs displays immunomodulatory properties. This is evident in the ability of MSCs to interfere with the cell cycle (G0/G1 phase arrest), hinder the responses of naïve and memory T cells, inhibit the activation and proliferation of effector T cells, and induce regulatory T cell (T_{reg}) function (Krampera et al., 2003; Siegel et al., 2009; Duffy et al., 2011; Haddad and Saldanha-Araujo, 2014). Such immunosuppressive activity essentially ensues in response to inflammatory signals including interferon-γ (IFN-γ), TNF-α, and interleukin-1 (IL-1). These pro-inflammatory molecules prime MSCs, such that they induce the secretion of multiple soluble immunosuppressive molecules and the upregulation of inhibitory surface co-receptors including programed death-ligand 1 (PD-L1) (Sheng et al., 2008). Those mechanisms are protective against immune cells such as natural killer (NK) cells which become cytolytic upon activation by inflammatory signals, the same signals inducing the upregulation of MHC class I/II on MSCs and subsequently their susceptibility to NK cell cytotoxicity. Interestingly, NK cells/MSCs ratio is the determinant of the inhibitory power balance. For example, lower ratios tip the suppressive balance in favor of MSCs which become capable of inducing phenotypic and secretory changes in NK cells *via* physical and paracrine interactions, thereby restricting their cytotoxicity and proliferation (Sotiropoulou et al., 2006; Jewett et al., 2010; Spaggiari and Moretta, 2012). Pro-inflammatory signals also support MSC differentiation through multiple receptors like TLRs and signaling pathways like NF-κB, p38 mitogen-activated protein (MAP) kinase, and β-catenin, ultimately inducing the transcription of lineage-specific genes (Cheng et al., 2008; Wei et al., 2013; Chen et al., 2016; Liu et al., 2018). For instance, NF-κB and MAP kinase pathways are activated by stromal cell-derived factor-1 (SDF-1), a pleotropic chemokine secreted by several cells and organs, which acts as a chemoattractant for MSCs in regenerative settings (Kucia et al., 2004). Elsewhere, however, NF-κB upregulation by pro-inflammatory cytokines was negatively correlated with MSC differentiation, particularly osteogenesis (Ansari et al., 2017). In contrast, the absence of strong inflammatory stimuli (e.g., low levels of inflammatory or anti-inflammatory cytokines) does not trigger the production of immunosuppressive factors, thus permitting a pro-inflammatory environment to takeover. This is evident in a few studies showing that *in vivo* transplantation of unchallenged allogeneic MSCs evokes cellular and humoral immune responses (Eliopoulos and Galipeau, 2002; Poncelet et al., 2007; Renner et al., 2009). Furthermore, inflammatory signals allow MSCs to govern the activity of multiple innate and adaptive immune cells including B cells, neutrophils, and macrophages through secreted soluble factors such as prostaglandins, chemokine ligands, interleukins (ILs), growth factors, and nitric oxide (NO) (Singer and Caplan, 2011). Those factors interfere with inflammatory signaling pathways (e.g., STAT3), ultimately mitigating antigen presentation and humoral immunity (Rafei et al., 2008; Loebinger and Janes, 2010). In addition to their secretome, MSCs can mitigate mixed lymphocyte reactions by physically hindering the contact of T cells with antigen presenting cells (APCs) (Krampera et al., 2003); JAG1-NOTCH interaction is shown to partake in the process (Liotta et al., 2008). Overall, immunosuppressive MSCs, later designated as MSC2, contribute to tissue healing and regeneration not only by impeding injury-driven autoimmune responses but also by educating macrophages, *via* IL-6, toward a proangiogenic M2 phenotype. M2 macrophages, therefore, tip the balance of T-cell responses in favor of immune regulation (anti-inflammatory T_{regs}) (Eggenhofer and Hoogduijn, 2012; Bernardo and Fibbe, 2013; Chung and Son, 2014).

Paradoxically, few reports have challenged the sole immunosuppressive dogma, offering a novel insight into the polarization of MSCs toward another "pro-inflammatory" type, in a similar fashion to "macrophage polarization" (Krampera, 2011). Waterman et al. designated this pro-inflammatory phenotype MSC1. Consequently, MSC2 identified its immunosuppressive counterpart (Waterman et al., 2010). The polarization into either phenotype is originally induced by TLRs and is ligand-specific. For instance, TLR3 and TLR4 priming by, respectively, poly(I:C) and lipopolysaccharide induce the MSC1 phenotype. In the process, downstream TLR signaling instigates pro-inflammatory secretome patterns (ILs, chemokine ligands, growth factors, apoptosis-inducing ligands) and impairs JAG1-NOTCH interaction between MSCs and T cells. This prevents MSC-mediated immunosuppression (Liotta et al., 2008; Romieu-Mourez et al., 2009) and permits IFN-γ-driven MSC antigen presentation to $CD4^+$ and $CD8^+$ T cells, thereby evoking immune activation (Chan et al., 2006; François et al., 2009). Similar observations are evident in co-cultures of MSCs and B cells, where the latter's proliferation, cytokine expression, and differentiation are improved (Rasmusson et al., 2007). On the other hand, immunosuppressive secretome patterns (IDO, prostaglandins) ensue downstream TLR signaling during MSC2 polarization (Waterman et al., 2010). Plus, MSC polarization is TLR type-specific. For instance, TLR4-primed MSCs polarize into MSC1, while TLR3 priming favors the immunosuppressive MSC2 profile in certain studies (Waterman et al., 2010) and MSC1 in others (Romieu-Mourez et al., 2009; Kota et al., 2014). Besides differences in TLR-ligand interactions and TLR type signaling, factors such as ligand concentrations (low concentrations license MSC1 phenotype), priming duration, microenvironment (cytokines, growth factors, stimulants), infections/diseases, tissue lesions, and MSC-T cell engagement timing are also at play in polarization licensing (Krampera, 2011; Strioga et al., 2012).

