The future of mesenchymal stem cell-based therapeutic approaches for cancer – from cells to ghosts

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent stromal cells which can differentiate into a variety of cell types including osteoblasts, adipocytes and chondrocytes. They are normally resident in adipose tissue, bone marrow and the umbilical cord, but can also be found in other tissues and are known to be recruited to sites of wound healing as well as growing tumours. The therapeutic potential of MSCs has been explored in a number of phase I/II and III clinical trials, of which several were targeted against graft-versus-host disease and to support engraftment of haematopoietic stem cells (HSCs), but currently only very few in the oncology field. There are now three clinical trials either ongoing or recruiting patients that use MSCs to treat tumour disease. In these, MSCs target gastrointestinal, lung and ovarian cancer, respectively. The first study uses MSCs loaded with a HSV-TK expression construct under the control of the CCL5 promoter, and has recently reported successful completion of Phase I/II. While no adverse side effects were seen during this study, no outcomes with respect to therapeutic benefits have been published. The other clinical trials targeting lung and ovarian cancer will be using MSCs expressing cytokines as therapeutic payload. Despite these encouraging early steps towards their clinical use, many questions are still unanswered regarding the biology of MSCs in normal and pathophysiological settings. In this review, in addition to summarising the current state of MSC-based therapeutic approaches for cancer, we will describe the remaining questions, obstacles and risks, as well as novel developments such as MSC-derived nanoghosts.

MSCs and their potential use in cancer treatment

MSCs were first isolated and characterised by Friedenstein and his colleagues in the 1960-1970s [1]. They are non-haematopoietic cell precursors, initially found in the bone marrow, but actually present in many other tissues [2]. The International Society of Cellular Therapy (ISCT) uses three criteria to define MSCs [3]: Firstly, MSCs can adhere to plastic under standard culture conditions; secondly, MSCs express cell surface markers including CD105, CD73 and CD90 with no expression of endothelial, haematopoietic, or immunological cell markers such as CD45, CD34, CD14, CD11b, CD79α, CD19 and HLA-DR; thirdly, MSCs have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts when exposed to the appropriate stimuli [4]. MSCs can be readily transduced by a variety of vectors such as Adenovirus, Lentivirus and Adeno-associated virus (AAV) [5-9]. Owing to their relative immune-privilege/-evasiveness and general immune-dampening activities, MSCs can be used in an allogenic setting and are therefore well suited as an off-the-shelf cell therapeutic agent [10, 11].

Even though MSCs have been found in and derived from various tissues, the most frequently used MSCs are from bone marrow (BM-MSCs), adipose tissue (AT-MSCs) and umbilical cord (UC-MSCs) [12-14]. As for this good availability and the relative straightforward culturing conditions, MSCs gained increasingly clinical attraction over the last ten years including the treatment of cancer. Generally, the use of MSCs as cellular vehicles in the latter context is based on their ability to home to tumours as they are recognised by MSCs as a "wound that never heals" [15]. This tumour tropism is part of the normal repair function in which MSCs are recruited by sites of tissue injury and inflammation. They are capable of extravasating into tumours when introduced into the organism via the blood stream [16], and although the molecular mechanisms behind the migration of MSCs are still not fully understood, studies have shown that the migration is regulated by various cytokines and their corresponding receptors, i.e. SDF-1/CXCR4, HGF/c-Met, VEGF/VEGFR, PDGF/PDGFR, MCP-1/CCR2, and HMGB1/RAGE [17].

In the context of such cell therapeutic approaches, MSCs are used as gene delivery vehicles for tumour targeted therapies. In several preclinical cancer models, MSCs

have been genetically modified to express cytokines, growth factor antagonists, antiangiogenic factors, prodrug-converting enzymes and proapoptotic proteins (Fig. 1 and Supplementary Table 1). Another relatively early-stage approach uses MSCs as carrier for oncolytic viruses [18, 19]. Such modified MSCs have been used in different tumour type models including colon cancer [20, 21], pancreatic cancer [22-24], lung cancer [25-29], breast carcinoma [30-32], ovarian cancer [33], prostate cancer [34, 35], hepatocellular carcinoma [36-39], glioma [40-44], melanoma [45], malignant mesothelioma [46] and lymphoma [47]. Although these pre-clinical studies clearly demonstrated therapeutic benefits of MSC-based targeted approaches, very few clinical trials utilising MSCs as delivery vehicles for anti-cancer treatments have been approved [48, 49]. This delay in transition from bench to bedside is at least in parts due to reports that MSCs not only display a potential to undergo malignant transformation, but can also lead to metastasis induction. Both of these issues embody possible barriers for the safe use of MSCs in cancer treatment and will be discussed below.

Potential problems with MSCs in cancer therapies

Do MSCs undergo malignant transformation and form tumours?

In the 2000s it was reported that MSCs could undergo spontaneous, malignant transformation and form tumours *in vivo*, dramatically increasing the risk of therapeutic use of MSCs [50-52]. However, these initial reports were subsequently retracted as it turned out that the observed tumour formation was the result of cross-contaminations with cancer cells [53, 54]. In detail, the subsequent analyses showed that the MSC cultures were cross-contaminated with a human sarcoma cell line in one case, and in the second case the presence of two glioma cell lines was detected by DNA fingerprinting and short tandem repeat (STR) analysis [54]. These results underscore the need for stringent cell culture procedures when it comes to the use of primary cell cultures, including MSCs, for therapeutic purposes. Notwithstanding, the acquisition of genetic abnormalities *in vitro* has been observed by several groups [55-57]. However, despite these chromosomal abnormalities no evidence of subsequent malignant transformation was found in these studies [58]. More importantly, there are no reports on MSC-related tumour formation in human patients after MSC administration [59, 60]. It cannot be ruled out though, that there is still a hypothetical and residual risk of developing tumours after treatment with MSCs, which harboured cytogenetic abnormalities at the time of injection or develop them later post-administration. Follow-up studies of patients who received MSCs as part of their treatment will add clarity to their tumorigenic potential. However, out of an abundance of caution standardised purification and expansion protocols should be established, as chromosomal abnormalities are mainly related to culture conditions [61]. As part of these considerations, culture conditions with low proliferation rates and minimal expansion rates are recommended to minimise the risk of acquired chromosomal aberrations [61].

