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DO MESENCHYMAL STEM CELLS FUNCTION ACROSS SPECIES BARRIERS? RELEVANCE FOR XENOTRANSPLANTATION

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Abstract

Background—Allogeneic mesenchymal stem (stromal) cells (MSC) are a promising therapy for various pathological conditions. Genetically-modified pig MSC have been demonstrated to downregulate the human T cell response to pig antigens in vitro. Before genetically-modified pig MSC can be used clinically, however, evidence needs to be provided to indicate whether they will survive in a human (xenogeneic) host.

Literature Search and Results—A literature search through the end of 2011 identified 94 reports of the *in vivo* cross-species administration of MSC in a variety of experimental models. The majority (n=89) involved the use of human MSC in various other species, with an occasional study using pig, rat, or guinea pig MSC. When human MSC were used, they were largely derived from the bone marrow, adipose tissue, or umbilical cord blood. The routes of administration were varied, though almost half of the studies utilized the intravenous route. In 88 experiments (93.6%) there was evidence that the MSC engrafted and functioned across the species barrier, and in only 6 cases (6.4%) was there evidence of failure to function. Importantly, MSC function was confirmed in several different cross-species models. For example, human MSC functioned in no fewer than 7 different recipient species.

Conclusions—The data provided by this literature search strengthen the hypothesis that pig MSC will function satisfactorily in a different species, e.g., humans. The data also suggest that our own *in vitro* observations on the efficacy of pig MSC in downregulating the strength of the human T cell response to pig antigens will likely be reproduced *in vivo* in preclinical large animal models and in clinical trials.

Keywords

Mesenchymal stem (stromal) cells; Pig; genetically-engineered; In vivo; Xenotransplantation

INTRODUCTION

Allogeneic mesenchymal stem (stromal) cells (MSC) may be therapeutic in several pathologic conditions [1,2], e.g., steroid-refractory acute graft-versus-host disease [3,4], autoimmune disorders [5], and islet transplantation [6–8]. Encouraging results have been

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CONFLICT OF INTEREST
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obtained in animal models of ischemic myocardial injury [9], pulmonary hypertension [10], sepsis [11], renal ischemia-reperfusion [12], spinal injury [13], and diabetes [14]. MSC have anti-inflammatory, anti-proliferative, angiogenic, and immunomodulatory functions, and may also be a vehicle for gene therapy and drug delivery [15]. Their therapeutic potential in inhibiting the immune response following organ transplantation is being studied [16–18].

Their immunomodulatory effects have been studied in vivo in various preclinical [19] and clinical models [3, 4]. MSC suppress the proliferation of $CD4^+$T cells [19], prevent maturation of dendritic cells [20], induce T regulatory cells [19], and produce soluble factors, such as prostaglandin E_2 (PGE_2), transforming growth factor-1 (TGF-1), interleukin-10 (IL-10), hepatocyte growth factor (HGF), and indoleamine 2,3-dioxygenase (IDO), all of which have immunomodulatory effects. MSC may therefore prove of value as cytotherapeutic agents. Increasing data suggest that both cell-cell contact and secretion of soluble cytokines play roles, with cell contact perhaps being more important [21,22].

Currently, MSC from humans are defined based upon 3 minimal criteria - (i) plastic adherence, (ii) trilineage differentiation, (iii) surface expression of CD73, CD90, CD105 and absence of expression of CD45, CD34, CD14 or CD11b, CD79α or CD19, and human leukocyte antigen (HLA)-DR. MSC from animal origin have been defined as cells that fulfill the first two criteria [23].

Kolf et al provide a useful comparison of human and mouse MSC phenotype. The phenotype of mouse MSC includes positivity for CD29, CD44, CD105, CD106, and negativity for CD11b, CD31, CD34, CD45, and CD117. Determining the phenotype of MSC from large animal species is limited by a lack of species-specific antibodies, and so anti-human antibodies have been used for common MSC-selective markers [24]. Boxall and Jones provide a valuable comparison of MSC phenotype between several species, including the human, mouse, and pig. Rho et al also reported on the phenotype of pig MSC [25]. To date, the accepted phenotype of pig MSC includes positivity for CD29, CD44, CD49, CD90, CD105, and SLA-I, and negativity for CD11b, CD14, CD31, CD34, CD45, CD73, CD117, CD133, and SLA-II [26].

Clinical allogeneic MSC therapy depends on effective ex vivo expansion of the cells, and is therefore dependent on the availability of relatively large volumes of bone marrow or adipose tissue and/or extended culture time. However, ex vivo expansion of MSC can be associated with a risk of chromosomal instability [27,28], reduction in cytokine production, and loss of multipotentiality [29] with each passage, and with risks of senescence [30,31] and malignant change [28,32,33]. Furthermore, during expansion, pro-inflammatory (instead of anti-inflammatory) forms of MSC can develop [34], and might account for some of the conflicting observations in MSC immunobiology that have been reported. A logical option that might avoid untoward complications of this nature would be to use low-passage MSC. Human MSC usually reach replicative senescence following 25 cell divisions [31], potentially limiting their expansion for therapeutic purposes.

