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# Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy

Neil Riordan is President and CEO of Medistem Laboratories. He directed a leading cancer laboratory for 10 years, Project RECNAC of The Centre for the Improvement of Human Functioning, and he has proved himself a successful entrepreneur. In 2003 Dr Riordan became the director of research at the Immunology Research Centre. His research findings have been published in many prestigious journals, including *British Journal of Cancer* and *Medical Hypotheses*. His educational qualifications include MUA, PhD, MS, and PA from University of Nebraska, College of Medicine, and BS *magna cum laude* from Wichita State University.

*Dr Neil Riordan*

Thomas E Ichim[1], Fabio Solano[2], Roberto Brenes[2], Eduardo Glenn[2], Junbiao Chang[3], Kyle Chan[1], Neil H Riordan[1,3,4]
[1]Medistem Laboratories Inc., 2027 E Cedar Street Suite 102 Tempe, AZ 85281, USA; [2]Institute for Cellular Medicine, San Jose, Costa Rica; [3]Zhengzhou University, Zhengzhou, China
[4]Correspondence: Tel: +1 954 7273662; Fax: +1 954 2060637; e-mail: riordan@medisteminc.com

## Abstract

Regenerative treatment of dilated, non-ischaemic cardiomyopathy represents a significant unmet clinical need. Intracoronary administration of autologous bone marrow stem cells has demonstrated positive results in treatment of post-infarct and chronic ischaemic patients. Limitations of this procedure include: invasiveness of bone marrow extraction and cardiac catheterization, and dependence on stem cell populations that are aged and possibly senescent. Here, the use of intravenously administered allogeneic placental matrix derived mesenchymal stem cells for treatment of dilated cardiomyopathy is discussed. Safety of this cell population has already been established in completed Phase I and II trials; however, to date, clinical implementation for dilated cardiomyopathy has not been reported. Preclinical studies have demonstrated that mesenchymal stem cells: (i) inhibit myocardial inflammation; (ii) inhibit cardiomyocyte apoptosis; (iii) stimulate angiogenesis; and (iv) display therapeutic activity in models of dilated cardiomyopathy. Clinical studies have demonstrated the ability of mesenchymal stem cells to inhibit post-infarct remodelling, as well as potently block inflammatory processes in graft versus host and Crohn disease. Presented here is case report of a patient with dilated cardiomyopathy treated with intravenous allogeneic mesenchymal stem cells and expanded umbilical cord blood CD34 cells who underwent a profound clinical improvement.

***Keywords:*** *angiogenesis, CD34, cord blood, dilated cardiomyopathy, mesenchymal, stem cell therapy*

## Introduction

Stem cell therapy in the post-myocardial infarct setting has yielded positive results in preclinical (Orlic *et al*., 2001; Kudo *et al*., 2003) and clinical studies (Chen *et al*., 2004; Fernandez-Aviles *et al*., 2004; Osterziel, 2007). However, the promise of regenerating myocardium appeals to other non-acute cardiac degenerative conditions besides myocardial infarction. For example, dilated cardiomyopathy is believed to have an annual incidence of approximately 400,000 per year in the USA alone, with a 50% survival at 5 years. Current therapies for this condition such as angiotensin-converting enzyme inhibitors, beta-blockers and vasodilators seek to reduce the rate at which myocardial damage accrues but do not have regenerative potential. This article begins by reviewing the disease and pathological mechanisms associated with its progression, and subsequently reviews various types of stem cell therapies that have demonstrated promise in cardiac degeneration in general and current work in dilated cardiomyopathy. Although embryonic stem cells have previously been demonstrated to possess cardiogenic potential (van de Stolpe *et al*., 2005), due to both technical and ethical limitations (Beeson and Lippman, 2006; Findikli *et al*., 2006), these cells will not be discussed in this review. The paper will conclude with a presentation of a case report of successful stem cell therapy for this condition.