In conclusion, while the risk from malignant transformation of MSCs has been overstated in the past, it will be essential to put stringent quality-control and standardisation procedures in place for MSCs to fulfil their potential in clinic applications.

MSCs and their pro-metastatic activity

Another issue that arose with MSCs is their potential to promote metastasis development in different cancer models [62-64]. In this context, MSCs can induce cancer cell dissemination in tumours that normally do not form metastatic lesions, whereas in tumours with a high potential to metastasise, MSCs cannot further increase the dissemination process [62]. The ability of MSCs to promote tumour metastasis was demonstrated in mammary carcinoma mouse models as well as osteosarcoma and colorectal cancer in these reports. While the initial results were obtained from cancer cells co-implanted with MSCs [63], it was later shown that established tumours could also be induced to form metastatic lesions by systemically administered MSCs, of both human and murine origin [62].

Currently, several hypotheses how MSCs increase the metastatic potential of tumour cells exist:

(a) MSCs within the tumour stroma secret soluble factors, e.g. CCL5 (also known as RANTES), which increases the metastatic abilities of cancer cells in a paracrine way [63]. In this context, it was also shown that tumour-derived osteopontin (OPN) acts on MSCs and induces the production and release of CCL5 [65]. CCL5 acting via its receptor CCR5 activates AKT/PKB in cancer cells enabling them to survive the different steps of the metastatic process and colonise distal organs [66]. However, other factors and pathways may exist that can also trigger cancer cell dissemination, of which some act in a cell type and context-specific manner and have not yet been identified.

(b) Within the tumour microenvironment, MSCs can differentiate into other stromal cell types, such as carcinoma-associated fibroblasts (CAFs). It is thought that this differentiation process can be triggered by the interaction of infiltrating MSCs with cancer cells within the primary tumour [67, 68]. CAFs are believed to exert their biological effect by secreting tumour growth-promoting factors such as growth factors and cytokines, as well as extracellular matrix- and angiogenesis-regulating proteins that together create a metastasis-promoting microenvironment [69]. Beyond the interaction with cancer cells in the primary tumour, CAFs can also affect cancer cells after they entered the circulation leading to increased survival of circulating tumour

cells if they are paired together with CAFs in heterotypic tumour-stroma cellular units, and consequently higher numbers of metastatic lesions [70, 71]. Despite the important role of CAFs in the tumour stroma and beyond, not all of them will be MSC-derived and it remains to be determined whether MSCs actively promote metastasis as differentiated CAFs or as pluripotent stem cells. For more details on CAFs and their ability to promote cancer metastasis, please refer to other dedicated review articles that have been published [72, 73].

(c) MSCs and their differentiated progeny protect cancer cells from destruction by dampening the immune system thereby increasing the likelihood of dissemination and formation of metastatic lesions [74, 75]. MSCs are known to suppress immune responses by producing immune-modulatory factors such as IDO, PGE2, TGF-β, IL-10 and NO acting on T- and B-cells [76-78]. Additionally, they can act via activation of potent cellular immune-suppressors such as CD4+FOXP3+ or CD8+FOXP3+ regulatory T-cells (Tregs) and myeloid-derived regulatory cells including dendritic cells (DCregs), monocytes/macrophages (M-MDSCs) and granulocytes (G-MDSCs) [79-81]. More details of the intricate and complex cross-talk of MSCs with immune-modulatory cells are discussed in a review by Koh & Kang [69].

(d) MSCs can stimulate epithelial-mesenchymal transition (EMT) of cancer cells [82] and thereby promote the invasiveness of cancer cells they intact with. EMT is a developmental process, in which epithelial cells acquire mesenchymal, fibroblast-like characteristics and show decreased intercellular adhesion and increased motility. As these are features, important for disseminating tumour cells, it was first hypothesised and now has been widely recognised that EMT is also involved in the metastatic process [83, 84]. HGF, EGF, PDGF, TGF-β and leptin are factors that can be produced by MSCs [85-87], which in turn activate a series of EMT-promoting transcription factors such ZEB1, ZEB2, Slug, Snail, and Twist as well as other EMT-inducing factors such as SERPINE1, MMP-2, and IL-6 [87-90]. Experimentally, a potential role of MSC-induced EMT has been shown for breast, melanoma, head and neck squamous cell carcinoma, ovarian, endometrial, pancreatic, gastric and colon cancer [88, 89, 91-94]. Therefore, the induction of EMT might be the mode of action by which MSCs promote

metastasis development, but obviously this function might overlap with some of the other activities ascribed to them and summarised above.

In contrast to these observations there are also reports describing a reduction in tumour growth even in responses to unmodified MSCs, at least in certain cancer models. Such anti-cancer properties were attributed to soluble factors secreted by MSCs [95]. However, the overall balance lies with cancer-progression-promoting functions of MSCs at this point. Therefore, in the short term MSCs should probably be used only after a careful risk-benefit analysis in humans, in particular in clinical cancer trials. Furthermore, the therapeutic payload should also target metastasising cells and thereby overcome the potential metastasis-promoting activities by stopping disseminating cancer cells in their tracks. In the mid-to-long term, the goal is to develop and use "safe" re-engineered MSCs that lack the expression of one or more pro-metastatic factors (e.g. CCL5, TGF-β). For this, further investigations in the underlying mechanisms and a deeper understanding of the pro-metastatic effect would be beneficial in the development of such safer MSCs for the treatment of cancer. However, it will also be crucial to investigate whether the deletion of these genes, while creating "safe" MSCs, also leads to a loss of tumour tropism and therapeutic activity.

