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EHJ BRIEF COMMUNICATION
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Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report

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Aims Comparative studies suggest that stem cells committed to a cardiac lineage are more effective for improving heart function than those featuring an extra-cardiac phenotype. We have therefore developed a population of human embryonic stem cell (ESC)-derived cardiac progenitor cells.

Methods and results Undifferentiated human ESCs (I6 line) were amplified and cardiac-committed by exposure to bone morphogenetic protein-2 and a fibroblast growth factor receptor inhibitor. Cells responding to these cardio-instructive cues express the cardiac transcription factor *Isl-1* and the stage-specific embryonic antigen SSEA-1 which was then used to purify them by immunomagnetic sorting. The *Isl-1*$^+$ SSEA-1$^+$ cells were then embedded into a fibrin scaffold which was surgically delivered onto the infarct area in a 68-year-old patient suffering from severe heart failure [New York Heart Association [NYHA] functional Class III; left ventricular ejection fraction (LVEF): 26%]. A coronary artery bypass was performed concomitantly in a non-infarcted area. The implanted cells featured a high degree of purity (99% were SSEA-1$^+$), had lost the expression of *Sox-2* and *Nanog*, taken as markers for pluripotency, and strongly expressed *Isl-1*. The intraoperative delivery of the patch was expeditious. The post-operative course was uncomplicated either. After 3 months, the patient is symptomatically improved (NYHA functional Class I; LVEF: 36%) and a new-onset contractility is echocardiographically evident in the previously akinetic cell/patch-treated, non-revascularized area. There have been no complications such as arrhythmias, tumour formation, or immunosuppression-related adverse events.

Conclusion This observation demonstrates the feasibility of generating a clinical-grade population of human ESC-derived cardiac progenitors and combining it within a tissue-engineered construct. While any conclusion pertaining to efficacy would be meaningless, the patient's functional outcome yet provides an encouraging hint. Beyond this case, the platform that has been set could be useful for generating different ESC-derived lineage-specific progenies.

Keywords Heart failure • Embryonic stem cells • Cell therapy

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Introduction

There is a reasonable hope that stem cells may help repairing the chronically damaged myocardium. In contrast to the initial hypothesis, these cells are unlikely to act through a structural integration into the recipient myocardium for generating a *de novo* myocardial tissue. Rather, they seem to activate host-associated endogenous pathways that may concur to improve heart function,[1] and this activation is mediated by the release of multiple factors possibly clustered in cell-derived microparticles.[2] Although the quest for the 'ideal' cell is still ongoing, head-to-head comparisons[3–5] suggest that the best outcomes are achieved by cells that are phenotypically as close as possible to those targeted for rescue and, importantly, this observation also applies to the above-mentioned paracrine paradigm.[6] Consequently, the second generation of clinical trials has entailed transplantation of cells committed to a cardiac lineage such as right atrium-derived c-*kit*$^+$ cardiac stem cells,[7] right ventricle-derived cardiosphere-derived cells,[8] or bone marrow-derived mesenchymal stem cells (MSC) engineered to express cardiac transcription factors.[9] We have adopted an alternate option that consists of leveraging the intrinsic pluripotency of human embryonic stem cells (ESCs) to drive them towards a cardiac lineage. At the completion of 10 years of preclinical[10–13] and translational studies,[14] we have obtained approval from the French regulatory agency and our Institutional Ethics Committee to deliver ESC-derived cardiac progenitor cells in six patients with advanced ischaemic heart failure (NCT02057900). Here we present the first case of a patient who has reached the 3-month follow-up time point.

