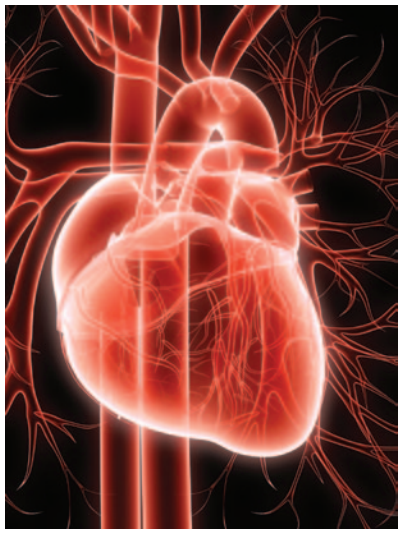
Cardiac stem cell therapies inch toward clinical litmus test

Upcoming phase 3 studies of adult/mesenchymal stem cell therapies in cardiac disease could provide definitive answers to the vexed question of whether these treatments can offer patients meaningful clinical benefits. Cardio3 BioSciences, of Mont-Saint-Guibert, Belgium, and Mesoblast, of Melbourne, Australia, are starting phase 3 trials of bone marrow–derived mesenchymal cell therapies in congestive heart failure, and the European Commission (EC) is funding an investigator-initiated trial of bone marrow–derived mesenchymal cell therapy in 3,000 patients who have experienced heart attack or acute myocardial infarction (AMI). Baxter, of Deerfield, Illinois, is already performing a phase 3 trial of $CD34^+$ endothelial progenitor cell therapy in chronic myocardial ischemia (refractory angina). Other firms are working on earlier-stage programs (**Table 1**). It will take several more years before these studies will deliver the data necessary to build a clear picture of the true potential of cell therapy in cardiac disease. But a field that has generated quite a lot of hype—and much confusion besides—looks finally poised to understand whether such therapies truly show potency in the clinic.



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Stem cell therapies for cardiac repair have yet to attract support from big pharma.

The challenges of developing cell therapies are manifold. The technology remains immature, and scientists' understanding of the underlying biology remains incomplete. "Overall it's still in an experimental state, absolutely no question about it," says Andreas Zeiher, professor of medicine at the Goethe University in Frankfurt, Germany, who is leading a long-term study evaluating 1,500 patients who have undergone bone marrow–derived cell therapy for cardiac disease at his institution during the past decade. "In cardiovascular disease you need treatments with hard endpoints," he says.

The first trials of stem cell therapies in cardiac disease were performed around a decade ago (*Circulation* **106**, 1913–1918, 2002). Progress since then has been mixed. Claims made on behalf of specific therapies have been quite 'bullish'. "The magnitude of change in symptoms here is what we accept in an angioplasty or stenting procedure and is approaching what we would expect from a successful bypass operation," says Douglas Losordo, Baxter's vice president of new therapeutic development, of the company's $CD34^+$ stem cell treatment.

The overall evidence base remains thin, however, as the trials that have been completed have had limited statistical power, due to their small size. Most have employed surrogate endpoints, which measure cardiac function, rather than the sterner test of mortality, which requires larger patient numbers. Nevertheless, the authors of a recent Cochrane review of bone marrow–derived cell therapy in AMI, which examined 33 trials that recruited 1,765 participants, concluded "that moderate improvement in global heart function is significant and sustained long-term" (*Cochrane Database Syst. Rev.* **2**, CD006536, 2012). The clinical significance of these improvements remains unclear, however, because of the very low mortality rates seen after revascularization therapy (which includes coronary arterial bypass surgery, and balloon angioplasty and stenting procedures) and because of the high degree of heterogeneity between different cell therapy treatments and different studies.

The criteria needed to ensure that a cell therapy is a consistent, pharmaceutical-grade medical product include the identity and dose of the different cells, their purity and their potency. With autologous approaches, patient-to-patient variability can arise, but this variation must be controlled for. "In our case, we have pretty strict quality criteria in terms of the definition of the product that is going out," says Ronnda Bartel, CSO at Aastrom Biosciences, of Ann Arbor, Michigan.