Despite its controversy, MSC polarization is thought to be part of tissue maintenance, where both distinct phenotypes homogeneously act in injury settings. To this extent, MSC1 may be important early in the process to drive chemotaxis and

subsequent reparative processes, while MSC2 may act later to resolve inflammatory tissue injury (Romieu-Mourez et al., 2009; Waterman et al., 2010). Similarly, the process can be exploited not only in regenerative medicine, which depends on inflammatory signals but also in cancer management which, as later discussed, depends on MSC inflammatory and migratory properties, both of which are induced by TLR priming (Waterman et al., 2010).

MSCs IN THERAPY: ACHIEVEMENTS AND PITFALLS

Regenerative Medicine

The regenerative and immunological assets of MSCs (see Sections "Regenerative Properties" and "Immunological Properties: A Paradigm") are widely exploited in degenerative settings. In animal models of myocardial infarction (MI), percutaneously injected allogeneic MSCs ameliorated ventricular fibrosis and scarring. Reduced infarct size, myocardial regeneration, enhanced cardiac metabolism and hemodynamics were also recorded (Amado et al., 2005; Cai et al., 2016). In *E. coli* endotoxin-injured human lungs, administration of allogeneic human MSCs reduced extravascular fluid and septal thickening, enhanced alveolar fluid transport, and restored the fluid balance of alveolar compartments (Lee et al., 2009). In rat models of retinal degeneration, the injection of MSCs into the subretinal space enhanced the viability of photoreceptor cells without replacing them (Inoue et al., 2007). In various mouse models of excisional wound healing, the application of MSC-conditioned media enriched in chemokines and cytokines increased the infiltration of macrophages and endothelial progenitor cells into the wounded area (Wu et al., 2007; Chen L. et al., 2008; Sasaki et al., 2008). Similar repair mechanisms induced by MSCs were described in the context of corneal injury (Roddy et al., 2011), colitis (Hayashi et al., 2008), neurodegenerative disorders (Tsai et al., 2019), hepatic injury (Anger et al., 2019), cardiac hypertrophy (Cai et al., 2015), and acute renal failure (Tögel et al., 2005).

A more sophisticated approach in regenerative medicine is MSC engineering on both genetic and architectural levels. In the former, MSC gene expression is altered through viral vector- or electroporation-mediated gene transfer; then their homing capacity to injured/ischemic sites is utilized for local delivery of overexpressed therapeutic genes. Examples on MSC-delivered genes are SDF-1 to ameliorate MI and ischemic brain injury (Penn and Khalil, 2008), glucagon-like peptide-1 to reduce amyloid deposition in Alzheimer's brains (Klinge et al., 2011), and IL-10 to restrain collagen-induced arthritis (Choi et al., 2008). Architectural MSC engineering involves cell culturing to obtain cellular sheets which can be further maintained in organ-specific stimulating media or assembled onto organ scaffolds to restore injured or defective tissue [e.g., bone regeneration (Yorukoglu et al., 2017) and spinal cord injury (Zeng et al., 2011) applications].

This preclinical success permitted the transit to human studies, with no records of toxicity or tumorigenicity with the use of GMP-compliant human MSCs suitable for clinical trial use (Tappenbeck et al., 2019). Up to this date, 921 clinical studies employing MSCs as the primary intervention have been registered, 704 of which date between 2011 and 2019 (U. S. National Library of Medicine, 2019). This booming, particularly in the last decade of the current century, is indicative of MSC potential to ameliorate a plethora of degenerative diseases (further elaborated in **Table 1**) (Wei et al., 2013), bearing simultaneously their major implication in physiological tissue maintenance (Murphy et al., 2002; Campeau et al., 2009).

Nevertheless, the clinical utility of MSCs faces various limitations including cell source availability (De Bari et al., 2001; Fitzsimmons et al., 2018) and specificity (De Ugarte et al., 2003; Sudres et al., 2006), clinical-grade production compliance with GMP (Sensebé, 2008), scalability (Fitzsimmons et al., 2018), administration timing (Tisato et al., 2007; Polchert et al., 2008; Le Blanc et al., 2008) and technique (Singh et al., 2016), engraftment rate (Fouillard et al., 2003; Le Blanc et al., 2008), polarization control (Polchert et al., 2008; Waterman et al., 2010), localization post-transplant (Law and Chaudhuri, 2013), and tissue persistence (Togel et al., 2005). This is explanatory of the limited number of MSC-based final stage trials and approved biopharmaceutical products. Until 2019, 50 studies have hit Phase III, with only 14 completed (NIH, 2019). Therefrom, 11 MSC-based therapies emanated (BioInformant, 2019) for the treatment of 7 degenerative and immune-based conditions including knee cartilage defects, hip joint avascular necrosis, and coronary angioplasty-reperfused acute MI (PHARMICELL, 2011; ANTEROGEN, 2012; Corestem, 2015; European Medicines Agency, 2017; MilliporeSigma, 2017; Orthocell, 2017; European Medicines Agency, 2018a; Regrow Biosciences®, 2019). However, none of these therapies are approved so far by the FDA (FDA, 2019a) which demands compelling clinical evidence from reliable well-controlled trials, stronger policy compliance, and extensive premarket reviews (Marks et al., 2017; FDA, 2019b).