Case presentation

An insulin-dependent diabetic woman aged 68 years presented with a New York Heart Association Class III heart failure despite maximal medical therapy due to an extensive antero-lateral myocardial infarction suffered previously. Echocardiographic left ventricular (LV) ejection fraction (EF) was 26% using the apical biplane Simpson's rule with a large akinesia involving the apical and median segments of the antero-lateral wall and a global hypokinesia of the remainder of the left ventricle. Magnetic resonance imaging (MRI) confirmed the akinesia of 8 out of 16 segments with a transmural late enhancement indicative of myocardial necrosis in the basal and mid-segment of the anterior wall. Angiography showed a critical stenosis of the left main stem with a proximal occlusion of the left circumflex coronary artery, the distal filling by collaterals of a tiny obtuse marginal branch, unsuitable for revascularization, and a good run-off of the left anterior descending coronary (LAD) artery. The patient's logistic Euroscore was 22%. As there was a clear indication for a surgical anterior myocardial revascularization, the patient was offered to receive a patch containing human ESC-derived cardiac progenitor cells in addition to the planned coronary artery bypass. After having received extensive information on the procedure, she gave her written informed consent. An internal cardioverter defibrillator (ICD) was implanted uneventfully 1 month before the expected date of surgery.

The technique for processing the cells, the description of the multiple quality controls performed throughout the protocol, and the main results of the preclinical studies have been previously described in details.[14] Briefly, a cryovial of pluripotent ESC from the I6 line (generously provided by J. Itskovitz and M. Amit; Technion Institute, Haïfa, Israël) was retrieved from the Master Cell Bank (Passage 38), thawed, and expanded in a defined medium (Nutristem^{TM}, Biological Industries, Kibbutz Beit-Haemek, Israel) on clinical-grade irradiated human foreskin fibroblasts used as feeder cells (Tissue Bank, Hôpital Edouard Herriot, Lyon, France). After three passages, commitment towards a mesodermal-cardiac lineage was induced by exposure for 4 days to bone morphogenetic protein (BMP)-2 [Dibodermine alpha, 10 ng/mL, marketed as InductOs® (Wyeth pharmaceuticals, New York, NY, USA)] and a fibroblast growth factor receptor (FGFR)-specific tyrosine kinase inhibitor, SU-5402 (1 μM; Merck, Whitehouse Station, NJ, USA) in a clinical-grade α-Minimum Essential Medium Eagle (MEM) solution (Macopharma, Tourcoing, France) enriched with 2% insulin-free B27 supplement (Invitrogen, Life Technologies, Carlsbad, CA, USA). Upon completion of the specification step, an aliquot of cells was analysed by flow cytometry for the expression of stage-specific embryonic antigen (SSEA)-1, used as a marker for loss of pluripotency, and 64% of the cell population were found SSEA-1$^+$, indicating a positive response to the inductive protocol. Elimination of the contaminating fraction of SSEA-1-negative cells was achieved by immunomagnetic sorting using a microbead-coupled anti-SSEA-1 antibody (Miltenyi, Teterow, Germany). The final cell yield achieved a high degree of viability (96.1%, as assessed by flow cytometry using 7-aminoactinomycine D as a marker) and purity (99% SSEA-1$^+$ cells) while polymerase chain reaction performed in duplicate showed that, compared with the starting material of pluripotent undifferentiated I6 ESC taken as the reference, the SSEA-1$^+$ cells featured a knock-down of the pluripotency genes *Nanog* and *Sox-2* (0.017 and 0.001%; 0.018 and 0.054%, respectively, for each set of measurements), which was mirrored by an up-regulation of the cardiac transcription factor *Isl-1* (184 and 134%). Aerobic and anaerobic sterility tests were also performed and failed to show any contamination.

Because pre-set release criteria had been met, we proceeded with the incorporation of the SSEA-1$^+$ progenitor cells into a fibrin patch by first mixing 4 million cells with 1.1 mL of a solution made of fibrinogen (20 mg/mL) and clinical-grade α-MEM medium in a 20 cm^2 agarose-coated Petri dish. Four units of thrombin (diluted in 1.1 mL of the culture medium) were then added to the mixture, which induced rapid polymerization of the gel. Both fibrinogen and thrombin were components of the clinically used Evicel® kit (Ethicon Biosurgery, Omrix Biopharmaceuticals-Ethicon Biosurgery, Rhode Saint Genèse, Belgium). The cell-loaded patch was then housed in a sterile box and transferred at room temperature to the operating room. The whole procedure lasted 18 days.