The potential impact of MSCs on anti-cancer therapies

The ability of MSCs to create an immunosuppressive environment can be potentially detrimental for their use in cancer therapy. Generally, the effects of anti-cancer therapies are thought to be amplified by immune cells attacking tumour cells marked and/or damaged by the treatment. Thus, MSCs either delivering the therapy or being used in combination with cytotoxic drugs, radiotherapy or biologicals could block or diminish this additional effect and limit the overall therapeutic outcome [96, 97]. In this context it is important to consider the mode of action of the treatments and what type of cell death they trigger. Programmed cell death or apoptosis has regularly been called the silent cell death because it does not lead to an immune response [98]. In such a context, the immune dampening effects of MSCs should be inconsequential and approaches of MSCs delivering bona fide apoptosis inducing agents such as TRAIL

should not be affected. However, recent studies have uncovered evidence of paracrine signals originating from dying cells [98-100], and in a setting like this, the therapeutic success could indeed be reduced. One way to address this potential problem is to prime MSCs with TLR4 to render them immune competent [101]. This is based on a concept of MSCs being polarised by downstream TLR signalling into two homogenously acting phenotypes classified as MSC1 (immune competent) and MSC2 (immune-suppressive) [102, 103]. Furthermore, the group who characterised the two types of MSCs could show that MSC1-based therapy attenuated tumour growth whereas MSC2-treatment promoted tumour progression [104]. However, further research needs to address whether MSC1-based cell therapies including different therapeutic genes can surpass the efficacy of unprimed MSCs.

MSCs in preclinical studies and clinical trials

Efficient tumour homing properties will be of importance in MSC-based cancer treatments to surmount the limitations of current therapies such as short drug half-lives and insufficient delivery. The use of an MSC-delivered and continuously produced therapeutic agent could help to overcome these hurdles given that sufficient numbers of MSCs are indeed recruited to tumour lesions. Efforts in increasing the tumour tropism by local irradiation or by overexpressing molecules involved in homing of MSCs (e.g. CXCR4, EGFR or artificial receptors targeting tumour-specific receptors) have been shown to increase the number of MSCs in the tumour microenvironment [105-109].

There are various therapeutic transgenes that have been studied and of these approaches three have been continuously developed and have reached the stage of clinical trials. The first one (TREAT-ME1) uses MSC-delivery of HSV-TK under the control of the CCL5 promoter (Fig. 2A) [48]. The preclinical studies demonstrated growth reduction of hepatocellular and pancreatic carcinoma and also a reduction in metastases [24, 37]. The CCL5 promoter restricts the HSV-TK expression to the tumour microenvironment, so side effects can be minimised. This is based on the fact that MSCs infiltrating tumour tissues start producing the chemokine CCL5 upon contact with cancer cells [63]. Thus, the CCL5 promoter becomes active and will drive therapeutic transgenes that are regulated by it. After cell delivery, the pro-drug ganciclovir will be administered, which is phosphorylated and activated by HSV-TK and consequently gives rise to cancer cell death. In the TREAT-ME1 trial autologous BM-MSCs that are isolated and expanded to passage 1 are used. They are transduced with a gamma-retroviral SIN-vector carrying the CCL5-promoter-HSV-TK expression cassette [48]. The successful completion of Phase I/II was recently announced.

The second clinical trial aims to treat women with recurrent ovarian cancer with IFN-β secreting MSCs. For this study, MSCs are isolated from healthy male donors, and genetically engineered MSCs will then be intraperitoneally administered into patients (Fig. 2B). The use of IFN-β is based on results from a study in the early 2000s that showed profound anti-cancer activities in a preclinical melanoma model [45]. IFN-β is

a cytokine that has been used to treat multiple sclerosis for many years. In cancer treatment it is thought to act through indirect immunomodulatory and antiangiogenic properties or through direct antiproliferative effects on malignant cells [110].

The third clinical approach using MSCs as gene-therapeutic vehicle aims to deliver the TNF-related apoptosis-inducing ligand (TRAIL). In this trial (TACTICAL), allogeneic MSCs expressing a full-length version of TRAIL (i.e. membrane bound) will be used for the treatment of lung cancer (Fig. 2C) [47]. TRAIL is a protein that can bind as a ligand to five different receptors, of which two are functional apoptosis-inducing receptors, whereas the other three are so called decoy-receptors [111, 112]. It has been shown to selectively induce apoptosis in cancer cells and has been clinically tested as recombinant protein and TRAIL receptor-targeting agonistic antibodies [113, 114]. MSC-delivered TRAIL has been shown to be more potent than these agents and can therefore induce cell death in relatively TRAIL resistant cells [115]. Due to its promising results in initial preclinical studies, MSC-based TRAIL therapies have been continuously improved over the last few years. Firstly, by engineering a soluble form of TRAIL (sTRAIL) enabling it to also act on distant cells, which appears to be important for a wider anti-cancer effect [116-119]. Secondly, by generating receptor specific variants of sTRAIL, which target specifically one of the two apoptosis-inducing TRAIL-receptors, and can therefore, overcome resistance [23, 120, 121]. Thirdly, MSCs delivering TRAIL have been successfully used in combination therapies [20].

Other approaches to tackle cancer use MSCs to package and deliver drugs like Palitaxel and Gemcitabine [118, 122]. In contrast to other studies, in which MSCs deliver an enzyme necessary to convert a prodrug into a pharmacologically active drug, primed MSCs do not need to be genetically modified. The loaded MSCs release their cytotoxic payload packed in exosomes at the sites of tumour or metastatic growth [123, 124]. Overall, MSCs can be loaded with a broad spectrum of anti-cancer agents [125]. To do so, multiple packaging methods have been described, ranging from silica nanorattles [126] to liposomes [127]. All approaches are relying on MSCs as efficient carriers. For this very reason, MSCs also play an important role in theranostics, which represent recent efforts to combine diagnostics and therapy with a single agent. In

this context, MSCs have been genetically modified to express the sodium iodide symporter protein under the control of the CCL5 promoter. The authors demonstrated that tumour stroma–targeted iodide led to a significant reduction of growth in a metastatic colon cancer model. At the same time, it was possible to monitor the MSC biodistribution *in vivo* by MRI [128]. Another attempt used fluorescent magnetic nanoparticle (FMNP)-labelled MSCs to target gastric cancer [129].