## Dilated cardiomyopathy

Cardiomyopathy is generally defined as weakening of the myocardium (Richardson *et al*., 1996). There are three main types of cardiomyopathy: (i) dilated cardiomyopathy, which

is associated with enlargement of the left ventricle and resulting suboptimal function. This condition can be the result of hypertension, post-infarct scar tissue formation, as well as other causes such as infections, cardiotoxic drugs and in some cases pregnancy; (ii) hypertrophic cardiomyopathy is a condition in which the myocardial muscle abnormally enlarges in an asymmetric manner; this is usually attributed to genetic factors although accurate gene testing has not been developed. Hypertrophic cardiomyopathy is a known cause of sudden death in young athletes; (iii) restrictive cardiomyopathy, a condition in which the myocardium does not properly enlarge during diastole, thus not allowing for proper filling and pumping. This condition is usually caused by amyloidosis, post-transplant chronic rejection, radiation fibrosis, haemochromatosis, sarcoidosis and in some cases cardiac tumours. The subject of the current paper is dilated cardiomyopathy, which is the most prevalent of the cardiomyopathies (60%), and believed to have an annual incidence of approximately 400,000 per year in the USA alone (Karkkainen and Peuhkurinen, 2007). Although in some cases dilated cardiomyopathy occurs post-infarct as a result of ventricular wall thinning, the majority of dilated cardiomyopathies are non-ischaemia associated and believed to be caused by idiotypic, viral-induced, and parasite-induced causes. For example, in a representative study of 673 patients referred for congestive heart failure due to dilated cardiomyopathy the most common causes of dilated cardiomyopathy were idiopathic origin (47%), idiopathic myocarditis (12%), coronary artery disease (11%) and known causes such as hypertension and post-infarct remodelling (31%) (Kasper *et al*., 1994). Although the instigating causes of cardiomyopathy are numerous and in many cases ill defined, the end result is often similar: decreased ejection fraction and progression to heart failure. Mechanisms of cardiac deterioration often include elaboration of inflammatory mediators, which cause functional impairment and apoptotic death of myocardial cells that leads to a self-feeding cascade.

## Inflammatory mediators as cause of myocardial damage

Inflammation is associated with heart failure. Acute inflammation during myocardial infarction results in production of cytokines such as tumour necrosis factor (TNF)α, interleukin (IL)-1 and IL-6, which directly induce myocardial 'stunning' as well as apoptosis of contractile cells (Paulus, 2000; Cailleret *et al*., 2004). Positive correlations have been made between the amount of TNF released into systemic circulation and the extent of myocardial cell death (Li *et al*., 1999). In less acute circumstances, inflammatory cytokines are also known to play a role in progression to heart failure. For example, patients with non-ischaemic, as well as ischaemic dilated cardiomyopathy, possess increased concentrations of circulating TNFα compared with healthy controls (Oral *et al*., 1999; De Biase *et al*., 2003). Spontaneous secretion of TNFα from leukocytes in patients with dilated cardiomyopathy but not controls has also been reported (Brooksbank *et al*., 2005). A correlative role of inflammatory cytokines in progression of heart failure is supported by studies demonstrating improved prognosis in patients with lower concentrations of TNFα and IL-6 (Hasper *et al*., 1998; Rauchhaus *et al*., 2000; Pan *et al*., 2004). The possible importance of inflammatory cytokines to disease progression is seen in studies using inhibitors of inflammatory cytokines, such as thalidomide or pentoxifyllin, which demonstrated reduction in TNFα concentrations in patients responding to treatment (Sliwa *et al*., 2004; Orea-Tejeda *et al*., 2006). In animal models of heart failure, blockade of TNFα (Li *et al*., 2002; Moe *et al*., 2004), as well as IL-1 (Thomas *et al*., 2003) signalling, has been demonstrated to ameliorate disease progression.