Immune-Based Disorders

As discussed earlier (see section "Immunological Properties: A Paradigm"), MSCs possess immunomodulatory functions exhibited by their direct (cytokine-mediated) or indirect (T_{regs} modulation-mediated) inhibition of immune cells (Singer and Caplan, 2011; Haddad and Saldanha-Araujo, 2014). Those features are advantageous in treating immune-based disorders (Fitzsimmons et al., 2018). As such, therapies in this context exploit the immunomodulatory nature of MSC secretome which comprises NO, transforming growth factor-β, indoleamine 2,3-dioxygenase (IDO), prostaglandin E2, tumor necrosis factor-inducible gene 6 protein (TSG6), CCL-2, and PD-L1 among others. This immunomodulatory pool induces other immune cells to either modify/reprogram their response type (e.g., Th2 humoral-to-Th1 cellular immune response; dendritic cells (DCs) types 1 and 2 cytokine profile changes; and Th17-to-T_{reg} cell reprograming) (Aggarwal and Pittenger, 2005; Figueroa et al., 2012; Le Blanc and Mougiakakos, 2012) or generate immunosuppressive factors (Aggarwal and Pittenger, 2005; Han et al., 2012; Wei et al., 2013). As a result, MSCs are able to ameliorate pronounced immunity which is manifested in animal models of sepsis (Németh et al., 2009), autoimmune diseases

TABLE 1 | Clinical outcomes of MSC utility in regenerative therapy.

Clinical condition	Regenerative outcomes	References/NCT
Osteogenesis imperfecta	- Improvement of bone growth - Alleviation of fracture	Horwitz et al., 1999
Crohn's disease	Coverage of fistula	NCT01157650 (García-Olmo et al., 2005)
Deep thermal skin burns	- Restoration of wounds - Trigger of neoangiogenesis	Rasulov et al., 2005
Periodontal defects	- Reduction of pocket depth - Suppression of bleeding - Amelioration of teeth mobility	Yamada et al., 2006
Drug-resistant pulmonary tuberculosis	- Halting bacterial discharge - Resolution of tissular cavity	Erokhin et al., 2008
Liver cirrhosis	Amelioration of liver injury	NCT00420134 (Kharaziha et al., 2009) NCT00956891 (Peng et al., 2011)
Diabetic foot	Enhancement of perfusion	Lu et al., 2011
Chondral defects	- Pain alleviation - Increased activity scores - Improved histological façades	Kyriakidis et al., 2019
Maxillofacial bone defects	Increased bone cyst density	NCT01389661 (Redondo et al., 2018)

(Constantin et al., 2009; Rafei et al., 2009), neurodegenerative disorders (Ma et al., 2013), and GvHD (Polchert et al., 2008). In particular, the earliest advancement in MSC immune-based clinical applications was recorded in GvHD, a serious complication arising from MHC-mismatched allografts affecting 20–70% of transplant recipients (Lee et al., 2003; Socié and Ritz, 2014). MSC administration in this setting drew the attention of the scientific community in 2004 after the remarkable response against resistant grade IV acute GvHD of the gut and liver in a 9-year-old boy who received the first transplantation of haploidentical MSCs (Le Blanc et al., 2004). Other phase II/III clinical trials followed, reporting variable levels of effectiveness (Introna et al., 2014; Van Der Wagen et al., 2014). In 2009, an industry-led large-scale phase III study evaluated the use of allogeneic BM-derived MSCs for treating steroid-refractory GvHD (NCT00366145) which occurs after failure of first-line corticosteroid treatment and affects 30–80% of graft recipients giving patients a 10–30% chance for long time survival (Luft et al., 2011). Despite the lack of a significant difference in clinical outcomes between placebo and treatment groups, a sub-group analysis led to the conditional approval of Prochymal^{TM} for the treatment of pediatric steroid-refractory GvHD (Kurtzberg et al., 2010; Martin et al., 2010) in Canada, New Zealand (2012) (Chisholm et al., 2019), and Japan (2015) (Sipp, 2015). Although the pass of Prochymal^{TM} was considered a breakthrough for MSC-based therapies, it remained largely unattainable in Canada and New Zealand due to strict prescription regulations and high manufacturing cost (USD 200,000) (Bersenev, 2016; Chisholm et al., 2019).