Every step in the production process is critical, beginning with harvesting source material, such as bone marrow, correctly. "That is the key to getting a consistent product at the other end," says Bartel. "If you don't do it right, really all you're doing is pulling peripheral blood." Obtaining a sufficient quantity of cells is also a challenge. Amorcyte, of Allendale, New Jersey, harvests 350 cubic centimeters of bone marrow fluid to ensure that it can generate a minimum threshold dose. Cardio3 Biosciences' current process is unable to obtain a sufficiently high yield from 15% of its patients, CEO Christian Homsy says, although efforts to improve its efficiency and lower its costs are ongoing.

Delivery of the end product is not a straightforward task either, as the beating heart is, literally, a moving target, and the majority of the transplanted cells are washed out through the coronary veins. Cardio3 Biosciences has invented a novel catheter to optimize the uptake and retention of the cells it delivers to the heart. "Our retention rate is north of 30%. It's about three times better than any catheter that we're aware of today," says Homsy. Several firms are using sophisticated cardiac navigation systems to pinpoint areas that border the infarct zone. These are the optimal sites for targeted delivery of cells, as the tissue remains alive, but is unable to function properly because of its proximity to the infarcted tissue.

In AMI, the overarching aim of stem cell therapy is to reduce the scar tissue that forms immediately after revascularization and thereby improve patients' long-term prospects. "In the acute situation, you want to get patients above a certain level of heart function," says Zeiher, who is also a clinical investigator on the EC-funded BAMI study (**Table 1**). Treating chronic or congestive heart failure is a more complex undertaking. "There we want to build new contracting heart muscle cells," he says.

Claims that cells obtained from bone marrow can differentiate into functioning cardiomyocytes (*Nature* **410**, 701–705, 2001; *Proc. Natl. Acad. USA* **104**, 17783–17788, 2007) have remained controversial. Many clinical researchers now believe that engraftment of the transplanted cells, if it occurs at all, is transient and that paracrine effects on resident stem cells or progenitor cells are more important. "I think it's clear allogeneic cells are cleared from the body fairly quickly," says Andrew Pecora, chief medical officer at Amorcyte. However, Cardio3 Biosciences maintains that its autologous therapy, C3BS-CQR-1, contains cells that mediate paracrine effects on existing stem cells as well as others that differentiate into functioning cardiac cells or vascular tissue. "We've been able to demonstrate the cells remain in place up to one year after the injection," says Homsy. The company employs a 'cardiopoietic cocktail' of growth factors, which stimulate mesenchymal stem cells to differentiate to cardiac progenitor cells (*J. Am. Coll. Cardiol.* **56**, 721–734, 2010). The technology is based on

Table 1 Selected companies with adult stem cell therapies in efficacy trials

Company	Therapy	Description	Dose	Delivery	Indication	Status
Baxter	CD34+ stem cells	Autologous bone marrow–derived CD34+ endothelial progenitor cells	1×10^6 cells per kg body weight	Endocardial catheter injection using Noga cardiac navigation system	Chronic myocardial ischemia	Phase 3
Cardio3 BioSciences	C3BS-CQR-1	Autologous bone marrow–derived stem cells reprogrammed to become cardiopoietic cells	600×10^6 cells	C-Cath proprietary catheter	Advanced chronic heart failure	Phase 3
Mesoblast, Teva	Revascor	Allogeneic bone marrow–derived mesenchymal precursor cells	150×10^6 cells	Coronary artery infusion by standard catheter immediately after angioplasty & stenting	Congestive heart failure	Phase 3
Barts and The London National Health Service Trust (BAMI study; investigator initiated)	BM-MNC	Autologous bone marrow–derived mononuclear cells	100ml bone marrow	Intracoronary infusion via over-the-wire balloon catheter	Acute myocardial infarction	Phase 3
t2cure (Frankfurt, Germany)	Bone marrow cell therapy	Autologous bone marrow–derived mononuclear cells	$>100 \times 10^6$	Intracoronary infusion	Acute myocardial infarction	Phase 3
					Heart failure	Phase 2/3
Aastrom Biosciences	Ixmyelocel-T	Autologous bone marrow–derived cells, including CD90+ mesenchymal cells, CD14+ monocytes	$100–150 \times 10^6$ cells	Endocardial catheter injection using Noga cardiac navigation system	Dilated cardiomyopathy	Phase 2
Bioheart (Sunrise, Florida)	Myocell	Autologous myoblasts or muscle stem cells	N.A.	N.A.	Congestive heart failure	Phase 2
Cytori Therapeutics (San Diego)	ADRC	Autologous adipose tissue–derived stem and regenerative cells	4×10^6 cells per kg body weight	Intramyocardial injection via Myostar injection catheter	Chronic myocardial ischemia	Phase 2
Amorcyte	AMR-001	Autologous bone marrow–derived stem cell population enriched for CD34+CXCR4+ cells	10×10^6 cells	Angioplasty balloon and catheterization	Acute myocardial infarction	Phase 2
Osiris Therapeutics (Columbia, Maryland)	Prochymal (remestemcel-L)[a]	Allogeneic bone marrow–derived mesenchymal stem cells	N.A.	Single intravenous infusion	Acute myocardial infarction	Phase 2
Capricor	CAP-1002	Allogeneic cardiosphere-derived cells	25×10^6 cells	Catheterization	Acute myocardial infarction	Phase 2