While it appears that inflammation plays a key role in the progression of heart failure in general, and specifically in dilated myocardiopathy, the next question is what causes this inflammation? In the context of infarction, it is obvious that release of intracellular components through necrosis produce a potent 'danger signal' that activates various innate immune cascades. For example, heat shock proteins (Satoh *et al*., 2006a), extracellular matrix degradation products (Samstein *et al*., 2004), soluble mediators such as mast cell released histamine (Frangogiannis and Entman, 2006), tissue factor resulting from activation of the coagulation cascade (Frangogiannis *et al*., 2002), and complement pathway products (Yasuda *et al*., 1990) are all known to either directly induce inflammatory cytokine production or to elicit innate immune cell infiltration; this subsequently results in cytokine production. In more chronic conditions such as toxin-induced dilated myocarditis, it is believed that 'danger receptors' such as the toll-like receptor family can recognize tissue death and activate immune cells. For example, doxorubicin-induced cardiac dilation is associated with a chronic remodelling of the myocardium subsequent to death of a small portion of cardiomyocytes. In animals that lack toll-like receptor-2 (TLR-2), progression of disease pathology in this model is markedly inhibited in comparison to wild-type mice (Nozaki *et al*., 2004). TLR-2 activation stimulates monocytes and dendritic cells to release inflammatory cytokines and its ligands include damage-associated proteins such as heat shock protein 60 (O'Neill, 2002; Direskeneli and Saruhan-Direskeneli, 2003). In addition, TLR-2 knockout mice also show inhibited progression to heart failure subsequent to infarct-induced chronic ventricular remodelling (Shishido *et al*., 2003). Clinically, heart failure is associated with up-regulation of TLR-4 expression both locally in the myocardium (Frantz *et al*. 1999) and systemically in circulating monocytes (Satoh *et al*., 2006b). Ligands of TLR-4 such as heat shock protein 70 are released by damaged myocardium and serum concentration is associated with poor prognosis (Satoh *et al*., 2006a). In addition to induction of inflammatory mediators by localized tissue damage, the simple increase of myocardial load is also associated with increased production of inflammatory cytokines by cardiomyocytes (Baumgarten *et al*., 2002; Roncon-Albuquerque *et al*., 2005).

Infectious causes of cardiomyopathy are described in the literature. Commonly known causes include Chagas' disease (Rodas *et al*., 1992), coxsackie virus (Spotnitz and Lesch, 2006), and *Chlamydia pneumoniae* (Song *et al*., 2001). Evidence exists that such diseases play an active role in stimulation of cytokine secretion, which leads to deleterious changes in the myocardium, as well as pathogens that induce initial tissue damage, which results in an autoimmune sequel. For example, Chagas' disease patients that progress to cardiomyopathy often display T-cell-mediated responses against myocardial antigens (Fuenmayor *et al*., 2005). Systemic elevations in TNFα are also observed in patients with Chagas' disease-associated cardiomyopathy (Talvani *et al*., 2004). The causative role of immune-mediated cardiac damage is revealed in this disease

by mice lacking IL-4 in which Chagas' infection clears at a more rapid rate as compared with wild-type mice; however cardiac pathology is exacerbated (Soares *et al.*, 2001). Similar observations linking immune attack against infectious pathogen with cardiac pathology are also seen in coxsackie virus (Fuse *et al.*, 2005) and *Chlamydia pneumoniae* models (Bachmaier and Penninger, 2005).

Numerous observations in addition to the above-mentioned studies report a strong association between ongoing inflammatory responses and progression of cardiac dysfunction. This is specifically noted in dilated cardiomyopathy where myocyte damage causes decrease in ventricular wall thickness and suppression of contractile function. In dilated cardiomyopathy, the reduction in wall thickness is associated with an elevated rate of apoptosis (Ibe *et al.*, 2007; Kietselaer *et al.*, 2007). Apoptosis is a tightly controlled process whose physiological purpose is regulating tissue mass, as well as clearing dysfunctional cells. Signals inducing programmed cell death include inflammatory cytokines, and in many cases membrane-bound molecules such as the death-inducing protein Fas ligand (FasL). In conditions of inflammation, up-regulation of myocardial Fas and FasL has been reported. For example, mice with mutations in this pathway have reduced myocardial damage in response to ischaemia (Jeremias *et al.*, 2000). A direct role of TNFα-induced Fas–FasL up-regulation has been demonstrated in myocardial cells *in vitro* (Chen and Tu, 2002). Mechanical overload (Liao *et al.*, 2005), chemical toxicity (Nitobe *et al.*, 2003; Kalivendi *et al.*, 2005), and viral infections (Seko *et al.*, 2002) have all been demonstrated to cause cardiomyocyte apoptosis through Fas–FasL either directly or indirectly through inflammatory cytokine mediated up-regulation of this pathway. Thus it appears that chronic inflammation and apoptosis form a positive feedback loop in heart failure, not only in post-infarct setting but also in chronic cardiac degeneration such as dilated cardiomyopathy.