In recent years, a number of studies have noted that the interactions between MSCs and human tumour cells mediate the exchange of biological material via exosomes [130-132]. Exosomes are small, extracellular membrane-enclosed vesicles encapsulating a variety of molecules, including proteins, DNA, mRNA and miRNAs, and are approximately 30-100 nm in size [133]. They have been shown to play diverse roles in tumorigenesis, angiogenesis and tumour progression, and have been mostly associated with tumour supportive functions [134-137]. However, there are other reports that show tumour growth inhibition [138, 139]. While some of these discrepancies can be explained by the differences in the tissue of origin of the underlying MSCs [140, 141], the exact roles and mechanisms of MSC-derived exosomes in tumour biology remain largely elusive. Notwithstanding, MSC-produced exosomes have been tested as part of experimental cell-free therapies for various diseases [142], of which some have been in cancer models [137, 139, 143]. In conclusion, exosomes might be able to substitute for MSC cell therapy, but their utility as a delivery vehicle needs to be further explored and the exact mechanisms of action elucidated.

A further development in the MSC-based delivery technology field, are so called nanoghosts (NGs) that are produced from the cytoplasmic membranes of MSCs. MSC surface markers are retained on the NGs and they broadly behave like MSCs in relation to *in vitro* and *in vivo* tumour targeting capabilities [144]. They can be produced in different sizes and loaded with a variety of therapeutics using a technologically scalable and pharmaceutically applicable process that involves the removal of the cytosol and nuclei residues. The loaded therapeutics can range from small molecule compounds to membrane-bound factors over-expressed in MSCs prior to NG generation and recombinant proteins and DNA constructs. Such MSC-based

NGs (MSC-NGs) are seen as a potentially safer alternative to MSCs, as they are not associated with the common risks arising from the administration of living proliferating cells. In preclinical tests, systemic administration of MSC-NGs loaded with recombinant TRAIL demonstrated a marked inhibition of human prostate cancer [144]. Furthermore, in a study to also demonstrate the applicability of MSC-NGs for gene therapy, loading with a plasmid expressing the hemopexin-like domain (PEX) of human matrix metalloprotease-2 gave rise to a significant therapeutic effect both on the primary cancer as well as metastatic lesions [145-147]. Thus, it might be possible to use MSC-NGs as a tumour cell therapy by proxy in the future. In this context, it is of interest that when MSCs were heat-inactivated (HI-MSC), which means they could no longer respond to inflammatory signals or secrete immunomodulatory factors, they showed the same biodistribution and persistence after infusion in mice with ischemic kidney injury [148]. While in contrast to MSCs, HI-MSC lacked the capability to suppress T-cell proliferation or induce regulatory B-cell formation, they, like MSCs were able to modulate monocyte function in response to lipopolysaccharides. Hence, in specific cases, the functions of MSC, in particular the immunomodulatory effects, do not depend on their set of secreted factors (secretome) or active cross-talk with immune cells, but on recognition of MSC by monocytic cells [148].

Outlook and remaining questions

The fate of MSCs in vivo

In contrast to other diseases [149], for the treatment of cancer it appears necessary for MSCs to engraft in the relevant tissues, i.e. primary cancer, dissemination routes (e.g. lymphatic system) and metastatic lesions [45]. However, currently, it is not entirely clear how exogenously administered MSCs behave in the human body but what we know is summarised in Supplementary Table 2. Multiple studies have demonstrated the presence of MSCs in the lung, immediately after injection [150-154]. The majority of cells are, however, cleared within the first days of treatment [62, 155]. Notwithstanding, even after 11 weeks MSCs were still detectable in the lungs, albeit at very low numbers [154] and several other tissues [62]. A human study, examining autopsy material from patients following MSC therapy, only found a low degree of MSC engraftment, and therefore concluded that MSCs exert their function more likely through a ''hit and run'' mechanism rather than through sustained engraftment [59]. However, all attempts to detect exogenously administered MSCs in recipients' organs suffer from limitations in relation to the respective detection method and can clearly lead to variabilities in the number of detected MSCs [156-158]. An extra level of variability can be added by using different sources of MSCs and having cultured these cells under different conditions and expansion rates. In this context, it has been shown that extensive expansion, which might be necessary for certain transplantation regimens, negatively impacts on the homing capabilities of MSCs [159], whereas hypoxic culture conditions increased their migratory potential [160]. Furthermore, the site of MSC delivery can also influence the biodistribution of MSCs and should therefore be considered when designing a study. As it has been shown that intravenously delivered MSCs are entrapped in the lung and cleared to the liver and spleen within a day, this mode of application is suitable for the treatment of tumours like lung cancer, pleural mesothelioma [46] as well as lung and liver metastases [26, 128]. Furthermore, MSCs could be found in the bone marrow and lymph nodes [62] after several weeks, expanding the utility to disseminating disease and those that form metastases in the bone such as prostate cancer. Going forward, it will be important to

control the different parameters that determine MSC biodistribution and find optimised administration routes for different cancer treatment applications.

Are Induced MSCs (iMSCs) the future?

