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Human adipose-derived cells: an update on the transition to clinical translation

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Abstract

The pace of discovery involving adipose-derived cells continues to accelerate at both the preclinical and clinical translational levels. Adipose tissue is a source of freshly isolated, heterogeneous stromal vascular fraction cells and culture-expanded, adherent and relatively homogeneous adipose stromal/stem cells. Both populations display regenerative capacity in soft and hard tissue repair, ischemic insults and autoimmune diseases. While their major mechanism of action has been attributed to both direct lineage differentiation and/or paracrine factor release, current evidence favors a paracrine mechanism. Over 40 clinical trials using adipose-derived cells conducted in 15 countries have been registered with the NIH, the majority of which are Phase I or Phase I/II safety studies. This review focuses on the literature of the past 2 years in order to assess the status of clinical and preclinical studies on adipose-derived cell therapies for regenerative medicine.

Keywords

adipose; adipose stromal/stem cell; autoimmune; bone repair; clinical translation; cosmetic surgery; ischemic injury; myocardial infarction; stromal vascular fraction

Over the past decade, adipose tissue has garnered considerable attention as a tissue source of cells for use in regenerative medicine [1,2]. As a result, literature on the isolation, characterization and preclinical application of adipose-derived cells has increased exponentially [3–9]. Two major populations have been evaluated extensively. First, stromal

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vascular fraction (SVF) cells are routinely isolated by collagenase digestion of adipose tissue. Prior to any subsequent fractionation or culture, this population displays a relatively heterogeneous immuno-phenotype based on flow cytometry. SVF cells contain a variety of cells types, including B and T lymphocytes, endothelial cells, fibroblasts, macrophages, pericytes, preadipocytes and related populations [10–13]. Subsequent culture of SVF cells on a tissue culture surface yields an adherent subpopulation termed adipose-derived stromal/stem cells (ASCs). The ASCs are relatively homogeneous based on their surface immunophenotype, displaying similar, but not identical, surface antigens to those found on bone marrow mesenchymal stromal/stem cells (BMSCs) [1,10,11,14,15]. *In vitro*, ASCs can differentiate along multiple pathways, including adipogenic, chondrogenic, endothelial, epithelial, hepatic, myogenic, neuronal-like, osteogenic and hematopoietic supporting lineages (reviewed in [3–9]). Furthermore, they secrete an array of cytokines and growth factors that are similar but not identical to those released by BMSCs [16]. Both ASCs and SVF cells display regenerative capacity when applied to a wide range of preclinical animal models of human disease [8].

Multiple mechanisms have been proposed to explain the regenerative properties of adipose-derived cells. Initial studies suggested that adipose-derived cells act by differentiating along a particular lineage pathway, thereby replacing a damaged or ablated cell population *in vivo*; however, tracking studies in many animal models do not consistently support this paradigm. Second, the adipose-derived cells may act through the paracrine release of growth factors required to accelerate and direct tissue repair by endogenous or host-derived cells [17,18]. For example, the introduction of adipose-derived cells into an ischemic area may result in their secretion of VEGF. In turn, this will recruit local endothelial cells to the site and promote host angiogenesis and vasculogenesis. Alternatively, adipose-derived cell secretion of immunomodulatory factors such as prostaglandin E2 may suppress host inflammatory responses following an ischemic event, thereby enhancing recovery [10,19–22]. Many investigators in the field currently favor such paracrine explanations of adipose-derived cell function.

This review will not present a comprehensive review of the adipose-derived cell literature; for such reviews, see [3–9,23–28]. Instead, it will provide an update focused on preclinical and clinical translational studies that have been reported during the past 2 years. This information will be presented in the context of the regulatory environments, GMP and enabling technologies.

International regulatory environment & state of the art

Explorations into the regenerative potential of adipose-derived cells occur throughout the world. Regulatory oversight varies on a national basis. In the USA, the Center for Biologics Evaluation and Research (CBER) section of the US FDA exerts major jurisdiction over stromal/stem cell products. In the EU, oversight is provided by the EMA, which acts as a centralized regulatory agency for EU members states. The equivalent body in Japan is the Pharmaceutical and Medical Devices Agency (PMDA). These are the three largest pharmaceutical markets internationally and, as such, have among the most rigorous approval guidelines for new biological products and related devices. In Asia and Europe, regulatory approval has been granted for closed mechanical devices for adipose tissue processing and SVF cell isolation using collagenase digestion [29]. The availability of these machines in operating rooms has facilitated the point-of-care delivery of SVF cells for investigators and clinicians in Asia and Europe; however, these devices have not yet received approval from the FDA in the USA. Clinical applications using adipose-derived cells are underway throughout Asia, Europe and North and South America. Some of these can be found on the NIH's website [201], where 55 studies are listed under the search term 'adipose stem cell'