N.A., not available. [a]Approved in Canada and New Zealand for treating graft-versus-host disease.

fundamental research on the differentiation of embryonic stem cells into cardiac cells conducted at the Mayo Clinic, in Rochester, Minnesota.

The majority of therapies that are currently in the clinic involve bone marrow–derived cells. The composition of the various therapies varies considerably, as do the *ex vivo* amplification and processing steps that they undergo. Amorcyte selects for cells that co-express the CD34 and the CXCR4 receptors. Its rationale is that the CD34+ hematopoietic stem cells it obtains will be capable of migrating to sites of injury, as the CXCR4 receptor binds stromal cell–derived factor-1, which is released in response to hypoxia. Aastrom deploys what Bartel calls its "secret sauce" on a mixed population of bone marrow–derived cells, which includes mesenchymal stem cells, anti-inflammatory macrophages, monocytes, granulocytes, and B and T lymphocytes. "We're going for the shotgun instead of the sniper rifle," she says. The different components of the cell therapy are thought to exert multiple effects, which, collectively, reduce localized inflammation, clear up scar tissue and cellular debris, and allow tissue remodeling to take place.

A newer generation of therapies, based on cells derived directly from heart tissue, has also reached the clinic and has offered early indications of efficacy. The recent Scipio (*Lancet* **378**, 1847–1857, 2011) and Caduceus (*Lancet* **379**, 895–904, 2012) trials studied the effects of administering cardiac stem cells and cardiosphere-derived cells, respectively. The term cardiosphere refers to multicellular clusters of cells that develop after cardiac biopsy specimens are grown in primary culture. The mixed population includes cardiac stem cells, endothelial progenitors and trace amounts of cardiac fibroblasts, but it is not fully characterized as yet. "It's fully characterized to the satisfaction of the FDA for phase 2," says Rachel Ruckdeschel Smith, vice president of R&D at Los Angeles–based Capricor. The Caduceus trial was based on autologous therapy, but its upcoming phase 2 trial will involve a switch to an allogeneic preparation. "The principle reason was the ability to control manufacturing," says Capricor CEO and co-founder Linda Marbán. The allogeneic preparation will eliminate concerns about obtaining sufficient yield from patients, while also improving the flexibility of the resulting therapy. "It expands the indication window enormously," she says.

For now, the field remains a work in progress. Apart from the notable exception of Mesoblast, which entered a potential $2-billion deal with Cephalon (now part of Teva, of Petah Tikva, Israel) in 2010, stem cell therapies for cardiac indications have yet to attract major backing from the pharmaceutical industry or large biotech companies. Solid data based on clinically meaningful endpoints could change the picture very quickly, but successful adoption of cell therapy will require a lot more clinical evidence than has been generated to date. "The effect is going to have to be pretty substantial to justify the cost," says Amorcyte's Pecora.

Cormac Sheridan, ***Dublin***

IN their words

"The agency has painted itself into a statistical corner." Scott Hopkins CMO of Rib-X of New Haven, Connecticut, speaking of the difficulty of getting new antibiotics approved by the FDA. (*Scientific American*, 4 December 2012)