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Review Article

Cardiac Progenitor Cell Transplantation and Functional Recovery in Ischaemic Models

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Abstract

Background: Cardiac regenerative medicine was built on the claim that resident c-kit-positive progenitors generate new cardiomyocytes and restore contractile function in ischaemic myocardium. That claim has since been tested genetically.

Objective: To reconstruct the evidence on progenitor transplantation, distinguish retracted from superseded work, and assess whether pluripotent-stem-cell-derived cardiomyocytes offer a route to genuine remuscularisation.

Methods: Narrative review of lineage-tracing experiments, preclinical models, randomised trials and retraction records.

Findings: Lineage tracing set the cardiomyogenic contribution of c-kit-positive cells at 0.002-0.04% of cardiomyocytes. Individual-patient meta-analysis of 12 randomised trials (n = 1252) gave an ejection fraction difference of 0.96% (95% CI -0.2 to 2.1), and 0.0 in discrepancy-free trials. Three cited papers have been retracted.

Conclusions: The evidence supports paracrine and immune mechanisms rather than new muscle from adult progenitors. Pluripotent-derived cardiomyocytes remuscularise but carry engraftment arrhythmia.

Keywords: Cardiac progenitor cells; Myocardial infarction; Lineage tracing; Cardiomyocyte regeneration; Engraftment arrhythmia

Introduction

Two decades of cardiac regenerative medicine were organised around a single proposition: that the adult mammalian heart harbours a resident progenitor population capable of generating cardiomyocytes, and that delivering such cells into ischaemic myocardium replaces lost muscle and restores contractile function. The proposition was attractive, testable and, as it turned out, wrong in its central mechanistic claim. Genetic lineage tracing set the cardiomyogenic contribution of c-kit⁺ cells at 0.002-0.04% of cardiomyocytes in mice, three orders of magnitude below what remuscularisation would require. Where functional benefit has been observed in animals, it is better explained by paracrine signalling and an acute innate immune response than by new muscle. In humans, the measured effect on ejection fraction contracts toward zero as trial reporting improves, and vanishes entirely in trials with no internal discrepancies.

This review reconstructs that trajectory from primary sources whose status was individually verified, and separates three categories that the secondary commentary on this field routinely merges: work that has been retracted, work that has been superseded, and work that remains contested but stands. It then sets out the case that pluripotent-stem-cell-derived cardiomyocytes, which do demonstrably form new myocardium in large animals, are the live route forward, and that engraftment arrhythmia is the problem standing between them and the clinic.

The founding claims and their first contradiction

The field opened with the report that bone marrow c-kit⁺ cells transplanted into infarcted mouse myocardium regenerated contractile tissue [1], followed by the identification of a resident adult cardiac cell population described as self-renewing, clonogenic and multipotent [2], and by evidence of extensive host-derived chimerism in sex-mismatched human cardiac allografts [3]. Together these established both a cell of interest and a mechanism:

progenitor engraftment, differentiation, and replacement of dead muscle.

The transdifferentiation limb of that mechanism was contradicted within three years. Two independent groups, using genetically labelled haematopoietic stem cells in infarcted mouse hearts, found that the transplanted cells adopted mature haematopoietic fates and did not become cardiac myocytes [4,5]. The resident-progenitor limb persisted longer, sustained by reports that adult c-kit-positive cardiac cells were both necessary and sufficient for functional regeneration and repair [6]. The chimerism figures in human allografts were never independently reproduced at anything approaching the reported magnitude, and should be treated as disputed.

Two features of this period deserve emphasis, because they shaped what followed. First, the cell-surface markers used to define the putative progenitor pool were never validated against a functional cardiomyogenic assay; they were adopted from haematopoiesis and assumed to carry the same meaning in myocardium. Second, functional endpoints in the animal literature were almost always echocardiographic and almost never blinded to allocation, so an effect on ejection fraction was accepted as evidence of new muscle without histological confirmation that new muscle existed. Both assumptions were tested directly only once genetic fate mapping became routine.

None of these four papers has been retracted. Crossref update relations and OpenAlex retraction flags carry no retraction or expression of concern for any of them. They are superseded or contested on the evidence, which is a different status and demands different language.

The retraction and expression-of-concern record

Three papers cited in this review have been withdrawn from the literature, and the record should be stated once, plainly. The SCIPIO phase 1 trial of autologous c-kit⁺ cardiac cells in ischaemic cardiomyopathy [7] received an

expression of concern on 12 April 2014 and was retracted on 14 March 2019. The report that human cardiac stem cell differentiation is governed by a mircrine mechanism [8] was corrected on 1 December 2015 and retracted on 12 December 2018. The report attributing developmental cardiomyogenesis to c-kit-positive cardiac stem cells [9] received an expression of concern on 20 November 2018 and was retracted on 12 December 2018.