(as of 22 October 2011). Of these, 44 studies actually employ adipose-derived cells or tissues for regenerative applications (Tables 1–4). Study sponsors include academic hospitals, governmental funding agencies and private biotechnology corporations. These listings are by no means comprehensive; additional studies are underway or under consideration in China, Costa Rica, Finland, India, Iran, Israel, Panama, Singapore and Turkey based on meeting reports, publications or word of mouth [30–34]. At this time, most studies are limited in size to less than 100 patients and are in their early stages. It will be important to maintain rigorous follow-up on these studies to facilitate future meta-analyses of both positive and negative outcomes [5].

Enabling technologies & infrastructure

As clinical applications of adipose-derived cells mature, the parallel validation of enabling technologies and infrastructure development will be of equal importance. While closed or hermetically sealed mechanical devices allow the extraction of SVF cells from lipoaspirates in the operating room without exposure to the ambient environment, thereby reducing the risk of contamination, clean room laboratories will be required for ASC production in compliance with current GMP guidelines [35–37]. Their operation requires standard operating procedures defining the in-process and lot-release criteria, functional assays and sterility testing of the ASCs. Novel approaches are being developed to expand adipose-derived cells with autologous serum or with xenoprotein-free medium in bioreactors [38–42]. Reagents and equipment must be calibrated and validated and source records maintained for all materials used during the tissue processing. Furthermore, cryopreservation and shipping protocols require similar evaluations in a time-dependent manner. It will be important to establish internationally recognized and accepted standards for each of these variables in order to harmonize the future development of adipose-derived cell therapies. The cooperation and involvement of academic, biotechnology, manufacturing and governmental regulatory agencies will be necessary to attain this goal.

Targets of opportunity

Soft tissue

Adipose-derived cells and adipose tissue continue to be employed in preclinical models of soft tissue injury and are progressing into clinical trials. Cultured ASCs have been used to treat full-thickness skin wounds in diabetic rodents [43,44]. In streptozotocin-induced diabetic rats, injection of GFP-labeled ASCs into the wound bed accelerated repair. The GFP plus ASCs were traced and observed to participate in vasculogenesis via differentiation into endothelial and epithelial cells [43]. In addition, the ASCs secreted angiogenic cytokines, including VEGF, HGF and FGF2 [43]. Similar outcomes were observed when human ASCs were applied topically to full-thickness skin wounds in obese diabetic (db/db) mice [44]. The human ASC secretion of HGF, VEGF and matrix metalloproteinases was correlated with the accelerated epithelialization and closure of the diabetic wounds [44]. Furthermore, culture of human ASCs as 3D aggregates increased cytokine secretion by as much as an order of magnitude relative to monolayer cultures, suggesting that human ASC spheroids provide a superior culture approach [44]. The enhanced secretion of angiogenic cytokines has been confirmed in independent experiments on human ASC spheroids [45]. Additional studies have examined TNF-α-induced human ASC conditioned medium in a rat skin wound model [46]. Application of the conditioned medium accelerated wound repair and increased angiogenesis [46]. The efficacy of the conditioned medium was reduced when IL-6 and IL-8 were selectively depleted [46]. Together, these studies support a paracrine mechanism for human ASC action.