Moreover, an official approval for Darvadstrocel (Alofisel), an adipose human MSC injection, was granted by the European commission for the management of complex perianal fistulas in adult patients with mildly or non-active luminal Crohn's disease (European Medicines Agency, 2018b; Panés et al., 2018). The approval emanated from a Phase III trial reporting that Darvadstrocel led to 50% combined remission, which was maintained after 1 year of treatment, in comparison with 34% in the control arm (Panés et al., 2016, 2018; Panes et al., 2017). Interestingly, several "orphan designation" approvals were granted by the European commission according to certain guidelines for the use of human MSCs in the treatment of GvHD, thromboangiitis obliterans (Buerger disease), and ALS (Yu et al., 2018; European Medicines Agency, 2019). Bader et al. (2018) the holders of one of the "orphan designations" in Germany (PEI.A.11748.01.1) for the treatment of steroid-resistant or treatment-refractory acute GvHD with their MSC preparation [MSC-Frankfurt am Main (MSC-FFM)], reported superior treatment outcomes in both adults and children as opposed to the limited efficacy of Prochymal^{TM} in children. According to their study, the effectiveness of MSC-FFM is due to donor selection in addition to strict collection and preparation processes (Bader et al., 2018), which yield adequate doses of MSCs with high batch-to-batch consistency (Elgaz et al., 2019). The distinguished data on MSC-FFM clearly elucidate the reasons behind the discrepancies (different survival rates and response levels to allogeneic MSC) and failures of other phase III clinical trials (Galipeau, 2013; Galipeau and Sensébé, 2018). In addition to the variation related to patient selection criteria (age, type, and disease clinical-grade), qualitative variabilities between MSC preparations play an important role. Lack of standardized manufacturing procedures such as donor heterogeneity, tissue origin variability (BM or adipose tissue), cell cryopreservation, culture expansion, administered dose and timing, heterogeneity of host inflammatory biomarkers, and immunogenicity are also among the variables (Galipeau, 2013; Squillaro et al., 2016; Galipeau and Sensébé, 2018). This also accords the fact that currently available MSC-based therapies for treating immune disorders – Remestemcel-L (Prochymal®) and TEMCELL® for GvHD (JCR Pharmaceuticals Co, 2015; Locatelli et al., 2017), NeuroNata-R® for ALS (Corestem, 2015), and Alofisel and

Cupistem® for Crohn's anal fistula (ANTEROGEN, 2012; MilliporeSigma, 2017; European Medicines Agency, 2018a) – are still not FDA-approved despite their worldwide regulatory approval (Bernardo and Fibbe, 2013). Henceforth, further standardization of clinical-grade MSCs will better serve future clinical trials and facilitate international clinical approval. Equally important is expanding the knowledge of MSC polarization mechanisms and fates post-delivery (Duijvestein et al., 2010; Lechanteur et al., 2016; Russell et al., 2018; Grégoire et al., 2019).

MSCs AND CANCER

Cancer Support or Suppression?

Cancer management using MSCs stems from the ability of these cells to home to tumors. Indeed, tumor tropism is a complex process involving multiple receptors and soluble factors. For example, SDF-1/C-X-C Motif Chemokine Receptor 4 (CXCR4), a chemokine/chemokine receptor axis involved in stem cell trafficking and cancer metastasis, plays a major role in MSC tumor infiltration (Phillips et al., 2003; Kucia et al., 2004). Tumor secretome induces MSC secretion of SDF-1, which activates in an autocrine fashion migratory signaling pathways (STAT3 and MAP kinase) and regulates cytoskeleton reorganization. According to certain studies, SDF-1 may also be part of tumor secretome (Gao et al., 2009; Lourenco et al., 2015). Overexpression of CXCR4 can, therefore, be considered therapeutically relevant due to its ability to augment MSC homing efficiency (Cheng et al., 2008). Macrophage Migration Inhibitory Factor (MIF), a pleotropic cytokine involved in multiple biological processes including tumor metastasis, is also implicated in MSC homing to tumors (Han et al., 2018). Like SDF-1, tumor-secreted MIF binds, among other receptors, to CXCR4 (G_i-protein coupled receptor) and activates MAP kinase signaling pathway, eventually inducing MSC migration through upregulating cell motility genes. Other cytokines/chemokine ligands secreted by tumors also act as MSC attractants and may even trigger MSC expression of CXCR4 (Lourenco et al., 2015). In a similar fashion to CXCR4 overexpression, tumor homing can be amplified by engineering MSCs to overexpress specific tumor-binding receptors (Komarova et al., 2010). The homing process can be tracked with various *in vivo* optical- and fluorescent-based imaging techniques (Reagan and Kaplan, 2011). It is important to note that a recent clinical study showed that BM-derived MSCs failed to home to prostate cancer sites, an observation linked to the absence of inflammatory signals, which usually dictate MSC migration (Schweizer et al., 2019). These data might also question the innateness of unmodified allogeneic MSCs to home to tumors without reprograming (Serakinci and Cagsin, 2019). Therefore, additional clinical studies are necessary for validating the facts.

What's more, current literature presents with data discrepancies as to whether unmodified MSCs support or suppress cancer growth. The first school reports that bearing the significant resemblance between mesenchymal tumor cells and MSCs in terms of proliferation/differentiation and pro-angiogenesis (Galiè et al., 2008), local mesenchymal progenitors or administered unmodified MSCs enhance cancer growth and metastasis, thus creating an "immunological sanctuary" in which tumor cells avoid immune surveillance (Hanahan and Weinberg, 2000; Krampera, 2011). These MSC properties of cancer support are originally licensed by tumor-infiltrating macrophages which establish a pro-inflammatory chemotactants-studded milieu (Coffelt et al., 2009; Rigo et al., 2010). This milieu evokes MSCs to (i) differentiate into highly proliferative myofibroblasts (Von Ahrens et al., 2017) and vascular cells (Peters et al., 2005), (ii) produce tumor-nurturing pro-angiogenic cytokines, miRNA, and exosomes (Roccaro et al., 2013; Zhang et al., 2013; Dong et al., 2018), (iii) secrete extracellular matrix-forming lysosomal oxidase (El-Haibi et al., 2012), (iv) provide a niche for malignant cells to thrive (Lin et al., 2019), and (v) adopt the immunomodulatory MSC2 phenotype (see section "Immunological Properties: A Paradigm") (Patel et al., 2010). As previously mentioned, MSC2 further polarizes macrophages into the M2 phenotype which is pro-tumorigenic (Rivera-Cruz et al., 2017).