Table 1: Verified status of the foundational cardiac progenitor reports cited here, separating retraction from correction, supersession and contestation [7,8,9,2,1,6,10].			
Paper	Claim made	Status	Notice date
Bolli 2011 (SCIPIO)	c-kit+ cells improve LVEF in ischaemic cardiomyopathy	Expression of concern, then retracted	12 Apr 2014; 14 Mar 2019
Hosoda 2011	Human cardiac stem cell differentiation is mircrine	Corrected, then retracted	1 Dec 2015; 12 Dec 2018
Ferreira-Martins 2012	Developmental cardiomyogenesis driven by c-kit+ cells	Expression of concern, then retracted	20 Nov 2018; 12 Dec 2018
Beltrami 2003	Adult c-kit+ cardiac cells are multipotent	Not retracted, no EoC; superseded	Checked 4 Sep 2026
Orlic 2001	Bone marrow c-kit+ cells regenerate myocardium	Not retracted, no EoC; contradicted	Checked 4 Sep 2026
Ellison 2013	c-kit+ cells necessary and sufficient for repair	Not retracted, no EoC; contested	Checked 4 Sep 2026

No quantitative claim anywhere in this review derives from those three papers, and none of their reported effect sizes should be pooled with the trial data discussed below. They are named because a review that discusses what the field believed must identify which of its evidence has been withdrawn.

Two further distinctions matter. The macaque remuscularisation study of Liu and colleagues [10] carries a correction dated 1 October 2018 whose entire content is the omission of a funding acknowledgement; no data were altered, and it is not a retracted paper. And the three foundational reports discussed above [1,2,6] are

frequently assumed to have been withdrawn along with the rest of the surrounding literature. They have not been. Getting this wrong in either direction misrepresents the record.

Lineage tracing and the ceiling on cardiomyogenesis

The decisive experiments were genetic, not therapeutic. Kit-Cre and Kit-MerCreMer knock-in lineage tracing in mice, with group sizes of two to six animals per condition, found that approximately 0.03% or fewer of cardiomyocytes derived from endogenous c-kit+ cells, falling below approximately 0.008% once cell fusion events were excluded; the same labelled population amply generated cardiac endothelial cells [11]. An independent laboratory using three separate c-kit reporter alleles reproduced the ceiling: fewer than 0.04% of cardiomyocytes were lineage-labelled between E13.5 and P37, fewer than 0.007% after P90, and after myocardial infarction fewer than 20 cTnT-positive labelled cells were recovered per heart, approximately 0.002% of total myocardial cells [12]. Flow cytometry in the same study showed that roughly 43% of PECAM-positive endothelial cells in the mouse ventricle were c-kit-positive, which explains what the marker had been tracking all along.

The result generalises beyond c-kit. Lineage tracing of Sca-1+ cells in mice likewise revealed an endothelial but not a myogenic contribution to the heart [13]. Independently, isotope-based approaches established that new cardiomyocytes in the adult mammalian heart arise by division of pre-existing cardiomyocytes rather than from a progenitor pool, and that this process increases in the border zone after infarction [14,15]. Carbon-14 birth dating in humans put the scale of that renewal at approximately 1% of cardiomyocytes annually at age 25, declining to 0.45% at age 75, with fewer than half of all cardiomyocytes exchanged over a normal lifespan [16,17]. A consensus statement subsequently formalised

the position that endogenous cardiomyocyte regeneration in adult mammals is real but marginal [18].

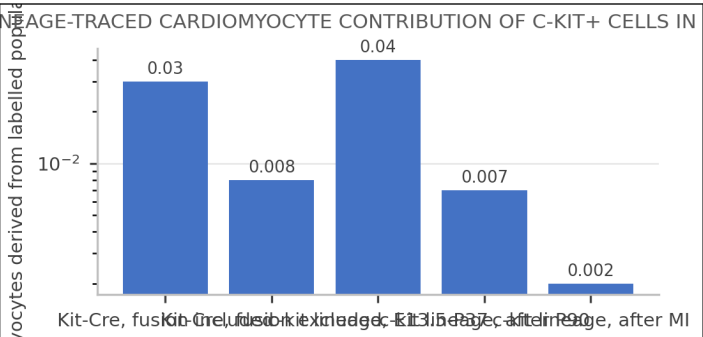


Figure 1: Genetic lineage tracing places the cardiomyocyte contribution of c-kit+ cells between 0.002% and 0.04% in mouse, with Kit-Cre and Kit-MerCreMer cohorts of n = 2-6 mice per condition and three independent c-kit reporter alleles; no bar derives from a retracted source, and the historical claim these results replaced cannot be plotted because its sources are retracted [11,12].