Even though MSCs can be cultured relatively easily, their life span is finite and it is a challenge to expand them to the numbers required for clinical trials, let alone routine clinical use in the future. MSCs derived from human induced pluripotent stem cells (iPSC) could offer a solution to these issues and become a virtually inexhaustibly, autologous source of MSCs [161, 162]. These cells, commonly referred to as iMSCs (even though this abbreviation is also used for immune-modulatory MSCs) are generated by culturing iPSCs under specific conditions that regularly involve the use of TGF-β inhibitors (e.g. SB-431542) and extracellular matrix material (e.g. Matrigel) [163, 164]. Recently a new method has been described to derive iMSCs directly from primary dermal fibroblasts without the need to go via iPSCs. [165]. iMSCs generated by these methods have been shown to possess high differentiation efficiency into adipocytes, chondrocytes and osteoblasts and to express characteristic MSCs markers. Functionally, iMSCs display similar strong immunosuppressive characteristics and produce the same range of cytokines as regular MSCs [166]. In the context of MSC-based cancer treatments it has been shown that iMSCs are tumour-tropic but have much less potential to promote tumour progression than bone marrow MSCs. The iMSCs in this study were readily expandable, underwent senescence after prolonged culture and did not form teratomas *in vivo* [167]. These findings suggest that iPSC-derived MSCs are a potentially safer and better option for therapeutic applications in cancer patients. The protocol used in this study is scalable and able to produce the substantial number of cells needed for "off-the-shelf" therapies and bioengineering applications.

Concluding remarks

MSCs provide a powerful treatment modality for tumours owing to a series of beneficial features. However, there are still remaining issues that should be addressed and optimised such as the choice of vector and/or therapeutic gene, the optimal route of administration, the question whether allogenic cells provide a good and safe source or whether they will be replaced by autologous iMSCs in the future. Furthermore, it might be possible to derive so called NGs or exosomes from MSCs to avoid many problems associated with the administration of viable cells, but more work surrounding their use is needed.

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Conflict of interest statement

The authors report no conflicts of interest.

Figure legends

Fig. 1. Overview of therapeutic transgenes delivered by MSCs in pre-clinical cancer studies.

Transgenes depicted inside the cells are either expressed as intracellular proteins (e.g. HSV-TK) or as transmembrane proteins (e.g. full-length TRAIL). Most pre-clinical approaches however, target cancer cells by MSCs expressing soluble and secreted proteins such as interleukins, interferons, death-ligands (e.g. sTRAIL) or various other proteins. Further details, including a detailed reference list, of MSC-based pre-clinical studies are provided in Supplementary Table 1.

Fig. 2. Current MSC clinical trials targeting cancer.

A. Schematic illustration of the TREAT-ME trial. Autologous BM-MSCs from patients with advanced, recurrent or metastatic gastrointestinal adenocarcinoma are isolated and transduced with a retroviral vector containing the HSV-TK gene under the control of the CCL5 promoter. The transduced MSCs are administered before Ganciclovir is given to the patient. HSV-TK is only expressed when MSCs infiltrate tumour tissues, cross-talk to cancer cells and the CCL5 promoter becomes active. The prodrug Ganciclovir is then converted to the phosphorylated and active form by HSV-TK.
B. Overview of a clinical trial using IFN-β secreting MSCs for the treatment of advanced ovarian cancer. BM-MSCs from male donors are transfected with plasmid constructs with an IFN-β expression cassette. The resulting IFN-β-secreting MSCs are intraperitonially administered.
C. Summary of the TACTICAL trial for lung cancer. Allogenic BM-MSCs are lentivirally transduced to express full-length TRAIL before being administered to patients with advanced lung cancer.

Abbreviation List

AAV	adeno-associated virus
AKT	RAC-alpha serine/threonine-protein kinase
AT	adipose tissue
BM	bone marrow
CAF	carcinoma-associated fibroblast
CCL5	chemokine (C-C motif) ligand 5
CCR2	C-C chemokine receptor type 2
CCR5	C-C chemokine receptor type 5
CD	cluster of differentiation
c-Met	tyrosine-protein kinase Met
CXCR4	C-X-C chemokine receptor type 4
DCregs	dendritic cells
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
FMNP	fluorescent magnetic nanoparticle
G-MDSC	granulocytic myeloid derived suppressor cells
HGF	hepatocyte growth factor
HI	heat-inactivated
HLA	human leukocyte antigen
HMGB1	high mobility group box 1
HSC	haematopoietic stem cell
HSV-TK	herpes simplex virus -thymidine kinase
IDO	indoleamine 2,3-dioxygenase
IFN-β	interferon-beta
IL-6	interleukin-6
IL-10	interleukin-10
iMSC	induced MSC
iPSC	induced pluripotent stem cells
ISCT	International Society of Cellular Therapy

MCP-1	monocyte chemoattractant protein-1
MDSC	myeloid-derived suppressor cell
M-MDSC	monocytic myeloid-derived suppressor cell
MMP-2	matrix metalloproteinase-2
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
NG	nanoghost
NO	nitric/nitrogen oxide
OPN	osteopontin
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PEX	hemopexin-like domain
PGE2	prostaglandin E2
PKB	protein kinase B
RAGE	receptor for advanced glycation endproducts
RANTES	regulated on activation, normal T cell expressed and secreted
SDF-1	stromal cell-derived factor-1
SERPINE1	serine proteinase inhibitor E1
SIN	self-inactivating
STR	short tandem repeat
sTRAIL	soluble/secreted TRAIL
TGF-β	transforming growth factor beta
TLR	Toll-like receptor
TNF	tumour necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
Tregs	regulatory T-cells
UC	umbilical cord
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
ZEB1	zinc finger E-box binding homeobox 1
ZEB2	zinc finger E-box binding homeobox 2