Cardiopulmonary bypass (CPB) was established between the right atrium and the ascending aorta. To minimize myocardial ischaemia, the heart was kept beating throughout the whole procedure (no aortic cross-clamping). The area of infarction was easily visualized on the LV lateral wall. A 20 cm^2 piece of autologous pericardium was harvested, and the posterior half of its circumference was first sutured to the epicardium along the borders of the infarct area by a running 15/100 polyester suture, thereby creating a pocket between the pericardial flap and the epicardium. Meanwhile, the cell-loaded patch had been taken from the shipment container and rinsed in saline for 3 min.

It was then slipped into the pocket (*Figure 1*), and a few interrupted sutures were finally used to complete anchoring the anterior half of the pericardial flap to the peri-infarct epicardium, thereby allowing to secure the 'sandwiched' cell-laden patch over the diseased area. The LAD was then bypassed with the left internal thoracic artery. Weaning from CPB was uneventful, and the patient was extubated 2 h and 30 min after admission into the intensive care unit. The remainder of her post-operative course was uneventful. A 240-mg dose of corticosteroids (Solumedrol®) was given twice at the onset of the operation and at the time of weaning from CPB and repeated thereafter over the first 24 post-operative hours. Cyclosporine (Neoral®) was started the evening of the operation and the doses were adjusted to maintain serum levels between 100 and 150 ng/mL. Serum creatinine levels and glomerular filtration rate were carefully monitored. Cyclosporine therapy was interrupted after 2 months. The immunosuppressive regimen was completed by mycophenolate mofetil (Cellcept®) at the dose of 2 g/day during 1 month and 1 g/day during one additional month.

The patient and the I6 cell line were typed for HLA (Human leukocyte Antigen) A B C, DR, DQA, DQB, DPA, and DPB by reverse SSO DNA typing (Labtype® One Lambda, Canoga Park, CA, USA). Furthermore, all sera were screened for the presence of anti-HLA antibodies by Class I and Class II SAFB Luminex assays (Labscreen® Single Antigen, One Lambda), pre-operatively and then at 15 days and 10 weeks after the procedure. Beads showing a normalized MFI $>$ 500 were considered positive. Finally, to provide an insight into the level of immunosuppression, the anti-viral T-cell response against Epstein–Barr Virus (EBV) and cytomegalovirus (CMV) was assessed at 15 days, 1, 2, and 3 months of follow-up using an *ex vivo* interferon (IFN)-γ ELIspot with immunodominant viral peptides, as previously described.[15]

Over the 3-month follow-up, no complications have occurred. In particular, repeated interrogation of the ICD did not show episodes of ventricular arrhythmias. Echocardiography equally failed to demonstrate any abnormal (tumour-like) morphological changes. Antibodies against I6 cell line mismatches were first detected transiently at Day 15 against HLA B44 Ag with low reactivity (MFI = 758) and then against Cw04 Ag (MFI = 600) at Week 10. The overall sensitization was negative against HLA Class II antigens and showed a limited reactivity against non-donor-specific Class I antigens (anti-A43 antibody) on all sera. At baseline (3 weeks before the surgery), the patient presented a positive T-cell response against peptides derived from EBV and CMV. Globally, the anti-viral T-cell response did not decrease and remained stable except a slight and transient induction of a T-cell response against an HLA-A24 restricted EBV peptide after 1 month of immunosuppression. A T-cell response against the HLA-A2 restricted EBV and CMV peptides was also detected at 2 months (at the time immunosuppression was discontinued) and was still present at the 3-month time point.