There may be considerable potential in obtaining the MSC from animal tissues. MSC can be obtained from genetically-modified pigs, e.g., α1,3-galactosyltransferase gene-knockout (GTKO) pigs that additionally express a human complement-regulatory gene and/or an immunosuppressive gene, which would protect the MSC against the human humoral and cellular immune responses. The frequency of MSC is low in adult bone marrow aspirates; the fibroblastoid colony-forming unit frequency from bone marrow has been found to be approximately 0.01% of nucleated cells. Adipose tissue has the highest frequency of MSC, approximately 2×10^4 fibroblastoid colony-forming units can be obtained initially from 10g of fat tissue, suggesting that approximately 2×10^8 bone marrow cells are equivalent to 10g

of fat tissue [22]. We have previously reported that the human T cell response to GTKO pig MSC is comparable to human MSC [35,36].

Before genetically-modified pig MSC can be used clinically, evidence needs to be provided to indicate whether pig MSC will survive in a human (xenogeneic) host, how efficiently they will suppress the human (xenogeneic) immune response, and whether any adverse effects can be anticipated. To gain some insight into the fate and effect of MSC that are administered across species barriers, we have reviewed the available literature. We have focused our attention on the efficacy of MSC to function across species barriers. We have not considered other aspects of the clinical use of MSC, such as their safety and the selection of suitable candidates for this form of therapy in relation to xenotransplantation.

LITERATURE SEARCH

We have searched the literature to determine what experience exists in the use of MSC derived from a different species from the recipient species into which the MSC are administered. We did not include studies that were solely in vitro. As of the end of 2011, we found a total of 94 reports of the in vivo cross-species administration of MSC (Table 1). The majority (n=89) involved the use of human MSC in various other species, with an occasional study using pig (n=3), rat (n=1) or guinea pig (n=1) MSC. When mice were the recipients of MSC, these included NOD/SCID (n=24), SCID (n=7), nude (n=13), autoimmune pathogenic (n=6), and unmodified (n=13) mice (Table 1).

Cross-species MSC were used in a variety of in vivo experimental models (Table 2). The routes of administration were varied (Table 3), though almost half of the studies utilized the intravenous route.

Details of all 94 experimental studies are provided in Tables 4–8. No studies included a strict comparison between the results of the administration of allogeneic and xenogeneic MSC, and therefore it has not been possible to make this comparison.

When human MSC were used (n=89), they were generally derived from the bone marrow (n=54) (Table 4), adipose tissue (n=7) (Table 5), or umbilical cord blood (n=20) (Table 6), with occasional use of MSC from embryonic stem cells (n=4), placenta, liver, and pancreas. Whenever pig, rat, or guinea pig MSC were used (n=5), they were usually bone marrow-derived (Table 7)

A small number of studies (n=9; included in Tables 4–7) involved the administration of MSCs together with some form of organ or cell transplantation (Table 8). The majority of these studies involved cotransplantation of MSC with hematopoietic stem cells (HSC).

RESULTS AND DISCUSSION

In 88 of the 94 reports (93.6%) there was evidence that the MSC engrafted and/or functioned across the species barrier. In only 6 reports (6.4%) was there evidence of failure to function or of a detrimental effect of MSC.

Niemeyer et al found that, on the basis of histological, radiological and biomechanical studies, xenogeneic MSC seemed to be associated with inferior results when compared with autogenous MSC. After application of xenogeneic MSC to a critical-size bone defect model, significantly less bone formation was observed histologically when compared with autogenous MSC [37].

Li et al reported that pre-injected MSC reduced the anti-tumor activities of CIK/NK cells in vivo. The probable mechanism is that MSC and CIK/NK cells have a greater opportunity to interact if they are injected simultaneously [38].

Baertschiger et al found that when human bone marrow-derived MSC were transplanted into an injured or regenerating liver, they differentiated into myofibroblasts with development of fibrous tissue. These results indicated that MSC in certain circumstances might be harmful due to their fibrogenic potential, and that this possibility should be considered before administering MSC as cell therapy [39].

Liu et al demonstrated that human bone marrow-derived MSC may accelerate human breast tumor growth in NOD/SCID mice by generating cytokines that affect the cancer stem cell population [40].

Pereira et al reported that co-transplantation of human umbilical cord-derived MSC with fibroblasts exacerbated neurodegeneration in a rat model of Parkinson's disease [41].