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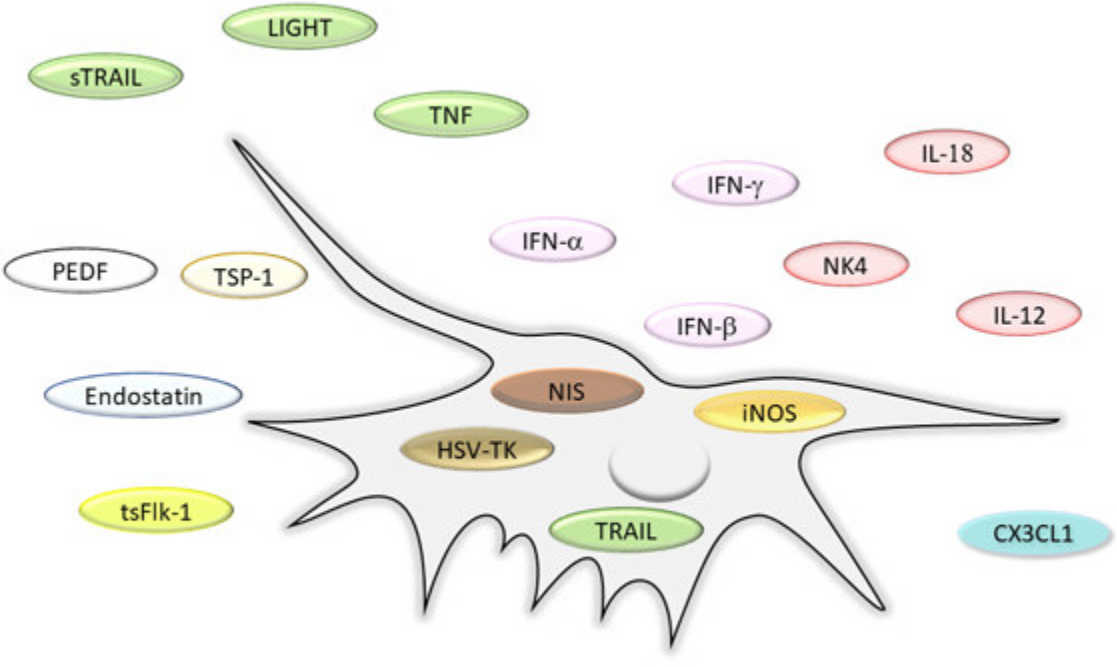
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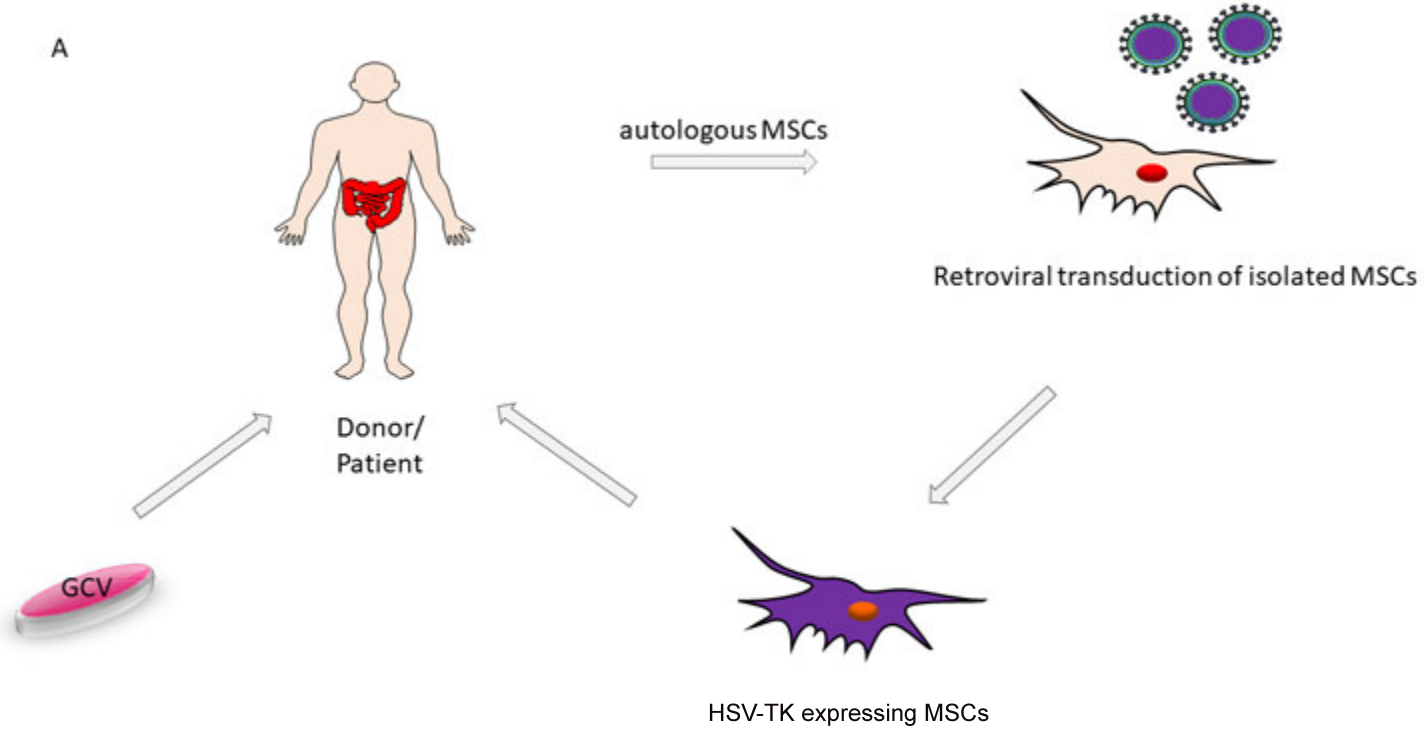
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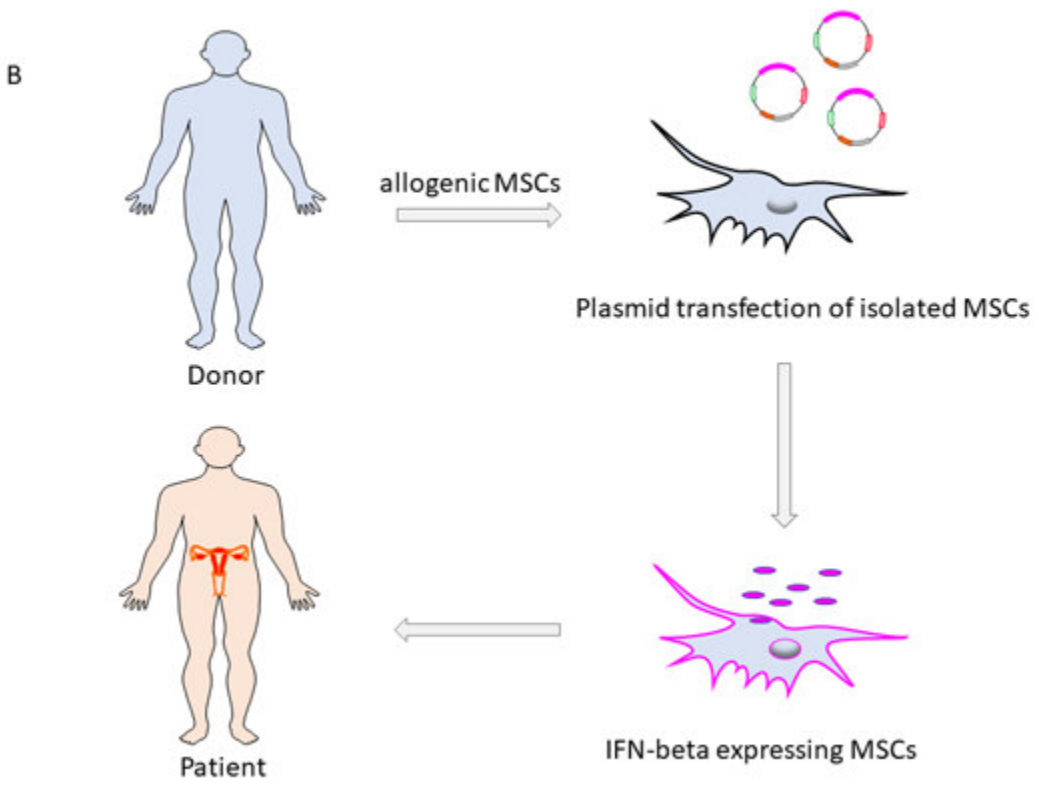
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Plasmid transfection of isolated MSCs
Donor
Patient
IFN-beta expressing MSCs