Paracrine signalling and the acute immune response

If transplanted cells do not become muscle, the functional improvements reported in animal models require another explanation. The most direct evidence came from a mouse ischaemia-reperfusion study, with group sizes from two to twelve depending on the experiment, in which injection of freeze-thaw-killed cells reproduced the functional benefit of live cardiac progenitor cells or bone marrow mononuclear cells, and in which zymosan, a purely chemical activator of innate immunity, produced a comparable regional accumulation of CCR2+ and CX3CR1+ macrophages and a comparable functional benefit; the macrophage response altered border-zone fibroblast behaviour and extracellular matrix content [19]. Benefit that a dead cell and a fungal cell-wall extract can both deliver is not evidence of regeneration.

Table 2: Confirmed cardiomyocyte contribution of marker-defined populations by lineage-tracing model, all from non-retracted primary sources in mouse [11,12,13,14].		
Model	Marker	Cardiomyocyte contribution
Kit-Cre / Kit-MerCreMer knock-in	c-kit	0.03% or less
Kit-Cre, cell fusion excluded	c-kit	Below 0.008%

Model	Marker	Cardiomyocyte contribution
c-kit reporter alleles, E13.5-P37	c-kit	Under 0.04%
c-kit reporter alleles, after P90	c-kit	Under 0.007%
c-kit MerCreMer, after infarction	c-kit	About 0.002%
Sca-1 lineage tracing	Sca-1	Endothelial, not myogenic

This is consistent with what was already known about retention. A study from the laboratory that ran SCPIO reported, in its title, that c-kit+ cardiac stem cells alleviate post-infarction left ventricular dysfunction in rats despite poor engraftment and negligible retention in the recipient heart [20]. Mechanistic reframings of cardiac cell therapy around paracrine and immunomodulatory action followed [21]. The reframing is not a rescue of the original hypothesis. A therapy that works by transiently activating macrophages in the infarct border zone is a different therapy, with different dose-response behaviour, different optimal timing and different comparators, and it should be tested against pharmacological immunomodulation rather than against placebo alone.

The historical preclinical estimate should be read against this background. A systematic review of 80 preclinical studies found a pooled ejection fraction improvement of 10.7% with cardiac stem cell therapy versus control, P<0.001, significantly larger in small animals than in large ones, P<0.001, with minor publication bias detected [22]. That study set was assembled before the 2018-2019 retractions and includes work since withdrawn. It is the number the field was working from, not a currently valid effect size.

The clinical record and the quality gradient

Human data track the mechanistic collapse. An individual-patient-data meta-analysis of 12 randomised trials, n = 1252 patients, found a weighted mean difference in ejection fraction of 0.96% (95% CI -0.2 to 2.1) against control, with major adverse cardiac and cerebrovascular

events at 14.0% versus 16.3%, hazard ratio 0.86 (95% CI 0.63 to 1.18), death 1.4% versus 2.1%, and death, reinfarction or stroke 2.9% versus 4.7% [23]. None of these differences reached significance.

The sharpest evidence is not the pooled estimate but its dependence on data quality. A weighted regression across 49 randomised trials reported in 133 documents identified more than 600 internal discrepancies, and the number of discrepancies in a trial's reports correlated with the ejection fraction increment it reported, Spearman $r = 0.4$, $P = 0.005$ [24]. The gradient is monotonic: trials with no discrepancies reported a mean effect of -0.4%, those with 1-10 discrepancies 2.1%, 11-20 discrepancies 3.0%, 21-30 discrepancies 5.7%, and more than 30 discrepancies 7.7%. In formal meta-analysis of the 31 trials with sufficient data, discrepancy-free trials gave a weighted mean effect of 0.0 (95% CI -4.67 to 4.65), and trials with more than 30 discrepancies gave 10.4 (95% CI 8.44 to 12.36). The reported benefit of autologous cell therapy is a function of how the trial was reported.

Blinded contemporary trials are consistent with the null. CADUCEUS randomised 31 patients, 25 analysed per protocol (17 cardiosphere-derived cells versus 8 standard care), and at six months scar mass fell, $P = 0.001$, and viable heart mass rose, $P = 0.01$, while end-diastolic volume, end-systolic volume and ejection fraction did not differ between groups [25]. ALLSTAR randomised 142 patients, 134 treated (90 versus 44), and found no difference in percentage change from baseline in scar size at six months, $P = 0.51$, with no primary safety endpoint events [26]. CONCERT-HF enrolled 125 participants at seven centres with baseline ejection fraction $28.6 \pm 6.1\%$ and scar size $19.4 \pm 5.8\%$; major adverse cardiac events fell by 22% versus placebo with cardiac progenitor cells alone, $P = 0.043$, and quality-of-life scores improved with mesenchymal stromal cells alone, $P = 0.050$, and in combination, $P = 0.023$, while ejection fraction, ventricular

volumes, scar size, six-minute walk distance and peak oxygen consumption did not differ among groups [27].