Lyngbaek et al found that transplantation of human bone marrow-derived MSC into a pig heart resulted in a rapid inflammatory response and cell degradation, which conflicted with previous studies that indicated a special immunoprivileged status for MSC [42].

When cotransplantation with donor-specific HSC was carried out, or MSC administration was combined with a skin or liver graft, there was almost uniform evidence of MSC function improving the outcome, e.g., improved engraftment of the HSC. There is, therefore, overwhelming evidence from in vivo studies in several different experimental models involving MSC from several species indicating that MSC function across species barriers.

Importantly, MSC function was confirmed in several different cross-species models (Figure 1). For example, human MSC functioned in no fewer than 7 different recipient species and MSC from 4 different species(human, pig, rat, guinea pig) were demonstrated to function across species barriers (Table 1).

The number of MSC administered in these various experimental models varied considerably (from $1x10^5$ to $16x10^6$ or $2x10^8$/kg) (Tables 4–6), and it would be unwise to attempt to determine from these data the optimum number of MSC that should be administered to ensure efficacy. The number of MSC administered (the dose) varied depending on the nature of the experiment and the condition for which the MSC were being administered, i.e., the disease model. Doses are unlikely to be the same in one model, e.g., spinal injury, as in another, e.g., diabetes or suppression of rejection of an allograft. In some conditions, MSC are administered locally at the site of a lesion, whereas in other conditions systemic administration is necessary. Dosing may therefore need to vary widely. In view of the great variety of models and species, current data do not allow an accurate conclusion to be drawn as to the 'optimal' number of MSC that should be administered.

Bone marrow was the original source of MSC, but there is increasing evidence that MSC can be harvested from a variety of sources, e.g., fat, umbilical cord blood, placenta. Adipose tissue probably has greater promise because the MSC can be harvested in very large numbers from this source, thus reducing the need for long-term culture in vitro. All the evidence is that adipose-derived MSC have similar characteristics (e.g., differentiation ability, phenotype, and immunomodulatory capacity) to bone marrow-derived MSC.

According to the literature, nearly half of all studies have selected the intravenous route, but this depends on the aim of the study. For example, for spinal cord and lumbar disc injury

models, local injection has been preferred. In contrast, as would be expected, for models of malignancy, systemic administration has been selected.

MSC from pigs are an attractive option as pig MSC may have advantages over human MSC. (i) It is easier to obtain very large volumes of bone marrow or, particularly, adipose tissue from pigs than humans, and unlimited numbers of source pigs can be made available for this purpose. Pig adipose-derived MSC also have the advantage over bone marrow-derived MSC in having a high frequency of fibroblastoid colony-forming units [43], and thus are a richer source of MSC (with less need for proliferation). (ii) As pig MSC would be plentiful, there would be no need for extensive ex vivo expansion, thus lowering the risks of replicative senescence or malignant change. (iii) Bone marrow- and adipose-derived pig MSC have been demonstrated to have similar immunomodulatory functions [34–36]. (iv) In association with xenografts, e.g., pig islets, pig MSC can be obtained from the same pig source and/or from identical cloned pigs, thus negating exposure to third-party, i.e., allogeneic, MSC. (v) Allogeneic human MSC are known to be hypo-immunogenic, but are usually eliminated by NK cells in a Major Histocompatibility Complex (MHC)-unrestricted manner [44]; NK cytotoxicity is also likely to play a role in the destruction of pig MSC. However, further genetic modifications in pigs, e.g., expression of HLA-E/β2 microglobulin and/or of HLA-G molecules, may decrease the cytotoxicity of human NK cells [45], and may therefore protect the MSC from NK cytotoxicity.

The data provided by this literature search strengthen the hypothesis that pig MSC will function effectively in a different species, e.g., humans. The data suggest that our own in vitro observations on the efficacy of pig MSC in downregulating the strength of the human T cell response to pig antigens will be reproduced in in vivo preclinical large animal models and in clinical trials. MSC from genetically-engineered pigs may therefore provide an alternative to human MSC, at least in the context of xenotransplantation [46].

There are a relatively large number of clinical trials continuing at the present time, but to our knowledge these all involve autologous or allogeneic MSC. They relate to the treatment of various pathological conditions, such as graft-versus-host disease (GVHD) and autoimmune disorders [1–4], but also include their application in organ transplantation. However, to our knowledge, none of the clinical trials has involved cross-species MSC. To our knowledge, clinical trials of autologous or allogeneic MSC have not been associated with major complications, but a discussion of the safety aspects of pig MSC is beyond the confines of this review.