Contrastingly, the other school reports that MSCs are anti-tumorigenic. This observation is upheld by studies on various tumor types which demonstrate size/metastasis reduction or inhibition of proliferation upon MSC injection (Klopp et al., 2011). In this course, MSCs home to tumor sites and reinforce their anti-neoplastic effects by interacting with cancer cells *via* cell-cell adhesive proteins (e.g., *E*-cadherin, Khakoo et al., 2006) or releasing soluble factors (Maestroni et al., 1999) [e.g., dickkopf-1, a Wnt signaling inhibitor (Qiao et al., 2008; Zhu et al., 2009)] and anti-proliferative miRNA-containing vesicles (Reza et al., 2016). Molecularly, the effects are sustained by (i) interference with pro-survival/proliferation signaling pathways [e.g., protein kinase Akt (Khakoo et al., 2006; Dasari et al., 2010a) and Wnt/β-catenin (Secchiero et al., 2010)], (ii) activation of apoptotic pathways (e.g., Smac/DIABLO) (Dasari et al., 2010b; Reza et al., 2016), and (iii) cell cycle arrest in G0/G1 phase (Lu et al., 2008; Cousin et al., 2009). The net signaling transduced favors an upregulation of cell cycle modulators (e.g., p21) and pro-apoptotic proteins (e.g., caspase 3, caspase 9, BAX) (Lu et al., 2008; Reza et al., 2016), opposed by a downregulation of anti-apoptotic mediators (e.g., XIAP, BCL2) (Dasari et al., 2010a,b; Reza et al., 2016). Besides, MSCs can inhibit neo-angiogenesis by forming gap junctions with endothelial cells and supplying them with reactive oxygen species, which induce their apoptosis (Otsu et al., 2009; Secchiero et al., 2010).

The inconsistencies between both schools are attributed to multiple factors including MSC source/preparation, administration timing/dose, polarization, and tumor variability (Klopp et al., 2011).

Therapeutic Management

Mesenchymal stem cell properties of tumor tropism and non-immunogenicity were used in antitumor research. The methodology involved transforming MSCs into a therapeutic platform able to inherently engraft in tumor architecture and genetically produce recombinant antitumor or antitumor immunity-driving molecules. Examples include tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Loebinger et al., 2009), C-X3-C motif chemokine ligand 1

(CX3CL1) (Xin et al., 2009), IFN-β (Studeny et al., 2002; Ren et al., 2008b), IFN-α (Ren et al., 2008a), IFN-γ (Li X. et al., 2006), IL-2 (Nakamura et al., 2004), and (modified) IL-12 (Chen X. et al., 2008; Seo et al., 2011). For example, a study by Li X. et al. (2006) showed that autologous MSCs derived from a leukemic patient then engineered to generate IFN-γ significantly inhibit the proliferation of leukemia cell lines and induce their apoptosis. In the same context, other genetic engineering-based methods include MSCs which express (i) replicative adenoviruses that infect cancer cells and induce oncolysis (e.g., ICOVIR5, Ad5-DNX-2401), (i) therapeutic gene-incorporating retroviral vectors, and (iii) suicidal gene-incorporating vectors. However, these efficient interventions confer toxicity and require simultaneous anti-retroviral drugs administration (Uchibori et al., 2009; Loebinger and Janes, 2010). Researchers also fostered MSC-based vehicles independent of genetic engineering. Those exploit the innateness of MSCs to uptake drugs *in vitro* allegedly through Golgi-derived vesicles (drug uptake mechanisms are insufficiently characterized and are not confined to MSCs, Girdlestone, 2016). Although their drug sensitivity varies according to cell source, MSCs rapidly internalize sufficient drug molecules, such that following MSC administration to animal models, captured drugs are slowly and sufficiently released in their original form (active or prodrug) into tumor vicinity (Pessina et al., 2011; Bonomi et al., 2013; Coccè et al., 2017). Likewise, MSCs can be loaded with prodrugs to effectively inhibit cancer growth (Levy et al., 2016). These observations led to few human cancer management studies, which are still taking their baby steps toward clinical efficacy. For example, in a phase I/II study (TREAT-ME1), autologous MSCs were isolated from patients according to GMP standards and transfected with replication-incompetent retroviral vectors to generate MSC_apceth_101, an investigational medicinal product containing a therapeutic promoter-gene construct aimed to treat advanced gastrointestinal tumors. The trial, however, did not advance to therapeutic confirmatory phase III due to adverse events and lack of disease amelioration (EudraCT Number 2012-003741-15) (Niess et al., 2015). Other challenges in MSC-based anticancer treatment are, paradoxically, cancer enhancement (Karnoub et al., 2007) even with induced anti-tumor immunity (vaccination) (Krampera et al., 2007) as well as insufficient cell homing to tumors to guarantee efficient delivery of therapeutic agents (Schweizer et al., 2019).

