Published in final edited form as:

Am Heart Hosp J. 2011 ; 9(1): E24–E27.

Cell Therapy—A 21st Century Hope for Treating Cardiovascular Disease—A Five-year Retrospective and Predictive View

Doris A Taylor, PhD, FAHA [Director]

Center for Cardiovascular Repair, University of Minnesota

Predicting the future of any innovative treatment is always risky and yet most of the predictions that were made in 2006 with regards to cell therapy have come to fruition. Let us look at where we were and where we are now. In 2006, we had moved from the idea of cell therapy through a number of preclinical models into early clinical applications, using a number of cell types, yet we were iterating between clinical application and unanswered basic questions. There were a huge number of unmet clinical needs and straightforward questions that had not been answered. Some of the general questions at the time were:

- ‘what cell should we choose for what patient?’;
- ‘what is the proper route of administration?’; and
- ‘how should we determine if cell therapy was efficacious (what endpoints should we use)?’

The more specialized questions were:

- ‘how can we improve cell delivery, retention, and tracking?’;
- ‘are any cells unsafe?’;
- ‘what is the mechanism of cell action?’;
- ‘are there better cells?’; and
- ‘do we need cells at all?’

In 2006, I predicted we would see surgical and percutaneous phase I studies with bone marrow, blood, and adipose-derived cells completed, and that we would likely see initiation of at least one trial with cardiac-derived cells. I also predicted that cell types would segregate with disease state, and that this would likely include the use of bone marrow-derived cells in the acute and subacute setting of myocardial infarction, and myoblasts or bone marrow or fat-derived mesenchymal cells in patients with heart failure (HF). How did I do?

Correspondence: Doris A Taylor, PhD, FAHA, Department of Integrative Biology and Physiology and of Medicine, Center for Cardiovascular Repair, 312 Church Street SE, 7-105A NHH, Minneapolis, MN 55455. ccvr@umn.edu.

Disclosure

Dr Taylor holds a financial interest in Miromatrix, Inc. and is entitled to sales royalty through the University of Minnesota for products related to the research described in this paper. This relationship has been reviewed and managed by the University in accordance with its conflict of interest policies. Dr Taylor also owns stock in Bioheart Inc.

As of May 2011, over 416 studies have been registered with www.clinicaltrials.gov under the terms 'stem cells' and 'heart', and at present, 144 of these studies are actively recruiting, which means over 250 studies have been completed or have stopped enrolling. According to a review of the field in 2009,¹ 95 studies were registered worldwide; 40 of them in Europe. The majority of the studies were phase II studies with 14 % having progressed to phase III and 1 % at phase IV. Almost half of the studies were on patients with acute coronary syndrome, around 30 % on patients with HF, and about a quarter on patients with chronic heart disease. The vast majority of cells being evaluated are blood- or bone marrow-derived cells (96 %) with myoblasts- and adipose-derived cells comprising the remainder. In 2011, at least two cardiac stem cell trials have begun in the US,^{2,3} and it is anticipated that others will emerge in the short term. At www.ncbi.nlm.nih.gov/pubmed over 6,400 manuscripts have been published with the keywords 'stem cells' and 'heart'. More publications are emerging every day.

I predicted we would gain insight into which cells are optimal in which patient populations; that we would better know how to deliver, track, and monitor the effects of cells *in vivo*; and that we would begin to understand how patient age, time after injury, and perhaps even gender impact the outcome of cell therapy studies.