In conclusion, MSC from one species can clearly differentiate and promote tissue recovery when transplanted into another species, resulting in improved function. In the unmodified host, MSC migrate and engraft in multiple tissues (bone marrow, spleen, liver, muscle), maintain multi-potential capacity, and have unique immunologic characteristics that allow persistence in a xenogeneic environment. Importantly, xenogeneic MSC would, of course, need to be fully protected themselves from the human immune response, and this could be achieved by genetic engineering of pigs [22,35,36]. The data we have reviewed suggest that cross-species MSC might prove valuable in numerous different disease states, e.g., GVHD, diabetes, myocardial infarction, organ transplantation, etc.

To summarize, in various experimental models the following effects have been documented across a species barrier:

Neurological – support axonal growth, induce functional improvement, reduce brain infarct size, and reduce pain-like behavior [47–50].

Musculoskeletal - MSC survive in the intervertebral discs and differentiate toward disc-like cells [51].

Cardiovascular – reduce myocardial infarct size and improve ventricular function, as well as improve acute myocarditis [52–54].

Diabetes mellitus - enhance insulin secretion, islet graft survival, and wound healing [55–57].

Tissue injury - (i) repair radiation damage, e.g., to liver and intestine [58,59], (ii) engraft in the host liver parenchyma, differentiate into hepatocyte-like cells, and enhance hepatic recovery [60,61], (iii) differentiate into renal tubular epithelial-like cells, and improve renal function [62], (iv) ossifiy calvarial defects [63], (v) accelerate healing of retinal defects [64], and (vi) have a beneficial effect on ischemic limb disease [65].

Malignancy - MSC possess intrinsic anti-neoplastic properties, inhibiting tumor growth and metastasis [66–68].

Autoimmune/inflammatory disease - inhibit progression of autoimmune disease and restore immune homeostasis [69] in myasthenia gravis [70], systemic lupus erythematosus [71], GVHD, and colitis [72].

Co-transplantation - enhance engraftment of HSC, and prolong skin graft Survival [73,74].

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ABBREVIATIONS

GTKO	α1,3-galactosyltransferase gene-knockout
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSC	hematopoietic stem cells
MSC	mesenchymal stem (stromal) cells
NK	natural killer
NOD/SCID	nonobese diabetic/severe combined immunodeficient

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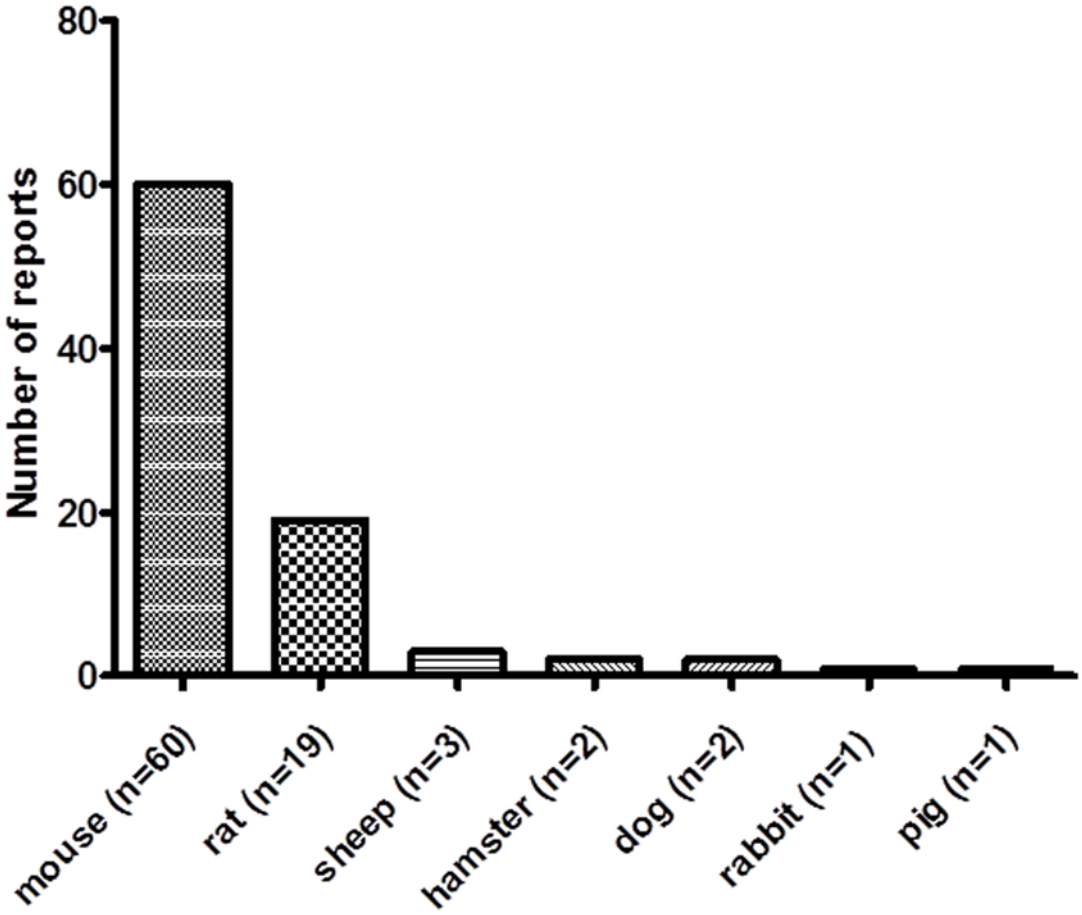

Figure 1.