Cancer Vaccination

Vaccination is a robust, safe, and cost-effective preventative or therapeutic method against pathogenic diseases (Tomchuck et al., 2012). While therapeutic vaccines induce cell-mediated immunity and are used to eliminate existing pathogens/lesions or prevent their progression, preventative vaccines trigger humoral immunity (serum antibody generation) for prophylaxis of futuristic pathogens/lesions (Nayereh and Khadem, 2012).

Traditionally, vaccine development employs the attenuation or inactivation of a pathogen to create long-term immune memory and/or mount a durable immune response against intact pathogens. Although efficient against several mortal diseases (smallpox, diphtheria, polio, measles), vaccines still lack in offering protection against their ilk (HIV, malaria, common cold, tuberculosis) due to robust microbial antigen shifting or difficult intracellular pathogen accessibility which complicates the selection of target antigens. In addition to intact antigenic peptides, alternative vaccines exist, such as *in situ* antigen production or presentation using plasmid vectors (DNA) and antigen-pulsed host cells (APCs, MSCs). However, they have not yet achieved any clinical benefits, mainly due to their low immunogenicity (MacGregor et al., 1998; Tomchuck et al., 2012; Hobernik and Bros, 2018).

The notion of cancer vaccination, an increasingly active research topic, stems from the inherent role of the immune system to eliminate cancer cells and the possibility thereof to develop immune enhancing therapies to adequately eradicate tumors (Butterfield, 2015). For this purpose, synthetic neo-antigens (Ott et al., 2017) as well as DNA- and cellular-based platforms exercising foreign antigen/cytokine production or expression have been used to devise tumor epitope-specific vaccines or instigate anti-tumor T-cell reactivity *in vitro*. This strategy was efficient as an *in vivo* cancer immunotherapy, especially if the regimen involves immune-checkpoint blocking antibodies to enhance effector T cells function by blocking their inhibitory receptors (PD-1 and CTLA-4) (Schumacher and Schreiber, 2015; Wraith, 2017).

Among the best candidates for cellular-based vaccine platforms, DCs are especially efficient APCs and primers of immune responses (Guéry and Adorini, 1995; Janikashvili et al., 2010; Le et al., 2010; Palucka and Banchereau, 2013). Plus, DCs are considered natural adjuvants as they can modulate and interconnect innate adaptive immune responses through their surface molecules and secretome (Mellman and Steinman, 2001; Steinman, 2001). In clinic, Sipuleucel-T, branded as Provenge, is the first and only FDA-approved DC vaccine for the treatment of asymptomatic or minimally symptomatic metastatic and castration-resistant prostate cancer (Small et al., 2006; Higano et al., 2010; Anassi and Ndefo, 2011; Cheever and Higano, 2011). However, other attempts at DC vaccine introduction in animal and clinical studies faced more complications than anticipated, demonstrating immense variation in reported outcomes (Le et al., 2010; Robson et al., 2010; Mantia-Smaldone and Chu, 2013). Reasons for such clinical discrepancies can be attributed to DC non-standardized *ex vivo* preparation and administration protocols which entail multiple variabilities at the level of (i) DCs source/phenotype, (ii) DCs maturation stimulus used, (iii) nature/procedure for antigen loading, (iv) route of administration, and (v) dose (Nicolette et al., 2007). Besides, their high production cost, low production grade, limited effectiveness, and immunogenicity hamper their clinical acceptance and advancement (Chambers and Neumann, 2011; Bhargava et al., 2012; Datta et al., 2014; Jarosławski and Toumi, 2015; Wei et al., 2015). Therefore, the search for other cellular-based vaccines with potentially better performance in these criteria was necessary, and so MSCs came forth as a fit vaccine platform in this regard.

MSCs can elicit general and/or antigen-specific immunity, without being immunogenic themselves, depending on three assets (**Figure 1**). First, MSCs are context-specific

pro-inflammatory (see Section "Immunological Properties: A Paradigm"), a property which ultimately renders them enhancers of humoral and cellular immunity. Second, MSCs are genetically modifiable, thereby representing suitable vehicles for producing and secreting cytokines or soluble antigens which evoke robust immune responses. A report by Wei et al. (2011) follows this scenario albeit to a certain extent. In the details, the group devised a combined vaccine consisting of a fusion protein vaccine which targets E7 tumor antigen and immortalized human MSCs designed to express E7 antigens. Compared to