## Autologous bone marrow stem cell therapy for post-infarct and chronic ischaemia associated heart failure

The introduction of bone marrow-derived stem cells in cardiology offers hope to a patient population that previously was restricted to transplantation and palliative procedures. Additionally, bone marrow stem cells are free of ethical issues associated with embryonic stem cells (Beeson and Lippman, 2006) Initial preclinical studies have shown that bone marrow stem cells are capable of augmenting cardiac function in a post-infarct setting (Orlic *et al.*, 2001; Kudo *et al.*, 2003). Mechanistically, these cells are believed to mediate therapeutic effects through production of paracrine trophic factors (Gnecchi *et al.*, 2006; Tse *et al.*, 2007), induction of angiogenesis (Mollmann *et al.*, 2006; Shyu *et al.*, 2006), and transdifferentiation into cardiomyocytes (Orlic, 2003; Xu *et al.*, 2004; Eisenberg *et al.*, 2006). Clinical translation of bone marrow stem cell therapy has resulted in observation of reduced scar tissue, ventricular wall dilation, and increased ejection fraction after myocardial infarction (Chen *et al.*, 2004; Fernandez-Aviles *et al.*, 2004; Osterziel, 2007). Although double-blinded Phase III trials are currently in progress, the consensus is that stem cell therapy will in one form or another play a role in the treatment of cardiac disorders. An example of stem cell trials in cardiology is presented in **Table 1**.

The attractiveness of autologous stem cell therapy comes from the fact that during cardiac infarction, stem cell mobilization to induce myocardial repair seems to be a natural response of the body. Stem cell chemoattractants such as vascular endothelial growth factor (VEGF) (Soeki *et al.*, 2000) are observed in systemic circulation subsequent to infarction. Peaking of serum VEGF at day 7 post-infarct has been correlated with mobilization of bone marrow CD34 stem cells into circulation (Shintani *et al.*, 2001). Subsequent studies have demonstrated that numerous cytokines are involved in the mobilization of endogenous bone marrow stem cells post-infarct, such as stromal-cell-derived factor-1 (SDF-1) (Deng *et al.*, 2006), granulocyte colony-stimulating factor (G-CSF) (Leone *et al.*, 2006), and IL-8 (Schomig *et al.* 2006). Accordingly, by administering stem cells into an area proximal to cardiac infarction, one anticipates that this procedure merely serves to augment efficacy of an existing natural response. In conditions associated with chronic ischaemic heart failure, for example caused by atherosclerotic occlusions, stem cell therapy is used not only for regenerating myocardium, but also to increase circulation through formation of collateral blood vessels. Intramyocardial administration of stem cells was initially performed in 2001 as an adjuvant to bypass with angiographic evidence of collateralization at the implant site in three of five patients (Hamano *et al.*, 2001). Subsequent studies have demonstrated that bone marrow derived stem cells either as mononuclear cells (Yaoita *et al.*, 2005) or purified into subsets (Stamm *et al.*, 2007), are capable of increasing oxygenation, as well as ejection fraction when implanted into chronically ischemic myocardium. Mechanistically, in the chronic ischaemia setting, the intramuscular injection of stem cells induces various cytokine cascades that stimulate migration of endogenous endothelial precursors and interaction with the exogenously administered precursors in order to cause new blood vessel formation. It is known that chronically ischaemic tissue has activation of the transcription factor hypoxia-inducible factor 1 (HIF-1)α (Blanco Pampin *et al.*, 2006) which is associated with localized production of fibroblast growth factor-1 (FGF-1) (Iwakura *et al.*, 2000), whose role is to chemoattract the administered endothelial precursors and induce the angiogenic cascade. From the mentioned studies it is apparent that strong logic exists for the use of stem cells either as bone marrow mononuclear cells, or as purified subpopulations for repairing post-acute myocardial infarction damage, as well as chronic ischaemia. However, in chronic cardiac indications such as dilated cardiomyopathy, which represent a significant burden on our society, is there rationale for the use of stem cells?