Recipient species in which cross-species MSC have been reported to engraft and/or function (total reports = 88). For example, human MSC functioned in no fewer than 7 different recipient species (see Table 1). **Furthermore, MSC from 4 different donor species (human, pig, rat, guinea pig) were demonstrated to function across species barriers, i.e., in recipients of different species (see** Table 1)

TABLE 1

REPORTS IN THE LITERATURE OF CROSS-SPECIES ADMINISTRATION OF MESENCHYMAL STEM CELLS

Donor Species	Recipient Species	Studies (n)	Reference #
human	NOD/SCID mouse	24	38–40,55,56,58,59,73,79,82,84,88,92–94,98–100,104,112,123,131–133
	nude mouse	13	61,63,66–68,80,86,105,111,120,121,124,127
	wild-type mouse	12	48,52,57,101,102,106,108–110,113,125,134
	autoimmune mouse	6	69,70,72,103,108,122
	SCID mouse	5	60,76,78,101,126
	rat	18	41,47,49,50,52,54,62,65,75,77,85,89,114–119
	hamster	2	87,90
	sheep	3	81,83,129
	dog	2	91,128
	pig	2	42,51
	rabbit	2	37,64
pig	SCID mouse	2	95,96
	rat	1	97
rat	wild type mouse	1	74
guinea pig	rat	1	130
TOTAL		**94**	

TABLE 2

EXPERIMENTAL MODELS IN WHICH THE EFFECTS OF CROSS-SPECIES MESENCHYMAL STEM CELLS HAVE BEEN STUDIED

Model	Studies (n)	Reference #
1) Unmodified (healthy)	18	42,80,81,83,91,94,97,104,107,108,114,119,120,124,125,129,133,134
2) Irradiation injury	7	58,59,82,84,88,99,131
3) Malignance model	11	38,40,66–68,76,105,109,111,113,123
4) Acute myocardial infarction	6	52,54,85,90,95,100
5) Acute liver dysfunction	5	39,60,61,86,126
6) Autoimmune disease	6	69–72,103,122
7) Acute cerebral infarction	5	49,50,75,89,115
8) Transplantation	9	73,74,92,93,96,98,112,130,132
9) Diabetes	4	55–57,78
10) Inflammatory	4	53,106,110,121
11) Spinal cord injury	3	47,77,128
12) Acute kidney injury	3	62,79,127
13) Muscle injury	3	65,87,118
14) Neuropathic	3	41,48,102
15) Lumbar disc injury	2	51,117
16) Bone defect	2	37,63
17) Acute lung injury	1	101
18) Retinal injury	1	64
19) Intracerebral hemorrhage	1	116
TOTAL	**94**	

TABLE 3

ROUTES OF ADMINISTRATION OF MESENCHYMAL STEM CELLS

Route (Site of injection)	Studies (n)	Reference #
1) Intravenous	47	38,48–50,53,57–59,62,66,68,70,72–74,76,77,79,80,82,84,89,92–94,96–98,100,103,106–108,111–113,115,120,123–125,127,130–134
2) Organ/Tissue	36	
heart	7	42,52,54,55,85,91,95
brain	7	41,75,102,105,109,114,122
liver	3	86,104,119
spinal cord	4	47,51,117,128
muscle	4	65,87,90,121
spleen	3	39,60,126
tissue defect area	3	37,63,118
bone marrow	2	40,88
eye	1	64
kidney	1	78
3) Intraperitoneal	9	61,69,71,81,83,94,110,116,129
4) Subcutaneous	2	67,94
5) Intratracheal	1	101
TOTAL	**94**	

TABLE 4

STUDIES INVOLVING THE ADMINISTRATION OF HUMAN BONE MARROW MESENCHYMAL STEM CELLS (n=54)