At 3 months, the functional status was found markedly improved. The patient is now in NYHA Class 1 with a LVEF of 36% and a reduction of both LV end-diastolic and end-systolic volumes (from 161 to 134 mL and from 117 to 84 mL, respectively) without any strengthening of her drug regimen. The 6-min walking test shows an increase from 350 to 467 m. The echocardiographic analysis of segmental wall motion fails to show any remaining akinetic area and, more specifically, the akinetic infarct zone which has been cell patch-treated but not revascularized has now become moderately hypokinetic (see Supplementary material online, Video).

Discussion

This paper presents the first clinical application of human ESC-derived cardiac progenitor cells embedded into a fibrin scaffold in a patient suffering from severe ischaemic LV dysfunction. It demonstrates the technical feasibility of the whole procedure, from amplification of the pluripotent ESC to the surgical epicardial delivery of the patch-embedded ESC-derived differentiated progeny, as well as the absence of adverse events at a 3-month post-operative follow-up. This report differs from previously published stem cell clinical transplantation studies by two major novel features.

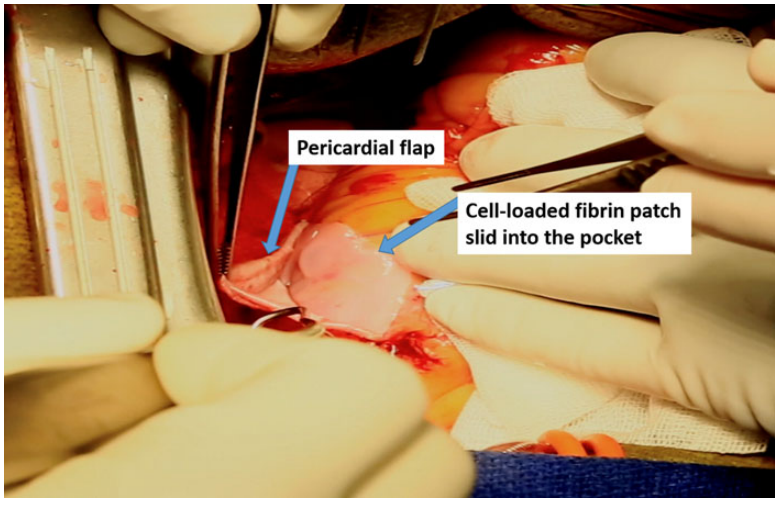

Figure 1 Intraoperative view of the progenitor cell-loaded fibrin patch that has been slid into the pocket between an autologous pericardial flap and the epicardial surface of the infarct area.

The first novelty is that the cells we have administered were of embryonic origin, whereas, so far, all cells used clinically have been collected in adult tissues, mostly in an autologous setting. Our choice of using ESC was initially based on the premise, now supported by head-to-head comparative studies, that, regardless of their mechanism of action, cardiac-committed cells are more effective than their non-cardiac counterparts for inducing structural heart repair, reducing malignant ventricular arrhythmias, producing cytoprotective cytokines, and improving LV function.[3–6] So far, the goal of producing such cardiac-committed cells has been achieved with three different cell types: right atrium-derived c-*kit*$^+$ stem cells, cardiosphere-derived cells harvested from the right ventricle, and bone marrow-derived MSC exposed to growth factors to engage them into a cardiopoietic differentiation pathway. These cell types have all yielded encouraging outcomes in Phase I trials[7–9] but also raise specific concerns. Indeed, fate-mapping studies have reported that c-*kit*$^+$ cells minimally contribute to generate cardiomyocytes;[16] furthermore, their low scalability potential resulted in that, in the SCIPIO trial,[7] a mean of 113 days were required to obtain 2 million cells. The cardiosphere-derived cells feature a predominant expression of the CD105 marker,[8] which points to their mesenchymal-type phenotype. The cocktail-primed MSC engaged into a guided cardiopoiesis express a broad array of cardiac transcription factors, but it is uncertain whether they can be assimilated to *bona fide* contracting cardiomyocytes. To better control and homogenize the ultimate cell phenotype, we have leveraged the intrinsic pluripotentiality of human ESC to commit them towards a mesodermal/cardiac lineage. This has allowed to yield a SSEA-1$^+$ cell population characterized by a predominant expression of *Isl-1*, which is one of the earliest transcription factors that labels a progenitor of the three main lineages (cardiomyocytes, endothelial cells, and smooth muscle cells) comprising heart tissue.[17] The growth kinetics of these cells are faster in that it only takes 2–3 weeks to generate several million of progenitors. Furthermore, although we chose to deliver cells at an early progenitor state, letting them grow under appropriate culture conditions unravels their ability to actively contract. Thus, put together, the characteristics of the cell population administered in our patient make it distinct from naïve or engineered adult stem cells tested so far. This specificity is supported by the finding that cardiac progenitor cells have a gene expression fingerprint distinct from that of bone marrow-derived progenitor (c-*kit*$^+$) cells or MSC.[18] Of note, human ESC-derived differentiated cells have already been used in patients with spinal cord injury[19] and ocular diseases,[20] but the present case represents the first clinical application of this approach in the heart.