## Mesenchymal stem cell therapy for inflammatory associated heart failure

While the regenerative and angiogenic properties of stem cells are well known, another therapeutic aspect of stem cells is their anti-inflammatory properties. Bone marrow mononuclear cells are known to contain not only haematopoietic/endothelial stem cells, designated by markers such as CD34 and CD133, but also mesenchymal stem cells. For decades it was known that bone

**Table 1.** Sample trials of autologous stem cell cardiac clinical trials.

| | *Institution* | *Patients treated* | *Findings* | *Reference* |
|---|---|---|---|---|
| Reperfused AMI | JW Goethe-University, Germany | 59 | Contrast-enhanced magnetic resonance imaging revealed an increased EF, reduced infarct size, and absence of hypertrophy | Schachinger *et al.* (2004) |
| Reperfused AMI | Military Medical Academy, Medicine, Belgrade | 4 | Significant improvement in myocardial perfusion in two patients 4 months after the infarction | Obradovic *et al.* (2004) |
| Reperfused AMI | Hanover Medical School, Germany | 30 | Increased mean global LVEF | Wollert *et al.* (2004) |
| Reperfused AMI | University of Frankfurt, Germany | 20 | Increase in global LVEF, and regional wall motion in the infarct zone, and profoundly reduced end-systolic left ventricular volumes | Assmus *et al.* (2002) |
| Anteroseptum AMI | Department of Cardiology, Athens | 11 | Improvement of myocardial contractility in one or more previously non-viable myocardial segments | Katritsis *et al.* (2005) |
| AMI | First Municipal Hospital, Nanjing, China | 34 | LVEF increased significantly compared with that preimplantation and with that of the control group at 3 months post-injection | Chen *et al.* (2004) |
| AMI | Liaoning Provincial People's Hospital, China | 35 | There was a significant improvement in global left ventricular function ejection fraction | Li ZQ *et al.* (2007) |
| AMI (recent and old) | Seoul National University | 41 | Significant improvement in LVEF and remodelling compared with controls | Kang *et al.* (2006) |
| Ischaemic cardiomyopathy | University of Pittsburgh | 10 | The ejection fractions of the untreated versus treated: pre-operative | Patel *et al.* (2005) |
| Ischaemic cardiomyopathy | Ege University, Turkey | 6 | There was a significant increase in life quality and NYHA class; some benefit was documented on echocardiography, scintigraphy and PET | Ozbaran *et al.* (2004) |
| End-stage heart failure | Navy General Hospital, Beijing | 14 | LVEF increased; left ventricular end-systolic volume decreased | Gao *et al.* (2006) |
| Refractory angina | Leiden University Medical Center | 25 | CCS and Quality of life improved; LVEF increased | Beeres *et al.* (2006) |
| Refractory angina | San Raffaele Hospital, Milan, Italy | 10 | Severity of angina improved by ≥ 2 classes in three patients and quality of life in all patients; myocardial perfusion improved in four of eight patients | Briguori *et al.* (2006) |
| Chronic myocardial ischaemia | Washington Hospital Center | 10 | CCS improved, as well as stress-induced ischaemia occurring within the injected territories | Fuchs *et al.* (2003) |
| Stable ischaemic heart disease | Goethe University, Frankfurt | 75 | Significant improvement in the left ventricular ejection fraction after 3 months | Assmus *et al.* (2006) |
| Dilated cardiomyopathy | Centro Medico Nacional Siglo XXI, Mexico | 39 | Pre-operatively, the functional class for 26 of these patients was III; post-operatively, functional classes were II in five cases and I in 15 patients | Arguero *et al.* (2006) |