We are closing in on understanding which cell type(s) offer benefit for acute myocardial infarction (AMI), refractory ischemia, or peripheral vascular disease (PVD), and are beginning to gain similar understanding in HF (see Table 1). The more specific questions we posed in 2006 are being evaluated. Several studies are underway, evaluating the appropriate timing after injury for cell therapy. The Late-transplantation in myocardial infarction evaluation (Late-TIME)⁴ and Transplantation in myocardial infarction evaluation (TIME)⁵ studies, underway by the National Heart, Lung, and Blood Institute (NHLBI) Cardiovascular Cell Therapy Research Network (CCTR), should begin to close in on the optimal time for patients post-infarction and address whether there is really an outside window beyond which bone marrow mononuclear cells are not useful. In chronic left ventricular (LV) dysfunction and HF, bone marrow- and adipose-derived mesenchymal cell studies are progressing, as are several myoblast studies. Perhaps one of the most exciting findings is that several cell types are on track for approval in Europe and the US. Adipose-derived mesenchymal cells were shown in the 27-patient Phase III randomized evaluation of convection enhanced delivery of IL13-PE38QQR compared to GLIADEL® wafer with survival endpoint in glioblastoma multiforme patients at first recurrence (PRECISE) trial⁶ to increase maximum oxygen consumption and aerobic capacity and decrease infarct size at six months in patients with non-revascularizable chronic myocardial ischemia. Likewise, CD34 cells harvested from peripheral blood after granulocyte colony-stimulating factor (G-CSF) administration may be approved in refractory ischemia patients within the next several years, based on data presented at the American College of Cardiology in 2011⁷ which showed that this subpopulation of bone marrow-derived cells could offer as much or greater benefit than ranolazine in improving six-minute exercise time in patients with vascular disease.

As predicted, cell delivery and cell tracking studies are underway. New catheters are being created, simpler (e.g. intravenous) delivery methods are being evaluated, and local delivery options are being developed for both cardiac and vascular studies. Based on an unmet need

to track cells, novel radiologic and magnetic resonance imaging (MRI)⁸ methods are being developed for clinical use.⁹ New combined endpoints are being developed as biologic understanding of cell therapy improves. Almost weekly, new cells are being generated, discovered, or proposed. Examples of some of the most frequent cell types and their clinical utilization are listed in Table 1. Table 2 lists common cell types in all clinical trials for cardiovascular applications, as well as the number of clinical trials in which they currently appear.

In 2006, the stem-cell landscape changed when a group of investigators¹⁰ used viruses to successfully reprogram fibroblasts to essentially reset their state back to early development and yield induced pluripotent stem cells (iPSCs). Within two years, the production of human-iPSCs was reported,^{11,12} and today these cells can be derived from fibroblasts, blood or bone marrow cells.¹³

The creation of iPSCs cells was heralded as eliminating the need for other cell types. But, as with all biology, the reality constraints of embryonic stem cell research (ESCs). However, by definition, iPSCs require transformation to a less differentiated and more proliferative phenotype. Thus, as with ESCs, they give rise to *teratomas in vivo* if transplanted in an undifferentiated state. In addition, iPSCs have at least one disadvantage compared with their younger counterparts—epigenetic modifications of the DNA, which may make them less safe.¹⁴ They also have benefits over ESCs. They can be derived in an autologous fashion and patient-specific cell lines have already been generated.¹⁵ They can be derived from skin, blood, or bone marrow and other sources are emerging. Finally, human iPSCs appear to be expandable to the large numbers needed for clinical applications and they can give rise to cardiac and vascular tissue. The stem cell landscape continues to expand. Clinical results with existing populations are maturing. Autologous and allogeneic cell sources are coming of age, yet similar questions remain for each new cell type discovered. What is its best use? How should it be delivered, and how does it work. If we can answer these questions for multiple cell populations we will begin to determine the best cell choice for a given individual. Beyond that determination, we will begin to understand the next therapies—beyond cells. I predict that capturing and manipulating endogenous repair¹⁶ will be the novel therapy of the next five years.