Remuscularisation with pluripotent stem cell derivatives

The one approach that demonstrably makes new myocardium starts from pluripotent cells. Human embryonic-stem-cell-derived cardiomyocytes remuscularised infarcted non-human primate hearts [28], and allogeneic iPSC-derived cardiomyocytes did the same in a major-histocompatibility-matched primate model [29]. In macaques receiving approximately 750 million cryopreserved hESC-derived cardiomyocytes, grafts averaged 11.6% of infarct size and were approximately 99% ventricular myocytes by three months; ejection fraction improved by $10.6 \pm 0.9\%$ in treated animals versus $2.5 \pm 0.8\%$ in controls at one month, and by a further 12.4% against a 3.5% decline in controls at three months [10]. In swine, engineered human cardiac muscle patches of iPSC-derived cardiomyocytes, smooth muscle cells and endothelial cells achieved an engraftment rate of $10.9 \pm 1.8\%$ at four weeks by quantitative PCR for human Y-chromosome sequences, across groups of 13 patched, 14 cell-free patch, 15 no patch and 8 sham animals [30]. A first-in-human study of embryonic-stem-cell-derived cardiovascular progenitors delivered in a fibrin patch established feasibility in severe ischaemic left ventricular dysfunction [31].

The unsolved problem is electrical. Human ESC-derived cardiomyocytes regenerated the infarcted pig heart but induced ventricular tachyarrhythmias [32], and a subset of treated macaques developed graft-associated arrhythmias arising from a point source behaving as an ectopic pacemaker [10]. In a systematic porcine study, every cell-treated animal developed engraftment arrhythmia within a week: untreated recipients showed 8.7 ± 2.8 hours of arrhythmia per day on 23.4 ± 0.6 of 28 observation days with a peak rate of 230.4 ± 18.7 b.p.m., whereas

antiarrhythmic drug treatment reduced this to 0.99 ± 0.34 hours per day, $P < 0.05$, on 11.2 ± 1.8 days, $P < 0.0005$, with a peak rate of 140.2 ± 8.0 b.p.m., $P < 0.005$, in groups of five and five [33]. Graft cellular heterogeneity was mechanistically linked to the arrhythmia, which makes it a manufacturing problem as much as a pharmacological one. The distinction from the progenitor literature is worth stating precisely: here the grafts are unambiguously present, unambiguously human, unambiguously cardiomyocyte, and the adverse effect is a direct consequence of their electrical activity. The failure mode is one of integration, not of existence, and it is amenable to cell-composition control, maturation protocols and adjunctive rhythm management.

Conclusion

The c-kit+ cardiomyocyte-generation hypothesis did not survive lineage tracing, and no reinterpretation of a 0.002-0.04% contribution recovers it. Functional benefit in animal models is reproduced by killed cells and by zymosan, which locates the mechanism in the acute immune response and in paracrine signalling rather than in new muscle. In patients, the pooled effect on ejection fraction is 0.96% (95% CI -0.2 to 2.1) across 1252 individuals, and 0.0 (95% CI -4.67 to 4.65) in trials whose reports contain no discrepancies. Three of the papers that built the field have been retracted; three others that are widely assumed to have been retracted have not been, and are better described as superseded or contested. Pluripotent-stem-cell-derived cardiomyocytes produce grafts averaging 11.6% of infarct size in macaques and measurable functional gain, and they carry an engraftment arrhythmia that appears in every treated large animal. That is where the remaining work is.

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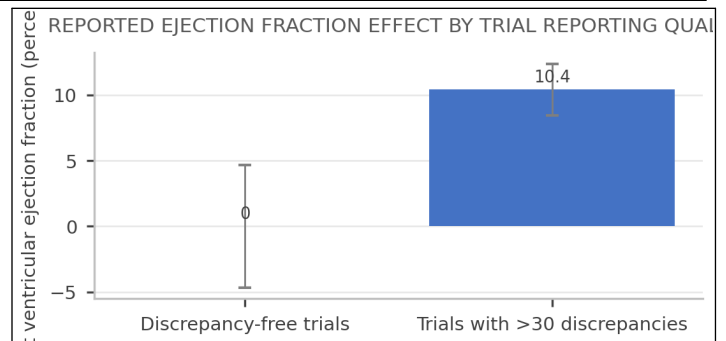


Figure 2: Weighted mean effect on left ventricular ejection fraction with 95% confidence intervals in the 31 autologous bone marrow trials with sufficient data for meta-analysis, drawn from 49 randomised trials and 133 reports in human patients: 0.0 (-4.67 to 4.65) where reports contain no internal discrepancies, against 10.4 (8.44 to 12.36) where they contain more than 30 [24].

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