Human adipose tissue grafting has been found to reduce cutaneous damage in rodents following burns or radiation exposure [47,48]. Implantation of adipose tissue reduced fibrosis, improved collagen organization and increased the number of vessels, consistent with revascularization [47,48]. Anecdotal reports have described the use of autologous human SVF cells, in combination with an angiogenic growth factor (FGF2) and artificial dermis, to repair a chronic radiation skin wound in a single patient [49,50]. A more extensive safety trial has evaluated outcomes after transplanting adipocyte-differentiated autologous ASCs into 31 patients with depressed scars [51]. At 12 weeks and 1 year postoperatively, follow-up analyses documented safety and efficacy for the use of human ASCs in repairing these cosmetic defects [51]. While clinicians have reported the transplant of SVF cells with autologous fat for cosmetic surgery [52,53], potential concerns remain for this application in postmastectomy breast cancer reconstruction [54]. *Invitro* and *in vivo* data demonstrate that human ASCs secrete multiple cytokines that can increase the proliferation of active breast cancer cells [55]. There is no question that the impact of SVF cells and ASCs on the growth of tumor cells requires further investigation. There is a growing body of evidence indicating that adipose-derived cells promote the growth of tumor cells from breast, prostate and Kaposi's sarcoma cancers [55–57]. Furthermore, the population of circulating mes-enchymal stem cells is altered as a function of obesity in colon cancer patients [58,59]. Concerns remain that adipose cell-derived paracrine factors might recruit the homing and promote the proliferation of breast, prostate or sarcomatous cancer cells following transplantation, whether introduced directly at a postmastectomy or other surgical site or indirectly via intravenous injection [55,57]. In summary, while recent literature supports a paracrine role for SVF cells and ASCs in promoting skin wound healing, these same secreted cytokines may have adverse effects in the presence of tumor cells. Clinical studies remain limited by a relatively low number of patients and a reliance on historical case controls as opposed to randomization protocols.

Skeletal tissue

Complementary studies using human ASCs demonstrate that similar mechanisms underlie their ability to promote repair in skeletal tissues [60–62]. Human ASCs implanted with scaffolds and BMP2 accelerated and improved repair of critical-sized calvarial defects in nude mice [62]. While the human ASCs differentiated into osteoblasts *in vivo*, their long-term presence was not detectable after 2 weeks, suggesting differentiation is not their sole mechanism of action [62]. These observations confirm and extend previous work from the same laboratory that had established the utility of murine ASCs for the repair of critical-sized cranial defects [63,64]. The timing of ASC transplantation is critically important [61]. While they are effective in the acute injury, delaying transplantation for 8 weeks significantly reduces their impact [61]. An exciting study provides consistent evidence supporting a paracrine action of human ASCs [60]. In an ovariectomized murine model of bone loss, systemic injection of human ASCs into the circulation reduced bone resorption by increasing the numbers of osteoblasts and osteoclasts [60]. *In vitro* studies documented that conditioned medium from the human ASCs contained HGF and matrix metalloproteinases. The conditioned medium stimulated osteoblast proliferation and differentiation via an extracellular signaling kinase (ERK/JNK) and its downstream transducer, the Smad transcription factor [60]. These findings have been extended to clinical practice [30,31,65]. In a single case report, autologous human ASCs were used in combination with an autologous bone graft to successfully repair a chronic critical-sized defect complicated by infection in a pediatric patient [65]. In an unrelated single case report, autologous human ASCs were used in combination with a tricalcium phosphate scaffold and BMP2 to repair a maxillofacial defect with successful outcomes [31]. More recently, the same group used a similar approach to perform cranioplasty in four subjects with calvarial defects [30]. The cranioplasty transplants approached the strength of intact cranial bone based on CT scan

follow-ups for up to 1 year postoperatively [30]. While these studies support the promise of human ASCs for hard tissue regeneration, preclinical mechanistic studies and randomized controlled clinical trials merit evaluation in the future. In particular, it will be important to evaluate cartilage defects and weight-bearing bone models more extensively.