I predicted that in 2011 we might be focusing on small molecules, proteins, and peptides in addition to cells. Even so, I thought cell therapy would survive. Both are true today. I thought another likely side benefit of cell therapy would be the critical insight into the body's reparative processes. As predicted, we have moved beyond cells to the idea of using a number of different small molecules and genes to begin to recruit cells and affect the process of endogenous repair. We have begun to show what changes occur prior to the onset of disease, which cell populations and serum cytokines/chemokines fail as disease progresses, and thus which molecules and cells could be new targets for the treatment of disease. In fact, we, along with others, have begun to correlate numbers of circulating stem or progenitor cells with age, sex, and disease state (Center for Cardiovascular Repair, University of Minnesota, unpublished data). Beyond five years, I discussed the idea of beginning to engineer truly regenerative solutions for cardiovascular disease, including the creation of bioartificial organs for end-stage heart failure. Today, the technology we

developed in 2008 for decellularizing cadaveric organs and engineering new beating heart constructs in a dish¹⁷ can be moved beyond small animal models of disease and into human-sized organs. We have applied this technology to human-sized hearts, livers, kidneys, lungs, pancreases and other organs, and have applied it directly to human hearts. This decellularization process, combined with advances in stem cell technology, has truly opened the door toward engineering complex human organs. In fact, clinical use of engineered simple organs is already a reality. Within the past two years, tissue engineered human tracheas have been used in compassionate use cases.¹⁸ Similarly, tissue engineered bladders are being evaluated clinically.¹⁹ Although these are simple tissues, their clinical successes to date suggest that whole-organ engineering is no longer simply a scientific dream.

So what do the next five years hold? Innovations will continue, even as existing cell therapies mature. In the next five years I predict we will see:

- approval of the first cell products for cardiac and vascular diseases;
- new stem cells and methods for deriving them emerging;
- preclinical ‘endogenous reprogramming’ of cells that allows us to stimulate stem cell proliferation in a damaged organ or tissue to repair damage without cells;
- a cadaveric tissue-based cardiac patch or vessel for first-in-human use;
- novel tissue engineered treatments for AMI or HF.

Endogenous repair, cell-based prevention and cell therapy have moved forward. New stem cells exist. New stem cell technologies have been created. Cardiac regeneration is no longer outside the realm of possibility. There is progress on all fronts. Instead of hope, I would say we have reached promise. Stay tuned.

Acknowledgements

This work has been supported in part by The Medtronic Foundation, the National Heart Lung and Blood Institute’s Progenitor Cell Biology Consortium #1U01HL100407-1, and the American Heart Association’s Jon Holden DeHaan Cardiac Myogenesis Research Center #AHA09070499N.

References

1. Scacciatella P, Amato G, Ebrille E, et al. [Current perspectives in cell therapy in cardiology: an overview of ongoing trials]. *G Ital Cardiol (Rome)*. 2010; 11(10):769–74. [PubMed: 21246779]
2. Cedars-Sinai Medical Center. [Accessed 22 July 2011] Cardiosphere-Derived autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS). Available at: <http://clinicaltrials.gov/ct2/show/NCT00893360?term=00893360&rank=1>
3. University of Louisville. [Accessed 22 July 2011] Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy (SCIPIO). Available at: <http://clinicaltrials.gov/ct2/show/NCT00474461?term=00474461&rank=1>
4. National Heart Lung and Blood Institute. Available at: <http://clinicaltrials.gov/ct2/show/NCT00684060?term=NCT00684060&rank=1>. [Accessed 22 July 2011] Use of Adult Autologous Stem Cells in Treating People 2 to 3 Weeks After Having a Heart Attack (The Late TIME Study). <http://clinicaltrials.gov/ct2/show/NCT00684060?term=NCT00684060&rank=1>