The second novelty of the present report relates to the mode of cell transfer. So far, cells have been transferred into the heart either by a percutaneous intracoronary or endoventricular catheter or by transepicardial injections during a surgical procedure. However, the limitations of injection-based techniques, including cell damage, poor retention, and potential triggering of ventricular arrhythmias,[21] have led to consider an alternate approach, specific for intraoperative applications, and based on the epicardial delivery of a cell-loaded patch. Several studies have documented the superiority of this patch-based approach over intramyocardial injections with regard to cell retention, survival,[22] and, ultimately, preservation of heart function.[21] Our choice of encaging the *Isl-1*$^+$ cardiac progenitors into a fibrin scaffold was made after testing of several other materials and was primarily based on the biocompatibility of fibrin, its potential to behave as an effective cell carrier[23,24] and a long-standing safety record when used as a surgical sealant. Furthermore, the tunability of the mechanical properties of fibrin was exploited to adjust the fibrinogen to thrombin ratio in a way that provided a scaffold with a cell-friendly elasticity modulus (in the range of 6 kPa) without compromising its handling characteristics. In a rat model of myocardial infarction, this composite human *Isl-1*$^+$ progenitor cell + scaffold construct has been shown to improve post-infarction LV function while reducing adverse remodelling.[13] To further enhance the viability of the tissue-engineered construct, we covered it with an autologous pericardial flap, which harbours mesothelial cells and several trophic growth factors. In addition to help securing the underlying patch over the target area, the pericardial flap was intended to act as a natural bioreactor supplying trophic factors, a concept which has already been successfully tested with the use of the omentum[25] and the periosteum.[26]

The first objective of this study was to demonstrate the feasibility of producing clinical-grade ESC-derived cardiac progenitor cells. Multiple methods are available for inducing the cardiomyogenic differentiation of ESC. In a clinical perspective, we designed a relatively simple and straightforward process involving only two compounds. The main one, BMP-2, is involved in embryonic cardiogenesis and already registered for clinical use, which diminished the regulatory issues, particularly in terms of safety profile; to enhance the cardiomyogenic differentiation, we further added a FGFR inhibitor since FGF cooperates with the Nodal/Activin pathway to maintain pluripotency.[27] The resulting population was characterized by a strong expression of the cardiac transcription factor *Isl-1*, the up-regulation of which was used as one of the release criteria. Admittedly, *Isl-1* is also a marker of the neural lineage,[28] but in this case, one would expect its expression to be associated with that of *Sox-2*.[29] Such was not the case in our observation since *Sox-2* was markedly down-regulated compared with the starting undifferentiated I6 ESC taken as the reference.