Recipient	Exp model	Route	# of MSCs	Conclusions	Reference
Unmodified (healthy)					
rat	unmodified	liver	1×10^6	Engrafted into liver, with hepatic differentiation.	119
nude mouse	unmodified	IV	2×10^5	Migrated to BM, spleen, and mesenchymal tissues after Tx.	120
nude mouse	unmodified	IV	Uncertain	Cartilage formation occurred after 6w.	124
pig	unmodified	Heart	$15–35\times10^5$	Caused inflammation.	42
NOD/SCID mouse	unmodified	IV	Uncertain	Potential of transformed cells in hMSC culture and highlight the need for karyotyping.	133
C57/B6 mouse	unmodified	IV	Uncertain	Undifferentiated MSC are detected in majority of case.	134
fetal sheep	fetal sheep	IP	$1–2\times10^8$/kg	Maintained multipotential capacity and unique immunologic characteristics after Tx.	81
fetal sheep	fetal sheep	IP	2×10^7	Engrafted and differentiated into multiple cell types. Survived >1y.	83
Neurological					
rat	spinal cord injury	spinal cord	5×10^5	Supported axonal growth after spinal cord injury.	47
rat	spinal cord injury	(1)IV (2)lumbar puncture (3)local injection	1×10^6	Lumbar puncture is an ideal technique to deliver MSCs which can get better cell engraftment and tissue sparing.	77
CD1 mouse	spared nerve injury	IV	2×10^6	Reduced pain-like behavior (mechanical allodynia, thermal hyperalgesia).	48
rat	cerebral ischemia	brain	5×10^5	MSC transfected with the brain-derived neurotrophic factor promoted functional recovery in cerebral ischemia.	75
rat	cerebral ischemia	IV	1×10^6	Promoted free fatty acid metabolism in cerebral ischemia.	89
rat	cerebral ischemia	IV	5×10^5	Produced structural/functional recovery.	49
rat	cerebral ischemia	IV	3×10^6	Induced functional improvement, reduced infarct size, provided neuroprotection.	50
rat	cerebral ischemia	IV	1×10^6	Elicited functional improvement compared with the control sham group.	115
C57/B6 mouse	Huntington's disease	brain	2×10^5	Neural differentiation improvement potential, neurotrophic support capability, anti-apoptotic effect.	102
Musculoskeletal					
minipig	lumbar discs injured	Intervertebral discs	5×10^5	Survived in disc >6m. Differentiated toward disc-like cells	51
rat	degenerative intervertebral discs	intervertebral discs	1×10^6	Increased the heights and signal intensities of intervertebral disc.	117
hamster	muscle dystrophy	IM	$5–10\times10^5$	Contributed to both preexisting and new muscle fibers, and mediated capillary formation.	87
rabbit	bone defect	bone defect	5×10^6	The xenogenic treatment group displayed inferior results in all parameters compared with the autogenous MSC treatment group.	37

Recipient	Exp model	Route	# of MSCs	Conclusions	Reference
Cardiovascular					
rat	myocardial infarction	heart	3×10^6	Survived and contributed to improvement in cardiac function.	85
hamster	cardiomyopathy	IM	$2–4\times10^6$	VEGF is a key therapeutic trophic factor in MSC- mediated myocardial regeneration.	90
rat	myocardial Infarction	heart	3×10^6	Improved cardiac function and reduced infarctionsize.	52
NOD/SCID mouse	myocardial infarction	IV	2×10^6	Enhanced cardiac function.	100
C57BL/6 mouse	inflammatoy cardiomyopathy	IV	5×10^5	Improved acute myocarditis.	53
rat	myocardial infarction	heart	1×10^7	MSC can improve left ventricular ejection fraction.	54
dog	pacemaker implantation	heart	$15\times10^4– 1\times10^6$	Provided a means for administering pacemakers that functioned 6w without cellular or humoral rejection.	91
Irradiation injury					
NOD/SCID mouse	TBI or ALI	IV	5×10^5	TBI can increase MSC implantation into bone marrow and other tissues	82
NOD/SCID mouse	TBI and/or ALI	IV	5×10^6	Repaired damaged tissues following irradiation.	84
NOD/SCID mouse	TBI	BM	1×10^6	Reconstituted hematopoietic microenvironment. Contributed to the maintenance human hematopoiesis.	88
NOD/SCID mouse	ALI	IV	5×10^6	MSC can prevent AST and ALT increasing after ALI.	58
NOD/SCID mouse	radiation-induced injury	IV	5×10^6	MSC bring fast recovery to small intestine function and structure.	59
NOD/SCID mouse	radiation injury of intestine	IV	5×10^6	Increased self-renewal of small intestinal epithelium. Accelerated structural recovery.	131
Malignancy					
SCID mouse	malignant melanoma	IV	$75\times10^4– 1\times10^6$	Engrafted and incorporated into tumor vessels to participate in angiogenesis	76
NOD/SCID mouse	chronic erythroleukemia	IV	1×10^5	Reduce the antitumor activities of cytokine- induced killer/natural killer cells in vivo.	38
NOD/SCID mice	breast cancer	BM	2×10^5	Accelerate human breast tumor growth.	40
Nude mouse	hepatocellular carcinoma.	SC/IV	$6\times10^6/5\times10^5$	Enhanced tumor growth but significantly inhibited the invasiveness and metastasis.	111
nude mouse	Kaposi’s sarcoma	IV	4×10^6	Possessed intrinsic antineoplastic properties.	66
nude mouse	renal cell carcinoma	SC	5×10^6	Reduced growth of renal cell carcinoma. Enhanced survival.	67
NOD/SCID mouse	multiple lung metastases	IV	75×10^4	Tracked to multiple lung metastases.	123
nude mouse	cancer metastasis	IV	uncertain	Reduced lung metastasis. Inhibited growth of human cancer by inducing apoptosis	68
Liver or kidney injury					
SCID mouse	hepatic injury	spleen	1×10^6	Engrafted into the host liver parenchyma, and differentiated into hepatocyte-like cells expressing human albumin and α-1-anti-trypsin.	60
NOD/SCID mouse	hepatic injury	spleen or liver	$5\times10^5 – 1\times10^6$	MSC in certain circumstances might be harmful due to their fibrogenic potential.	39
NOD/SCID mouse	acute kidney injury	IV	5×10^5	Reduced proximal tubular epithelial cell injury and ameliorated the deficit in renal function.	79