Ischemic injuries

There has been increased attention paid to the application of ASCs and SVF cells for the treatment of ischemic injuries, with particular interest in myocardial infarction (MI) [66,67]. In a murine study, injection of either human SVF cells or ASCs into the myocardium following infarcts improved cardiac recovery [68]. A sub-fraction of the human cells engrafted as both cardiomyocytes and endothelial cells within the murine cardiac muscle and could be tracked for up to 10 weeks using bioluminescent tracers [68,69]. In an independent analysis, transplantation of human ASCs into nude rats following a MI resulted in improved cardiac function, increased capillary density and reduced infarct size [70]. This occurred without histologically detectable engraftment of the human cells [70]. Improved function was attributed to the human ASC secretion of VEGF, FGF2 and SDF1α, and the subsequent recruitment of host-derived bone marrow progenitor cells to the ischemic injury site [70]. The source of the adipose-derived cells may contribute to their functionality. Analyses of ASCs isolated from human cardiac adipose tissue found that these cells differentiated *in vitro* into cardiac myocytes and endothelial cells, but not adipocytes, and secreted angiogenic cytokines when exposed to hypoxia [71]. When injected into both murine and rat MI models, the human cardiac ASCs improved ejection fraction and wall thickness after 30 days [71]. A direct comparison of human ASCs, BMSCs and umbilical cord-derived mesenchymal stromal/stem cells concluded that BMSCs displayed the most robust regenerative capacity in a murine MI model; nevertheless, all stromal/stem cells improved capillary density relative to controls [72]. Similar studies have been performed in the pig as a large animal model, where intra-arterial administration of autologous SVF cells or ASCs was found to improve left ventricular ejection fraction 4–8 weeks postischemia in a manner comparable to BMSCs [73–75]. While the majority of studies have delivered ASCs by direct injection into the myocardial tissue, investigators have continued to explore the use of cell sheets as an alternative [76,77]. In studies using rhesus monkeys, sheets of autologous ASCs provided a matrix for the delivery of allogeneic rhesus embryonic stem cells that had been differentiated along the cardiomyogenic lineage [77]. A total of 2 months after the MI, the presence of the ASCs had improved angiogenesis [77]. The study supported the safety of the ASC and embryonic stem cell combination [77]. While the work in animal models is promising, the modest overall degree of improvement in these myocardial ischemia models has potentially deterred more aggressive clinical translation protocols. While a number of MI clinical trials are underway (Tables 1–4), it is too early for any major reports regarding patient outcomes. Further preclinical studies documenting the paracrine and/or differentiation mechanism of ASC and SVF cell cardiac repair and their subsequent efficacy will likely accelerate the clinical translation process.

The potential of adipose-derived cells to treat hindlimb ischemia or stroke models has been investigated in several models as well. Transplantation of human ASCs cultured as spheroids and preconditioned under hypoxic conditions was found to improve recovery from hindlimb ischemia in murine models [45]. This effect has been attributed to their secretion of angiogenic factors [45]. Additional studies have determined that ASCs exposed to ischemia or hypoxia secrete cytokines that can improve cell proliferation and vasculogenesis directly, without the presence of the ASCs themselves [78]. Exposure of ASCs to these hypoxia-induced cytokines promotes their differentiation along the adipocyte and endothelial pathways [78]. This suggests that ASC-conditioned medium alone may be sufficient to treat ischemic injuries without the need for direct cell transplantation [78].

Finally, studies have evaluated the efficacy of autologous ASCs in a rat model of cerebral ischemia [79]. When ASCs induced to undergo neuronal differentiation were transplanted, the rats displayed improved neurological recovery and reduced infarct size relative to controls [79].

Immune disorders

In a manner similar to BMSCs, human ASCs are known to display immunomodulatory and immunosuppressive functions [10,19,80,81]. The mechanism underlying ASC immunomodulatory function remains an area of active investigation. Independent *in vitro* studies have confirmed that both IFN-γ/indoleamine 2,3-dioxygenase and prostaglandin E2 secreted by ASCs account for their suppression of T-cell proliferation [21,82]. Additional evidence suggests that the ASC expression of Jagged 1 contributes to the suppression of T-cell proliferation via its activation of the Notch receptor pathway and subsequent inhibition of the NF-κB pathway [83]. In parallel with this interest in their immunosuppressive activity, studies have explored the immunostimulatory function of ASCs [84–87]. When cultured with ASCs directly or separated by a transwell membrane, nonactivated peripheral blood mononuclear cells exhibited a robust proliferation that continued even after the removal of the ASCs themselves [84]. The $CD4^+$ T cells with associated CD25 or FoxP3 positivity accounted for the proliferative response, consistent with a Treg phenotype [84]. Independent groups found that while ASCs suppressed proinflammatory cytokine secretion by activated peripheral blood mononuclear cells, they stimulated secretion from purified T cells [85]. These observations may reflect differential cytokine-mediated feedback loops between the immune cells and ASCs that may be active *in vitro* and *in vivo* [85]. Indeed, the differentiation status of the ASC may alter its immunomodulatory function [86]. While undifferentiated ASCs did not display the surface antigen HLA-DR, this protein was upregulated in response to TGF-β3 during chondrogenic induction [86]. This change correlated with increased secretion of IFN-γ by the ASCs themselves [86]. Similarly, the lymphoid-proliferative response to ASCs changed in the presence of cardiomyocytes *in vitro* [87]. Together, these studies indicate that the immunomodulatory function of ASCs must be reassessed following cytokine induction, differentiation or coculture with other cell types [86,87].