Aside from feasibility, safety is the primary endpoint of the trial, particularly because ESC raises the concern of tumour development arising from still pluripotent 'contaminating' cells that could persist in the final differentiated cell population. Thus, while the lack of genetic aberrations, both in the starting material of pluripotent ESC and in the final progenitor cell product, was still a reassuring observation,[14] it remained critical to develop an efficient purification method. To this end, we identified a surface marker, SSEA-1, which labels cells engaged in a differentiation pathway[30] and used immunomagnetic sorting to eliminate cells that had failed to respond to the cardio-instructive cues and therefore lacked the SSEA-1 expression. In the present observation, the final SSEA-1$^+$ progenitor cell population attained a high purity rate (99%) and was also characterized by a marked down-regulation of the pluripotency markers *Nanog* and *Sox-2*, thereby achieving the pre-specified batch release criteria. Indeed, the ca. 40 000 'contaminating' SSEA-1-negative cell dose which was delivered to our patient (1% of the total 4 million cell load) is 10-fold lower than the dose that still failed to be tumourigenic in our preclinical immunodeficient mouse model.[14] Finally, the short duration of the immunosuppressive regimen, intended to temporally match the expected persistence of the cells,

along with its low dosing, was targeted at further mitigating the risk of tumourigenicity. Indeed, at the 3-month follow-up, echocardiography does not show any morphological abnormality suggestive of a cardiac mass development. However, although most literature data suggest a relatively early timing (i.e. 2–3 months) of tumour development following transplantation of undifferentiated pluripotent stem cells (a worst-case scenario compared with our protocol that entailed the use of an almost fully differentiated progeny), we acknowledge that a single case does not allow to definitely establish the safety profile of the procedure and that this will require a much longer follow-up. Additionally, there were no intra- or post-operative procedure-related adverse events. Repeat interrogations of the ICD have also not detected ventricular arrhythmias. The transient alloimmunization to the administered cells which was detected was clinically silent but will be followed-up.

Even though the patient is symptomatically improved with a 10% increase of EF at the 3-month study point, no meaningful conclusion can obviously be drawn from a single case, further confounded by the concomitant performance of a surgical coronary artery bypass which was, nevertheless, ethically mandatory. At most, the new-onset contractility of the patch-treated area, which was not revascularized since the mammary artery graft was placed in an anatomically distinct area (the anterior LV wall), provides an encouraging signal. As mentioned above, there is increasingly compelling evidence that the mechanism underpinning this functional improvement involves the cell-induced paracrine stimulation of endogenous repair pathways (possibly including mobilization of resident cardiac stem cells and/or new-onset multiplication of adult cardiomyocytes) rather than a *de novo* generation of graft-derived myocardial tissue.[1] While the use of a composite construct does not allow either to distinguish between the effects of the fibrin scaffold itself from those of the progenitors embedded into it, previous data from our laboratory strongly suggest that the fibrin patch alone has only a modest cardioprotective effect and that cellularization of the scaffold is required to enhance it.[13] We acknowledge that a further mechanistic insight could be provided by the study of both epicardial and endocardial ventricular activation patterns using a non-invasive technology through a multiple-lead electrocardiogram-based three-dimensional imaging,[31] although, in the particular setting of our protocol, the feasibility of such an assessment is uncertain since the signal/voltage could be attenuated by both the necrotic myocardium (endocardial side) and the fibrin shield around the progenitor cells (epicardial side).