Recipient	Exp model	Route	# of MSCs	Conclusions	Reference
Nude mouse	glomerulonep hropathy	IV	5×10^5	Found in renal glomeruli. Differentiated into mesangial cells after glomerular injury.	127
rat	acute renal failure	IV	uncertain	Ameliorated acute renal failure by differentiation into renal tubular epithelial-like cells.	62
Diabetes mellitus					
SCID mouse	diabetes (STZ)	kidney	3×10^6	MSCs transfected with three genes: PDX-1, NeuroD1 and Ngn3 can be induced to express insulin sufficient to reduce blood glucose.	78
NOD/SCID mouse	diabetes (STZ)	heart	2.5×10^6	Enhanced insulin secretion and perhaps improved the renal pathology	55
NOD/SCID mouse	diabetic (STZ)	IV	42×10^6/kg	Safe and effective for blood glucose stabilization.	56
Transplantation					
NOD/SCID mouse	$CD34^+$ human HSC Tx (TBI)	IV	$1–2\times10^6$	CoTx with CD34+ HSCs enhanced myelopoiesis and megakaryocytopoiesis.	73
NOD/SCID mouse	HSC Tx	IV	$1–16\times10^6$	CoTx with HSCs enhanced engraftment as the dose of MSCs increased.	92
Autoimmune disease					
MRL/lpr mouse	autoimmune diseases	IP	1×10^6	Significantly inhibited autoimmune progression.	69
C57/B6 mouse	autoimmune myasthenia gravis	IV	1×10^6	Homed specifically to spleen tissue. Improved functional deficits of autoimmune myasthenia gravis.	70

Abbreviations used in Tables 4–8:

Ad = adipose; ALI = additional local irradiation; BM = bone marrow; GVHD = graft-versus-host disease; HSC = hematopoietic stem cells; IM = intramuscular; IP = intraperitoneal; IV = intravenous; LP = lumbar puncture; MSC = mesenchymal stromal (stem) cells; SC = subcutaneous; STZ = streptozotocin; TBI = total body irradiation; Tx = transplantation; UCB = umbilical cord blood;

TABLE 5

STUDIES INVOLVING THE ADMINISTRATION OF HUMAN ADIPOSE MESENCHYMAL STEM CELLS (n=7)

Recipient	Exp model	Route	# of MSCs	Conclusions	Reference
NOD/SCID Mouse	unmodified	IV	1×10^6	Migrated to multiple tissues.	94
MRL/lpr mouse	unmodified	IV	5×10^5	Ameliorated systemic lupus erythematosus. Restored immune homeostasis.	71
SCID mouse	unmodified	IV	5×10^6 –25×10^7/kg	Even at the high numbers (2.5×108 cells/kg), no side effects.	107
C57BL/6 mouse	unmodified	IV	5×10^5	Reduced inflammatory immune response. Improved, Th1/Th2 balance.	108
Nude mouse	skull defect	local injection	15×10^4	Ossified calvarial defect without need for pre-differentiation.	63
Rabbit	retinal defect	retinal defect area	1×10^5	Engrafted in retinal defect. Accelerated healing process. Ameliorated injury recovery.	64
nude mouse	hepatic injury	IP	15×10^5	Hepatocyte differentiation in vitro. Liver regeneration in vivo.	61

TABLE 6

STUDIES INVOLVING THE ADMINISTRATION OF HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS (n=20)