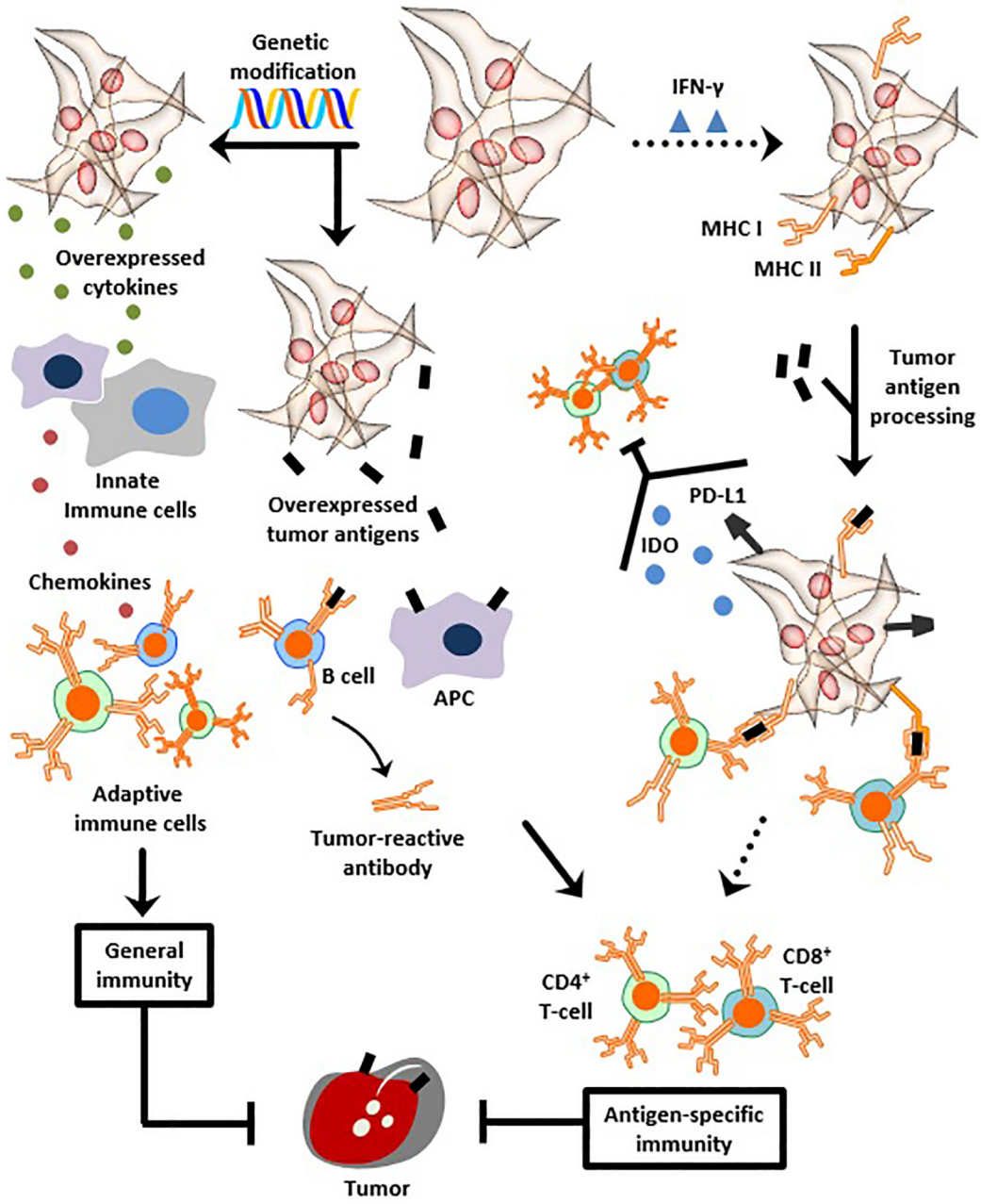

FIGURE 1 | MSCs as anti-cancer vaccines. MSCs can be genetically modified to overexpress cytokines to instigate innate and adaptive immunity, as a means to protect against neoplasms. Genetic modification can be also used to overexpress tumor antigens and instill anti-tumor humoral and cellular immunity. Likewise, dose- and time-dependent exposure to IFN-γ transforms MSCs, albeit transiently, into APCs capable of providing antigen-specific immune protection. This occurs through induction of MHC class I and II expression, followed by tumor antigen processing and MHC-mediated presentation to T-cells. Despite IFN-γ-induced antigen presentation, other observations report that MSCs simultaneously up-regulate PD-L1 and secrete IDO, both of which inhibit T-cells. Henceforth, overcoming the transient and temporary antigen presenting properties of IFN-γ-exposed MSCs is necessary to achieve vigorous stability and abundance of presented neoantigens, thus helping to create a clinically efficient anti-cancer vaccine.

the fusion protein vaccine alone, the combined vaccine elicited significantly stronger tumoricidal immunological reactions when administered to subcutaneous and lung metastasis mice models. The authors propose that those effects ensue after the tagging of tumor cells with E7 antigens released by infiltrating MSCs along with the instigation of humoral immunity by the fusion protein vaccine. The generated anti-E7 antibodies were, therefore, able to recognize tumors and eventually suppress their growth (Wei et al., 2011). Third and most importantly, MSCs can act as APCs capable of processing and presenting exogenous antigens to activate immune cells; this asset surfaces in response to IFN-γ treatment which induces MSC expression of MHCI/II molecules (Majumdar et al., 2003; Stagg et al., 2006; François et al., 2009; Tomchuck et al., 2012; van Megen et al., 2019). This property was exploited in cancer vaccination studies, which are hitherto limited. For instance, mice vaccinated with IFN-γ-licensed MSCs pulsed with ovalbumin antigen are completely protected when challenged with ovalbumin-expressing E.G7 lymphatic tumors (Stagg et al., 2006; François et al., 2009; Stagg and Galipeau, 2013). Protection against tumors using IFN-γ-treated MSCs is conferred through MHC I upregulation, MHC II induction, and, in part, through the upregulation of the antigen processing machinery responsible for translocation of processed antigens into the ER before trafficking toward the plasma membrane. Overall, this enhances antigen presentation to $CD4^+$ T-cells (MHC II-restricted) and cross-presentation to $CD8^+$ T-cells (MHC I-restricted), both of which respond by increased activation and proliferation (François et al., 2009). Another study further shows that the strong anti-tumorigenic immune responses evoked by IFN-γ-treated MSCs involve CD80 (co-stimulatory molecule) and MHC class II- but not class I-mediated antigen presentation, albeit the induction of strong $CD8^+$ T-cell responses *in vivo*. The authors argue that antigen cross-presentation which is not observed *in vitro* can develop *in vivo* not in MSCs themselves but in other host APCs which can acquire their antigens from MSCs in a process termed cross-priming (Stagg et al., 2006). Paralleling, a recent study reports that although IFN-γ-licensed human MSCs uptake and process antigens and upregulate MHC class II but not CD80, their pro-inflammatory secretome remains intact. Importantly, the study also shows that despite their IFN-γ-induced antigen presentation, MSCs inhibit autoreactive T-cells, an observation associated with PD-L1 upregulation and IDO secretion (**Figure 1**). The inhibitory effect even lasted beyond the removal of MSCs and the introduction of activation signals (antigen-pulsed DCs) (van Megen et al., 2019). However, in another report, IFN-γ-induced upregulation of PD-L1 on antigen-presenting MSCs is believed to be tied to T-cell induction rather than inhibition (Stagg et al., 2006). This discrepancy adds to the many layers of MSC character.