AMI = acute myocardial infarction; CCS = Cleveland Clinic Score; EF = ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PET = positron emission tomography.

marrow cells contain immune regulatory cells. For example, in the 1970s, bone marrow-derived 'natural suppressor' cells were demonstrated to possess antigen-non-specific immune regulatory activity (Adler *et al.*, 1976). These cells were subsequently found to secrete large amounts of transforming growth factor (TGF)β, which inhibits T cell and antigen-presenting cell activity (Moore *et al.*, 1992). Subsequent studies have found that mesenchymal stem cells of the bone marrow compartment also produce large amounts of this cytokine and can mediate potent immune suppressive activity *in vitro* and *in vivo* (Li H *et al.* 2007).

Currently, expanded bone marrow derived allogeneic mesenchymal stem cells are being used in Phase III clinical trials for treatment of the inflammatory conditions graft versus host disease and Crohn disease (http://www.osiris.com, accessed 18 January 2008). A recently completed Phase I trial demonstrated profound activity of these cells in preserving left ventricular ejection fraction in patients followingt myocardial infarction (http://files.shareholder.com/downloads/OSIR/280683646x0x86980/8a03c252-36c7-412d-8c9f-0526e0de0993/OSIR_News_2007_3_25_General.pdf). The authors believe that in conditions such as dilated cardiomyopathy, which possess a chronic inflammatory component, the use of mesenchymal stem cells may be more optimal than bone marrow stem cells alone. This rationale is based on findings that while mesenchymal stem cells exert similar functions as bone marrow stem cells such as induction of cardiac angiogenesis (Tang *et al.*, 2006), prevention of myocardial apoptosis (Gnecchi *et al.*, 2006), and inhibition pathological cardiac remodelling associated with left ventricle dilation and wall thinning (Berry *et al.*, 2006), these cells also have a potent anti-inflammatory component. Specifically, mesenchymal stem cells have been shown to inhibit a wide variety of chronic inflammatory conditions such as experimental allergic encephalomyelitis (Zappia *et al.*, 2005), collagen-induced arthritis (Djouad *et al.*, 2005), and protect from immune-mediated diabetes (Lee *et al.*, 2006). Mesenchymal stem cells have also been shown to inhibit myocardial specific inflammation including TNFα production, matrix-metalloproteinase activation, and release of scar tissue formation (Guo *et al.*, 2007). Furthermore, mesenchymal stem cells have been demonstrated effective in animal models of dilated cardiomyopathy (Nagaya *et al.*, 2005). An added advantage of mesenchymal stem cell therapy is that these cells have demonstrated efficacy by intravenous administration both in animal models of cardiac failure (Boomsma *et al.*, 2006), as well as in clinical trials (http://files.shareholder.com/downloads/OSIR/280683646x0x86980/8a03c252-36c7-412d-8c9f-0526e0de0993/OSIR_News_2007_3_25_General.pdf).

Another reason supporting the use of mesenchymal stem cells as opposed to bone marrow stem cells alone are findings that stem cells from older patients have reduced homing activity *in vitro* as compared with stem cells from younger patients. Importantly, stem cells from patients with heart disease exhibit profoundly reduced neovascularization and angiogenic ability when administered to immune deficient mice with experimental ischemia (Heeschen *et al.*, 2004). The use of allogeneic mesenchymal stem cells allows for selection of 'younger' donor sources without the limitation of the autologous donor age.