Recipient	Exp model	Route	# of MSCs	Conclusions	Reference
Liver injury					
nude mouse	hepatic injury	liver	3×10^6	Enhanced recovery of CCl4-injured liver.	86
SCID mouse	hepatic injury	spleen	1×10^6	Engrafted. Expressed human albumin and alpha fetoprotein.	126
Transplantation					
NOD/SCID mouse	HSCs Tx	IV	1×10^6	Promoted hematopoietic engraftment. Limited GVHD.	93
NOD/SCID mouse	HSCs Tx (TBI)	IV	25×10^5	Enhanced engraftment of human HSCs.	98
NOD/SCID mouse	HSCs Tx (TBI)	IV	25×10^5	Enhanced engraftment of HSCs.	112
Autoimmune and inflammatory					
SJL mouse	spontaneous myopathy	IV	1×10^6	Engrafted in muscle.	72
BALB/c mouse	colitis	IV	1×10^6	Homed to inflamed colon. Ameliorated colitis.	106
rat	Parkinson's disease	brain	1×10^5	Co-Tx with fibroblasts abrogated therapeutic efficacy and had damaging effects.	41
nude mouse	Buerger's disease	skeletal muscle	1×10^6	Beneficial effect on ischemic limb disease.	121
transgenic mouse	Alzheimer's disease	intracerebral	1×10^5	Ameliorated pathophysiology. Reversed cognitive decline.	122
Neurological					
ICR mouse	ataxic model	IV	2×10^6	Alleviated cerebellar atrophy. Decreased apoptotis.	103
rat	intracerebral hemorrhage	IP	2×10^5	Accelerated neurological functional recovery.	116
dog	spinal cords injured	spinal cord	1×10^6 or 2×10^6	Enhanced remyelination.	127
Irradiation injury					
NOD/SCID mouse	TBI	IP	10×10^6	Inhibited GVHD.	99
NOD/SCID mouse.	TBI	IV	1×10^5	Promoted hematopoietic reconstitution. Improved survival.	132
Malignancy					
C57BL/6 mouse	glioma-bearing	brain	1×10^5	Inhibited tumor growth. Prolonged survival.	109
C57BL/6 mouse	lung carcinoma	IV	1×10^6	Inhibited lung metastases.	113
Other					
nude mouse	unmodified	IV	5×10^4	Homed and survived in BM.	80
ICR mouse	acute lung injury	Intratracheal	1×10^5	Attenuated E. coli-induced acute lung injury. Down- modulated inflammatory process.	101
db/db mouse	diabetic wound	IV/local injection	2×10^6	Improved wound healing.	57

TABLE 7

STUDIES INVOLVING THE ADMINISTRATION OF NONHUMAN MESENCHYMAL STEM CELLS INTO RODENTS (n=5)

MSC Species	Recipient	Exp model	Route	Conclusions	Reference
Pig	NOD/SCID mouse	myocardial infarction	Heart	Improved left ventricular ejection fraction.	95
Pig	NOD/SCID mouse	BM Tx (TBI)	IV	Co-Tx with HSCs improved short-term engraftment.	96
Pig	Rat	unmodified	IV	Differentiated along a neural lineage.	97
Rat	NOD/SCID mouse	skin Tx (TBI)	IV	Skin graft survival prolonged.	74
Guinea pig	Rat	liver Tx	IV	Possible immunomodulation of hyperacute rejection.	130

TABLE 8

STUDIES INVOLVING THE ADMINISTRATION OF MESENCHYMAL STEM CELLS CO-TRANSPLANTED WITH A SPECIES-SPECIFIC XENOGRAFT (n=9)

MSC Species	Recipient	Exp model	Route	Conclusions	Reference
human	NOD/SCID mouse	HSC Tx	IV	CoTx with $CD34^+$ HSCs enhanced myelopoiesis and megakaryocytopoiesis.	73
human	NOD/SCID mouse	HSC Tx (TBI)	IV	CoTx with HSCs enhanced engraftment as dose of MSCs increased.	92
human	NOD/SCID mouse	UCB cell Tx	IV	Promoted hematopoietic engraftment. Limited GVHD.	93
human	NOD/SCID mouse	HSC Tx (TBI)	IV	Enhanced engraftment of human HSCs.	98
human	NOD/SCID mouse	UCB cell Tx	IV	Promoted hematopoietic reconstitution.	132
human	NOD/SCID mouse	HSCs Tx (TBI)	IV	Enhanced engraftment of HSCs.	112
rat	C57BL/6 mouse	skin Tx (TBI)	IV	Prolonged skin graft survival.	74
guinea pig	Rat	liver Tx	IV	Possible immunomodulation of hyperacute rejection.	130
pig	NOD/SCID mouse	BM Tx (TBI)	IV or BM	CoTx with HSCs improved short-term engraftment	96