A side note, more prevalent is the therapeutic induction of general rather than antigen-specific anti-tumor immunity (Wei et al., 2011). This is evident in the variety of researched MSC vaccines which, as mentioned in Section "Cancer Support or Suppression?", genetically express recombinant immunostimulatory molecules (Studeny et al., 2002; Nakamura et al., 2004; Li X. et al., 2006; Chen X. et al., 2008; Ren et al., 2008a,b; Xin et al., 2009; Seo et al., 2011). Furthermore, while prophylactic MSC-based anti-cancer vaccines are more strenuous to devise compared to their therapeutic counterparts (tumor antigens have unique expression patterns), prophylactic MSC-based anti-microbial vaccines attain their purpose of triggering antigen-specific humoral and adaptive immunity against, respectively, HIV and tetanus (Tomchuck et al., 2012). In sharp contrast, the clinical knowledge available thus far on MSCs as cancer vaccines is, unfortunately, insufficient to advance further their proof of concept. **Table 2** demonstrates the only registered human studies utilizing MSC-based anti-cancer therapeutic vaccines.

CONCLUSION AND FUTURE RECOMMENDATIONS

In summary, due to their regenerative abilities, immunomodulation, tumor homing, and multiple other advantages, MSCs have demonstrated unprecedented potential in cellular therapy *in vivo*, specifically against immunological, degenerative, and cancer pathologies. Therefrom, their international clinical approval is a matter of time. Likewise, the growing notion of MSC vaccination has demonstrated promising potential for cancer prophylaxis or therapy, despite the scarcity of relevant clinical data. Reflecting on the reasons behind this, it is legit to say that MSC vaccine-based cancer research requires further understanding not only of the intervention itself but also of the multiple intricacies characterizing the interplay between MSCs and both tumors and immune cells. More specifically, an efficient MSC-based anti-cancer vaccine first needs to overcome the transient and temporary antigen presenting properties observed after IFN-γ exposure. As mentioned earlier, our current understanding of MSCs as APCs is indispensable of the dose-dependent temporary exposure to IFN-γ alongside the phenotypic responses arising therefrom (**Figure 1**) (Chan et al., 2006).

Other immunomodulatory observations upon IFN-γ licensing of antigen-pulsed MSCs are also recorded (van Megen et al., 2019). For example, IFN-γ treatment is associated

TABLE 2 | The clinical trials assessing MSC-based vaccines for cancer treatment.

NCT	Study phase	Start date	Vaccine properties	Cancer type	Results/Status
02079324	1	2014	aka GX-051, IL-12-expressing, induces IFN-γ production and subsequently cellular immunity	Head and neck	Unknown
02530047	1	2016	IFN-β-expressing, immunostimulatory	Ovarian	Completed, no disclosed results

with the upregulation of B7-H1 (PD-L1) (Krampera et al., 2006). These intricacies show that we need to understand the antigen presenting properties of MSCs beyond IFN-γ. Bypassing this conditional APC state thus warrants vigorous stability and abundance of MHCI/II-presented neo-antigens. Also, sufficient molecular knowledge of protein translation, proteasome degradation of proteins, endoplasmic reticulum transport, and affinity for MHC molecules – all in direct link to antigen presentation – is necessary (Schumacher and Schreiber, 2015). Equally important is realizing cancer complexity and the burden of tumor stromal cells in oncological settings (Brahmer et al., 2012; Joyce and Fearon, 2015). Since tumor stromal cells induce massive alterations in local metabolome and secretome profiles and are thought to ensnare $CD8^+$ T cells and other APCs (Joyce and Fearon, 2015; Hammerich et al., 2019) in the tumor microenvironment, their contribution to immune suppression, evasion, and unresponsiveness to immune-checkpoint blockers (Brahmer et al., 2012) should be investigated more in depth. Consequently, surpassing these obstacles, perhaps by instilling potent and stable antigen cross-presentation properties in properly treated MSCs, as well as ensuring that adaptive immunity is actively triggered and always one step ahead of tumor intelligence, will allow us to harness the full capacity of MSCs as robust APCs.

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Conflict of Interest: RS is the founder of IntelliStem Technologies Inc. (Toronto, ON, Canada).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.