In vivo studies have evaluated the immunomodulatory effects of ASCs in autoimmune and immunological diseases. Chronic intravenous administration of human ASCs to a mouse model of systemic lupus erythematosis improved animal survival, decreased anti-DNA antibody levels and increased the level of Tregs [88]. Administration of ASCs early in the disease showed improved efficacy relative to delayed treatment, which was associated with increased levels of the anti-inflammatory cytokines IL-4 and IL-10 [88]. Similar outcomes were observed in a murine model of experimental arthritis [89,90]. Following disease initiation by immunization with collagen, intravenous administration of human ASCs reduced the levels of inflammatory cytokines and autoimmune Th1 cells [89]. This was accompanied by an increased production of $CD4^+CD25^+FoxP3^+$ Tregs [89,90]. In murine models of experimental colitis, intravenous administration of human ASCs reduced weight loss, inflammation and mortality [91,92]. This was associated with reduced levels of inflammatory cytokines and increased levels of IL-10 [91,92]. Furthermore, autoimmune Th1 cell proliferation decreased, while the number of Tregs was increased [91,92]. These outcomes are consistent with multiple clinical trials documenting the beneficial effects of human ASCs in the treatment of Crohn's disease (Table 4); however, it should be noted that the majority of clinical studies injected the autologous ASCs directly into the fistula lesions rather than systemically [93–97]. In a murine model of experimental auto-immune encephalomyelitis, which is homologous to multiple sclerosis in humans, intravenous administration of ASCs reduced demyelination and axonal loss when given prior to disease

onset [98]. This was accompanied by increased production of anti-inflammatory cytokines (IL-4 and IL-10) and homing of the ASCs to lymph nodes and the CNS lesions [98]. Clinical trials have begun to evaluate the efficacy and safety of autologous SVF cells administered to patients with multiple sclerosis (Table 4) [32]. Anecdotal reports in three patients suggest that intravenous injection of SVF cells is tolerated and may have some symptomatic benefit; however, randomized control clinical trials in a larger patient cohort are needed [32].

Insulin-dependent diabetes has attracted substantial attention as an autoimmune disease amenable to adipose-derived cell intervention. Human ASCs isolated from the eyelid were analyzed due to their neural crest-like origins [99]. Following induction with a combination of activin, nicotinamide and GLP-1, the differentiated ASCs expressed insulin and were capable of improving glucose sensitivity when transplanted into streptozotocin-induced diabetic mice [99]. Similar *in vitro* and *in vivo* outcomes were obtained by an independent group using a $CD29^{+}CD44^{+}Sca1^{+}$ clonal population derived from murine epididymal ASCs [100,101]. Further studies have found that the coimplantation of ASCs improved the engraftment of pancreatic β-islets in diabetic mice, in part by enhancing vascularization and reducing immune cell infiltration [102,103]. A single clinical study in India has reported the transplant of insulin-expressing human ASCs in combination with BMSCs in a cohort of 11 consenting diabetic patients [33]. The patients displayed a mean decrease in HbA1c of 1%, a reduction in their requirement for exogenous insulin and an elevation in C-peptide levels, which is consistent with the production of endogenous insulin [33]. While this work is promising, confirmatory studies and randomized controlled clinical trials will be required.

Graft-versus-host disease (GVHD) is an iat-rogenic induced immune disorder resulting from the destruction of host or recipient cells by the donor lymphocytes following a bone marrow or hematopoietic stem cell transplantation. Even when it is not lethal, GVHD causes considerable morbidity in the recipient. In a murine model of GVHD, cotransplantation of ASCs with the hematopoietic stem cells significantly reduced mortality, which is consistent with the immunosuppressive function of the ASCs *in vitro* [20]. A single group in China has reported anecdotal findings in GVHD patients treated with ASCs [104,105]. In patients with GVHD refractory to steroid treatment, infusion of ASCs improved the disease complications in four out of six subjects who were followed for a median of 40 months postprocedure [104]. While employing ASCs and other mesenchymal stem cells to treat GVHD shows promise, additional preclinical safety and efficacy studies may be required to set the stage for large-scale, randomized controlled clinical trials of ASCs for GVHD [106].