Of note, 10 patients were screened for their potential eligibility in this trial before the one reported in this paper was included. Causes for non-inclusion were patient refusal ($n = 2$), fortuitous detection of a cancer ($n = 2$), coronary artery lesions not critical enough to warrant revascularization ($n = 2$), too recent myocardial infarction ($n = 1$), and incomplete akinesia of the infarct area ($n = 1$). One included patient was not treated, because one of the release criteria for the final patch was not satisfactorily met. Finally, one patient was included early on as a compassionate indication. This 77-year-old man had end-stage heart failure with an EF of 20% and multiple co-morbidities including morbid obesity (body mass index: 31.5), chronic atrial fibrillation, respiratory insufficiency, diabetes, and peripheral vascular disease. The intraoperative delivery of a fibrin scaffold harbouring a 96% pure *Isl-1*$^+$ cell population was uneventful. Post-operatively, the patient could be extubated, but he died 10 days later from a cardio-respiratory failure. The pathological examination confirmed a major cardiomegaly (the heart weighted 700 g) and an extensive coronary atherosclerosis. While the absence of cell labelling prior to their implantation precluded any conclusion pertaining to their potential engraftment, it was yet important, from a safety perspective, to note that there was no unusual histological pattern in the cell implantation area, in particular no significant inflammation, thereby supporting, at least in the short term, the lack of patch-related specific adverse events. This prompted both the independent Data Safety Monitoring Board and the Regulatory Agency to give clearance for the continuation of the trial.

We acknowledge that the process used in this study needs to be improved in multiple ways, which might include the elimination of feeder cells, the tighter control of scaffold elasticity, and microtopography to further enhance the cardiac specification rate and the use of a negative type of selection targeting markers of pluripotency to avoid magnetic microbeads to remain transiently tethered to the cells.

Nevertheless, the present report yet demonstrates the feasibility of transferring ESC-derived clinical-grade progenitor cells embedded in a fibrin patch to the myocardial diseased area and its short-term good tolerance. However, only a greater number of patients with a more extensive follow-up will allow to further document the safety of this cell population. If this endpoint is met, efficacy trials could then be considered to assess whether this ESC-based strategy is warranted in selected patients with a history of myocardial infarction, a drug-refractory symptomatic heart failure, and a requirement for coronary artery bypass, although the hoped accumulation of safety data might then lead to deliver the cell-loaded patch as a stand-alone procedure taking advantage of minimally invasive techniques to access the heart. In any case, the current data may hopefully serve as a platform aimed at being fueled by multi-faceted improvements to move the field forward.

Note added in proof

Since submission of this paper, the patient has completed her 6-month follow-up visit. She is still in NYHA Class 1; likewise, the improved kinetics of the non-bypassed cell-patched area seen at 3 months have remained stable; a 18Fluorodeoxyglucose Positron Emission Tomography performed, per protocol, is normal and comparable to the pre-operative one. A second patient has also been operated on successfully and will soon complete his 3-month follow-up visit.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

P.M. performed the surgery, co-ordinated the whole project, participated in the study design, data review and interpretation, and wrote the initial and final drafts of the report; V.V. co-ordinated the translational steps of the project and directly participated in the preparation of the cell product used in the patient, along with I.C. and A.P.; A.H. and M.D. participated in the study design, data review, and interpretation and supervised the pre- and post-operative

management of the patient; A.B. performed most of the preclinical animal studies and was involved in the surgery of the patient; B.C. was responsible for the anaesthesia and post-operative intensive care of the patient; G.T. and L.T. performed all the cytogenetic studies of the pluripotent cells and the derived cardiac progenitors; J.H.T. and J.R.F. supervised the regulatory framework of the trial; V.B. co-ordinated the preclinical steps of the project; R.G., C.S., N.B., and E.T. designed the immunosuppression regimen and performed its medical and biological monitoring; J.L. co-ordinated the translational steps of the project and supervised the preparation of the cell product used in the patient. In addition, all co-authors participated in data review and interpretation and writing of the paper. P.M. is a member of the SHAPEHEART LeDucq network.

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Conflict of interest: V.V., I.C., A.P., and J.L. have received a grant from Association Française contre les Myopathies. B.C.'s department has received funds from Carmat, a company involved in the development of a totally implantable artificial heart. P.M. and J.L. are co-owners of a patent entitled 'Method for generating primate cardiac progenitor cells for clinical use from primate embryonic stem cells or embryonic-like stem cells, and their applications' (PCT/EP 2009052797). This method is based on the seminal studies of Michel Pucéat (INSERM UMR S910, Marseille, France), co-owner of the patent.

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