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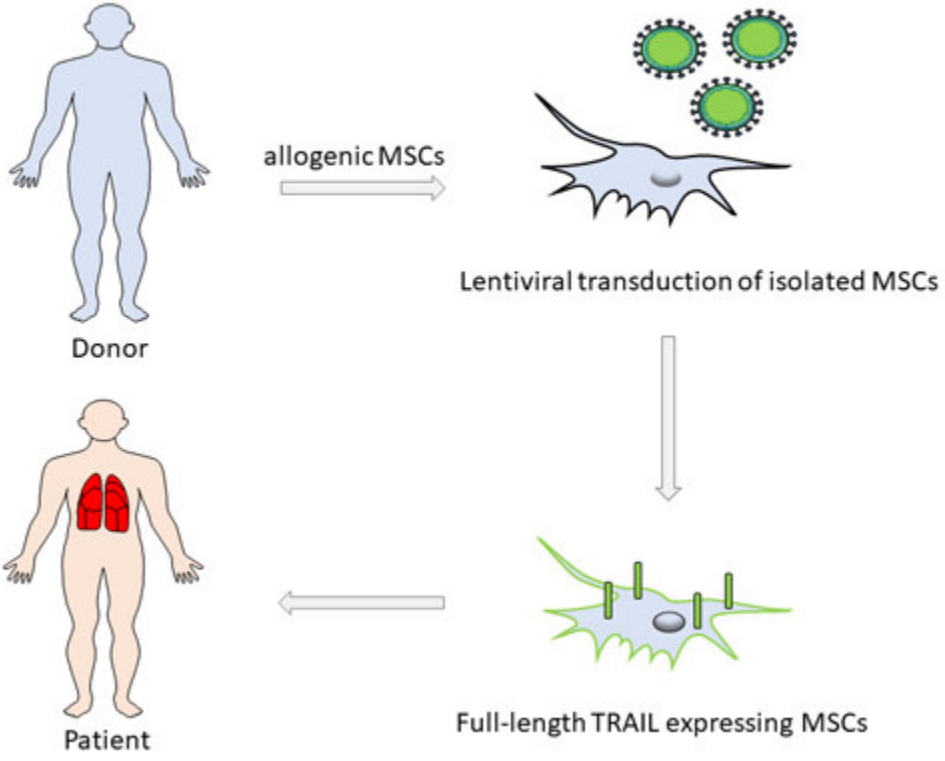
allogenic MSCs
Lentiviral transduction of isolated MSCs
Donor
Full-length TRAIL expressing MSCs
Patient

Supplementary Table1. List of therapeutic transgenes used in MSC-based experimental pre-clinical studies.

Expressed transgene	Targeted tumour in pre-clinical studies
IFN-α	B16F10, mouse melanoma cells, established as lung metastases model [1].
IFN-β	TRAMP-C2, murine prostate cancer cells, established as lung metastases model [2]. 4T1, murine breast cancer cells, established as orthotopic mouse model [3]. LMeC canine melanoma cells established as xenograft model [4]. B16F10 mouse melanoma xenograft model [5]. In combination with IL-18 in a rat intracranial glioma model [6]. PANC-1, human pancreatic carcinoma cells, orthotopically implanted [7]. Huh7 hepatocellular carcinoma xenograft model [8].
IFN-γ	H460 human non-small cell lung carcinoma model [9]. In combination with TRAIL, B16F10 mouse melanoma cells in xenograft and metastasis models [10].
IL-12	B16F10, mouse melanoma cells, established as lung metastases model [11]. B16 mouse melanoma cells, LLC murine Lewis lung cancer - and murine HCC hepatoma cells in unestablished tumour models [12]. B16 melanoma cell xenograft models [13, 14]. Hepatoma cell xenograft models [13]. Ast11.9-2 murine glioma cells implanted into mouse brains [15]. GL26, mouse glioma cells, implanted into mouse brains [16]. 4T1, murine breast cancer cell xenograft model [13, 17]. 786-O, human renal cell carcinoma cell xenograft model [18]. TC-1 cervical cancer cells in a xenograft and lung metastases model [14]. HCa-I and Hepa 1-6 cells in heterotopic murine hepatoma models [19]. Liver cancer H22 and MethA ascites models [20].
IL-18	C6 glioma-bearing rat models [21] In combination with IFN-β in a rat intracranial glioma model [22].
CX3CL1	C26 mouse colorectal carcinoma cells, B16F10 mouse melanoma cells and LLC Lewis lung