Gene therapy

Adipose-derived cells can be transduced with viral vectors and used effectively as gene delivery vehicles [107]. Using an adeno-associated viral vector, investigators have transplanted ASCs transduced with α1-antitrypsin into the liver of mice [108]. This approach documents the potential utility of ASCs to treat inborn metabolic errors involving the liver. In an independent study, investigators transduced human ASCs with a virus expressing a cytotoxic T-lymphocyte antibody [109]. When either untransduced or transduced ASCs were transplanted into mice with autoimmune thyroiditis, production of inflammatory cytokines and lymphocyte infiltration of the thyroid was reduced relative to controls [109]. While such cell and gene therapy approaches offer promise for the future, the regulatory issues for these combination therapies are daunting. Substantial preclinical safety and efficacy data will be needed before they can advance to the clinic internationally.

Future perspective

The past 2 years have witnessed considerable advances in the knowledge base relating to the use of adipose-derived cells for regenerative medicine. The field has matured to the point

where it is poised for clinical trials treating a number of acute and chronic disease states. A recent publication from a Korean biotechnology company reflects the current state of the art [110,111]. The authors reported a detailed description of the assays and results they employed to address concerns and questions relevant to their national regulatory agency. These data documented the safety and efficacy of their manufactured human ASC product based on *in vitro* and *in vivo* (murine) findings. In addition, they reported the initial Phase I safety testing of autologous ASCs administered intravenously to eight spinal cord injury subjects who had provided informed consent under an Institutional Review Board-approved protocol [110]. It is anticipated that similar publications will document the outcomes of combined pre-clinical and clinical translational studies that are now underway. The peer-reviewed publication of new information on SVF cell and ASC manufacturing, safety and efficacy will likely accelerate the delivery of adipose-derived cell therapies to physicians and their patients. In the next decade, it is anticipated that regenerative medical applications using adipose-derived cells will be approved by regulatory authorities in Asia and Europe for bone, cosmetic, ischemic and immune-related disorders. It is expected that regulatory approval in the USA will occur only after sizable safety outcomes have been evaluated overseas. These clinical advances will be accompanied by continued growth in the bio-technology sector to provide a supporting infrastructure including current GMP reagents, kits, equipment and services.

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Executive summary

- Adipose tissue is a rich source of stromal/stem cells for regenerative medicine.
- The mechanism of adipose-derived cell action is via direct differentiation and paracrine factor secretion.
- Preclinical studies continue to advance using adipose-derived cells for soft and hard tissue repair, ischemic insults and autoimmune disorders.
- Published Phase I/II clinical trials have used human adipose-derived cells for soft tissue cosmesis, cranioplasty, Crohn's disease, diabetes and spinal cord injury.
- Future growth will require internationally coordinated, randomized controlled clinical trials suitable for meta-analyses evaluating the safety and efficacy of adipose-derived cells.

Table 1

Phase of clinical studies from clinicaltrials.gov as of 22 October 2011.

Phase	Sites (n)
I	8
I/II	21
II	6
III	2
IV	1
Unknown	6

Table 2

Activity status of clinical studies from clinicaltrials.gov as of 22 October 2011.

Status	Sites (n)
Not yet recruiting	1
Active, not recruiting	3
Recruiting	22
Completed	8
Suspended	2
Terminated	2
Unknown	6

Table 3

Geographic location of clinical studies from clinicaltrials.gov as of 22 October 2011.

Country	Studies (n)
Asia	
Japan	1
Philippines	1
South Korea	10
Taiwan	1
Europe	
Belgium	1
Denmark	2
France	1
Italy	1
The Netherlands	2
Spain	13
Switzerland	1
UK	2
North America	
Mexico	6
USA	3
South America	
Brazil	1

Table 4

Disease category of clinical studies from clinicaltrials.gov as of 22 October 2011.

Disease	Studies (n)
Endocrine	
Diabetes and complications	4
Gastrointestinal	
Crohn's disease/fistulas/fecal incontinence	13
Ischemic	
Angiogenesis/Berger's disease/ischemic limb	6
Myocardial infarction	3
Hard and soft tissue	
Arthritis/bone/cartilage	3
Cosmetic reconstruction	2
Other	
CNS/MS/Parkinson's disease/ stroke	5
GVHD	1
SCI	1
Renal failure	1

GVHD: Graft-versus-host disease; MS: Multiple sclerosis; SCI: Spinal cord injury.