## Case report: placental matrix-derived mesenchymal stem cells and cord blood CD34 cells in treatment of dilated cardiomyopathy

The use of cord blood stem cells in the absence of recipient conditioning has previously been reported by Ghen *et al.* (2006) for the treatment of amyotrophic lateral sclerosis with some degree of success. Additionally, numerous other reports have been published in which cord blood and/or placentally derived cells have been administered across allogeneic barriers without adverse effect, reviewed in Ghen *et al.*, (2006). In order to augment the number of potentially therapeutic stem cells from this source, the authors' laboratory has developed methods of expanding mesenchymal stem cells from placental matrix. This source of stem cells is potently angiogenic and possesses higher regenerative activity as compared with mesenchymal stem cells from bone marrow and adipose tissue (Kern *et al.*, 2006; Musina *et al.*, 2006; Edwards and Hollands, 2007). Additionally, several technologies have been developed for expansion of cord blood-derived CD34 stem cells using a serum-free protocol. All placental material used for these investigations was collected in a sterile manner with informed consent of the donor. Here, a case of a 50-year-old patient with dilated cardiomyopathy treated with this combination is reported.

The patient was diagnosed with dilated, non-ischaemic cardiomyopathy in February 2002, with an ejection fraction of 30% as measured by echocardiogram (ECHO). The clinical presentation at diagnosis was indicative of congestive heart failure, including marked dyspnoea, inability to exercise, dizziness, and irregular heart beat; New York Heart Association (NYHA) classification of II (see http://www.abouthf.org/questions_stages.htm). ECHO analysis in April 2003 indicated ejection fraction of approximately 40%. Consultation in December of 2005 revealed ejection fraction remained at 30–40% and the patient was placed on carvedilol 25 mg p.o. b.i.d., valsartan 325 mg p.o. q.d., amlodipine besilate 10 mg p.o. q.d., hydrochlorothiazide 25 mg/day, aldosterone, and acetylsalicylic acid 81 mg/day. Weekly blood pressure measurements from the middle of November to the middle of December 2005 were: 145/100, 150/100, 145/90 and 150/95. Quality of life assessment using the Minnesota Living with Heart Failure Questionnaire (Middel *et al.*, 2001) revealed a score of 90. The Minnesota Living with Heart Failure Questionnaire consists of 21 questions to assess a patient's perception of how he or she is affected by heart failure, physically and emotionally. The patient presented in December 2006 and subsequent to being explained the experimental nature of the therapy proposed, the patient signed informed consent. At the time of the treatment the patient had a NYHA classification of III and was taking the above medications, low-dose human growth hormone, testosterone, and the following dietary supplements: co-enzyme Q10, magnesium, L-carnitine, omega 3, 6 and 9 fatty acids, and D-ribose. The patient was treated with cord blood expanded allogeneic CD34 cells (2.5 million) and placentally derived allogeneic mesenchymal stem cells (3 million) three times over the period of a week. Cellular therapy was well tolerated

and no adverse side effects were observed either acutely or as of this writing, 11 months post-treatment. Notably the patient did not experience either symptoms of either acute (skin rash of diarrhoea) or chronic (skin rash, skin inflammation, mouth lesions, hair loss, indigestion) graft- versus host- disease. Two weeks prior to an ECHO in April 2007, the patient voluntarily discontinued all above-mentioned medications and supplements. The ECHO revealed an ejection fraction of 50–55%. The patient reports profound clinical benefit at time of writing (November 2007), including resolution of heart-failure-associated symptoms of dizziness, fatigue, dyspnea, rapid heart beat, irregular heart beat, depression, blackouts, and loss of sleep secondary to orthopnoea. The Minnesota Living with Heart Failure Questionnaire score was zero. The patient has a normal ejection fraction and no symptoms of heart failure and is no longer classifiable on the NYHA scale. Weekly blood pressure measurements for the month of April 2007 were 120/80, 110/85, 120/90 and 110/86. Given that the patient was treated under compassionate-use exemptions and not as part of a clinical trial, no blood gas or pulmonary function data were collected. Although no firm conclusions can be drawn from a single patient case report, and no cytokine analysis was performed to demonstrate potential anti-inflammatory effects of stem cells, these findings suggest that stem cell therapy using CD34 and mesenchymal cells should be investigated in larger groups of cardiomyopathy patients under controlled settings.

## Declaration

Neil Riordan and Thomas Ichim own stocks in Medistem Inc. (mdsm.ob) and are involved in the company's day-to-day operations.

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