5. National Heart Lung and Blood Institute. [Accessed 22 July 2011] Use of Adult Autologous Stem Cells in Treating People Who Have Had a Heart Attack (The TIME Study). Available at: <http://clinicaltrials.gov/ct2/show/NCT00684021>
6. Cytori Therapeutics. [Accessed 22 July 2011] A Randomized Clinical Trial of Adipose-derived Stem Cells in Treatment of Non-Revascularizable Ischemic Myocardium (PRECISE-01). Available at: <http://clinicaltrials.gov/ct2/show/NCT00076986?term=NCT00076986&rank=1>
7. Losordo, D. [Accessed 22 July 2011] Injection of Autologous CD34-Positive Cells for Critical Limb Ischemia (ACT34-CLI). Available at: <http://clinicaltrials.gov/ct2/show/NCT00616980?term=NCT00616980&rank=1>
8. Petersen JW, Forder JR, Thomas JD, et al. Quantification of Myocardial Segmental Function in Acute and Chronic Ischemic Heart Disease and Implications for Cardiovascular Cell Therapy Trials A Review From the NHLBI-Cardiovascular Cell Therapy Research Network. JACC Cardiovasc Imaging. 2011; 4(6):671–9. [PubMed: 21679903]
9. Lucignani G, Rodriguez-Porcel M. In vivo imaging for stem cell therapy: new developments and future challenges. Eur J Nucl Med Mol Imaging. 2011; 38(2):400–5. [PubMed: 21203755]
10. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126(4):663–76. [PubMed: 16904174]
11. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131(5):861–72. [PubMed: 18035408]
12. Vogel G, Holden C. Developmental biology. Field leaps forward with new stem cell advances. Science. 2007; 318(5854):1224–5. [PubMed: 18033853]
13. Yu J, Vodyanik MA, Smuga-Otto K, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007; 318(5858):1917–20. [PubMed: 18029452]
14. Maherali N, Sridharan R, Xie W, et al. Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. Cell Stem Cell. 2007; 1(1):55–70. [PubMed: 18371336]
15. Lengner CJ. iPS cell technology in regenerative medicine. Ann N Y Acad Sci. 2010; 1192:38–44. [PubMed: 20392216]
16. Zenovich AG, Taylor DA. Atherosclerosis as a disease of failed endogenous repair. Front Biosci. 2008; 13:3621–36. [PubMed: 18508460]
17. Ott HC, Matthiesen TS, Goh SK, et al. Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med. 2008; 14(2):213–21. [PubMed: 18193059]
18. Baiguera S, Jungebluth P, Burns A, et al. Tissue engineered human tracheas for in vivo implantation. Biomaterials. 2010; 31(34):8931–8. [PubMed: 20800273]
19. Atala A, Bauer SB, Soker S, et al. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet. 2006; 367(9518):1241–6. [PubMed: 16631879]

Table 1
Examples of Stem Cells in Phase III Clinical Trials for Treatment of Cardiovascular
Disease Listed at www.clinicaltrials.gov

Cell Type	Phase	Disease State	Number of Trials
Bone marrow mononuclear cells	III	Myocardial infarction	5
Bone marrow mononuclear cells	III	Critical limb ischemia	2
Bone marrow mononuclear cells	III	Dilated cardiomyopathy	1
Bone marrow mononuclear cells	III	Coronary artery disease	1
Bone marrow mesenchymal stem cells	III	Myocardial infarction	2
Bone marrow mesenchymal stem cells	III	Ischemic cardiomyopathy	1
CD34+ cells	III	Myocardial infarction	1
AC133+ cells	III	Myocardial infarction	2
AC133+ cells	III	Chronic ischemic coronary artery disease	2
Myoblasts	III	Myocardial infarction	1
Adipose-derived regenerative cell	III	Myocardial infarction	1

The information presented in Table 1 is taken from active or recruiting Phase III clinical trials related to cardiovascular disease and repair, including the types of cells involved in those trials. This list is ever changing, as new cell types and therapeutic applications are continually being explored.

Table 2
Stem Cells for Cardiovascular Applications in Clinical Trials

Cell Type	Number of Cardiac Clinical Trials Listed at WWW.CLINICALTRIALS.GOV
Bone marrow cells	360
Bone marrow mononuclear cells	44
Endothelial progenitor cells	76
Bone marrow mesenchymal stem cells	29
CD34+ cells	49
AC133+ cells	3
Myoblasts	12
Adipose-derived mesenchymal stem cells	3

These are all listed clinical trials for cardiovascular applications, including the types of cells involved in those trials. While bone marrow cells still appear to be the cell type of choice, other options are also becoming available.