	carcinoma cells established as lung metastases model [23].
HSV-TK	Intracranial 9L rat glioma model [24]. 9L, rat glioma cell xenograft model [25]. Intracranial glioma model [26]. In combination with TRAIL, Gli36vIII-FmC, human glioblastoma multiforme cells implanted into mouse brains [27]. U-87 glioma cells in an intracranial xenograft model [28]. Orthotopic PANC02 pancreatic carcinoma model [29]. Hepatocellular carcinoma xenograft model [30]. In combination with dodecameric TRAIL, RENCA murine renal carcinoma cells established as lung metastases model [31].
iNOS	Rif-1 fibrosarcoma-bearing mice [32].
NK4	C-26, colon cancer cells as lung metastasis model [33]. MKN45, gastric carcinoma xenograft model [34].
TSP-1	In combination with sTRAIL, LN229-Fluc-mCherry cells in an intracranial glioma model [35].
PEDF	U-87 glioma cells in an intracranial xenograft model [36]. Lewis lung carcinoma cells established as lung metastases model [37]. CT26 cells in a colorectal peritoneal carcinomatosis model [38]. Orthotopic model of hepatocellular carcinoma [39].
Endostatin	U87MG-EGFRvIII-driven intracranial xenograft model [40]. A2780 human ovarian cancer xenograft model [41]. CT26 cells in a colorectal peritoneal carcinomatosis model [42].
NIS	MDA-MB-231, breast cancer xenograft model [43]. Huh7, human hepatocellular carcinoma xenograft model [44, 45]. LS174t, colon cancer liver metastasis model [46].
TRAIL	Primary human-derived TRAIL resistant glioblastoma stem cells mouse intracranial xenograft model [35, 47]. U87MG glioma xenografts [48]. U-87 glioma cells in an intracranial xenograft model [49, 50]. U87MG intracranial xenograft model [51, 52].

	U87-mC-FL tumour model [53]. Gli36-EGFRvIII-FD-driven intracranial xenograft model [54]. MK886, orthotopic glioma xenograft model [55]. Intracranial F98 rat glioma model [56]. U87-EGFRvIII glioma cells in an intracranial xenograft model [57]. Gli36vIII and LN229 human glioblastoma multiforme intracranial xenograft model [58]. In combination with HSV-tk, Gli36vIII-FmC, human glioblastoma multiforme intracranial xenograft [27]. DAOY and UW426 medulloblastoma cells in an intracranial xenograft model [59]. MSTO-211H, pleural mesothelioma model [60]. MESO, pleural mesothelioma model [61]. Tongue squamous cell carcinoma [62]. A549 lung cancer xenograft model [63]. MDA-MB-231, breast cancer xenograft model [64]. MDA-MB-231, breast cancer lung metastases model [64, 65]. MDA-MB-231, orthotopic breast cancer xenograft model [66]. In combination with HSV-tk, RENCA murine renal carcinoma cells established as lung metastases model [31]. HeLa, cervical cancer xenograft model [67]. Malignant fibrous histiocytoma model [68]. In combination with IFN-γ, RFP-melanoma cells in xenograft and metastasis models [10]. PancTu1 pancreatic cancer xenograft model [69]. Mia-PaCa2, human pancreatic cancer cells, transplanted to the chorioallantoic membrane of fertilized eggs hybrid LB chicks [70]. Colo205 xenograft tumour model [71]. HT29 colorectal cancer xenograft model [72]. DLD-1 colorectal cancer xenograft model [73]. HCT116 colorectal cancer xenograft model [74]. Orthotopic model of hepatocellular carcinoma [75]. MHCC97-H hepatocellular carcinoma xenograft model [76].
TNF	A375 melanoma cells in a lung metastases model [77]. Fused to fusing Tumstatin; PC3 prostate cancer xenograft model [78].

	SGC-7901, human gastric cancer cells in a xenograft model [79].
LIGHT	Murine gastric cancer models [80].
tsFlk-1	Raji, Burkitt's lymphoma cells, subcutaneously injected [81].

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Supplementary Table2. Biodistribution of MSCs

MSC type	Model	Organs in which MSCs were detected	Method of MSC delivery	Reference
autologous hBM-MSCs	patients with mammary carcinoma	blood	i.v.	[1]
^{111}In-oxine labelled human MSCs	patients with liver cirrhosis	lungs, liver, spleen	i.v.	[2]
murine MSCs from different age groups	transgenic APP/PS1 Alzheimer's disease mice	lungs, lymph nodes, blood, kidney, bone marrow, spleen, liver, heart, and brain cortex	i.v.	[3]
murine umbilical cord-derived mesenchymal stem cells	carbon tetrachloride-induced acute liver injury	lungs, lymph nodes	i.v.	[4]
human MSCs	hepatocellular carcinoma model	tumour, spleen	i.v.	[5]
human umbilical cord-derived mesenchymal stem cells	spinal cord injury model	spinal cord, lungs, liver, spleen	i.v.	[6]
hBM-MSCs	rat	liver, spleen, heart, and lungs	i.v.	[7]
hBM-MSCs	glioma model	lungs, liver, spleen, brain	i.v.	[8]
human umbilical cord-derived mesenchymal stem cells, hBM-MSC, porcine BM-MSC, rat MSC	mouse, rat, and porcine models	lungs, heart, liver, spleen, pancreas, kidney, GI tract, femur	i.v.	[9]
hBM-MSCs, murine MSC	mouse	BM, liver, lymph nodes, lungs, spleen	i.v.	[10]
MSC-nanoghosts	prostate cancer model	tumour, liver	i.v. and i.p.	[11]

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