FROM THE ANALYST'S COUCH

# Stem cell therapy market

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Mabel sofa by Donna Wilson, courtesy of www.scp.co.uk

Stem cells (SCs) have been used in medicine since 1968, when bone marrow transplantation (BMT) was first achieved. Today, BMT is still used for treating cancers and genetic blood disorders, but the transplanted haematopoietic SCs (HSCs) are increasingly sourced from peripheral and umbilical cord blood rather than the bone marrow. Worldwide, ~60,000 BMT operations are performed yearly (~35,000 using autologous HSCs; ~25,000 using allogeneic HSCs). Beyond BMT, there are high near-term expectations for SC therapeutics derived from multipotent mesenchymal SCs (MSCs); in the long term, pluripotent embryonic SCs (ESCs) and induced pluripotent SCs (iPSCs) are promising.

## Marketed products

Most of the SC therapies on the market and in development utilize MSCs. At least three osteobiologic products, Osteocel (NuVasive), Trinity (Orthofix) and LiquidGen (Skye Orthbiologics), use MSCs as a component of an allograft matrix and are believed to promote osteogenesis and reduce inflammation. SC grafts are the fastest-growing area of the bone graft market, with a projected value of US$600 million by 2015.

MSC products have also been approved for other indications in South Korea and Canada. Hearticellgram-AMI (FCB-Pharmicell), an autologous MSC intracoronary injection for the treatment of acute myocardial infarction, was approved in South Korea in 2011. Cupistem (Anterogen) for anal fistula, and Cartistem (Medipost) for cartilage injury and osteoarthritis, were approved in January 2012 in South Korea. Cartistem is an allogeneic product and Cupistem is an autologous MSC product. Full clinical trial data to support the approvals have not been released to date.

In May 2012, Prochymal (Osiris Therapeutics), consisting of allogeneic MSCs, was approved in Canada for refractory paediatric graft versus host disease (GVHD). Phase III data for Prochymal were mostly negative; approval was based on positive data for a limited subset of the patient population.

## Emerging pipeline candidates

Several MSC products are nearing approval (TABLE 1). StemEx (Gamida Cell) is an allogeneic 'off-the-shelf' treatment based on an expanded unit of cord blood, intended to offer a substitute for BMT. It has been granted orphan drug status by the FDA and should reach the market in 2013. A competitor is Mesoblast's MSC product, consisting of cord blood with 40-fold HSC expansion to improve engraftment, which is in Phase III trials. These products fit into an existing niche and are potential blockbusters.

Another promising Phase III candidate is Cx601 (TiGenix; aquired in a merger with Cellerix in 2011), consisting of allogeneic adipose-derived MSCs, for the treatment of complex perianal fistula. Final results are expected in the second quarter of 2014.

***SCs for cardiovascular disease.*** Although MSCs do not normally contribute to the cell lineages that require repair in cardiovascular pathologies, some positive clinical data have been reported in this setting. These results are generally attributed to trophic effects, although the administered MSCs are cleared rapidly while the effects continue, so the mechanism is unclear.

Leading the way is Baxter Healthcare's Phase III trial of intramyocardially administered autologous HSCs (harvested from peripheral blood), intended to reduce angina in patients with refractory chronic myocardial ischaemia. The primary completion date is June 2016. Findings to date indicate that the product can repair heart tissue, increase blood flow, reduce angina episodes and allow the patient to exercise.

One direct competitor to Baxter's treatment is AMR-001 (NeoStem), which uses autologous enriched HSCs from the bone marrow to treat ST elevation myocardial infarction (STEMI). Injected into the infarct-related artery, AMR-001 targets the site of ischaemic injury, where chemokine CXC receptor 4 (CXCR4) on HSCs binds to stromal-derived factor 1 (SDF1), which is induced by hypoxia-inducible factor (HIF) produced by ischaemic tissue. AMR-001 is in Phase II trials, which have an estimated primary completion date of July 2013. The product has a better characterized mechanism of action than Baxter's candidate, which may be an advantage from a regulatory perspective. ▸

Table 1 | **Stem cell therapies: selected late-stage pipeline**

| Company | Product or process | Indication | Development stage |
|---|---|---|---|
| Aastrom Biosciences | Ixmyelocel-T (patient-specific autologous multicellular therapy) | Critical limb ischaemia | Phase III |
| Gamida Cell | StemEx (umbilical cord blood stem and progenitor cells expanded *ex vivo*) | HSCT in haematological malignancies | Phase II/III |
| Mesoblast | 'Off-the-shelf' mesenchymal precursors | HSCT in haematological malignancies | Phase III |
| Osiris Therapeutics | Prochymal (adult human mesenchymal stem cells) | Crohn's disease | Phase III (three trials) |
| Osiris Therapeutics | Prochymal (adult human mesenchymal stem cells) | Graft versus host disease | Phase III (two trials) |
| Baxter Healthcare | Auto-CD34$^+$ cells (adult autologous CD34$^+$ cells) | Chronic myocardial ischaemia | Phase III |
| TiGenix | Cx601 (adipose-derived allogeneic stem cell suspension) | Complex perianal fistula | Phase III |
| Bioheart | MyoCell (autologous myoblasts) | Congestive heart failure | Phase II/III |
| Cytori Therapeutics | Adipose-derived stem and regenerative cells (two dosages) | Acute myocardial infarction | Phase II/III |
| Stempeutics Research | Stempeucel (adult mesenchymal stem cells) | Critical leg ischaemia | Phase II/III |
| Cardio3 Sciences (Belgium) | C-Cure (BM-derived stem cells treated with cardiopoietic cocktail) | Congestive heart failure | Phase III |

BM, bone marrow; HSCT, haematopoietic stem cell transplantation.

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Other late-stage candidates include Aastrom's Ixmyelocel-T, which consists of autologous cells (including monocytes and macrophages in addition to MSCs) derived from bone marrow using a minimally invasive procedure. The cells are believed to promote immunomodulation, angiogenesis and tissue remodelling. The product is in Phase III trials for critical limb ischaemia and dilated cardiomyopathy, with an estimated primary completion date in the first quarter of 2015. Bioheart and Cytori also have Phase II candidates. C-Cure (Cardio3 Bioscience) is based on autologous MSCs differentiated via its cardiopoiesis platform into cardiac cells, which are re-injected into the heart. A Phase II/III trial was completed in January 2012. Cytori's adipose-derived MSCs for acute myocardial infarction underwent Phase II/III trials. The primary completion date was February 2012; however, results have not been published to date. Other companies developing SC treatments for cardiovascular disease include Aldagen, Cardiogenesis Corporation and Pluristem Therapeutics.

***Other indications for SC therapies.*** The cytoprotective and immunosuppressive qualities of MSCs make them interesting for the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease. However, Osiris Therapeutics' Prochymal, the leader in this area, struggled to show efficacy in a range of clinical trials in autoimmune diseases. Alliancells Bioscience Corporation and AlloCure are among the companies investigating this area.

Diabetes is a significant target for SC treatment, as stem-cell derived pancreatic islet β-cells can be transplanted into the pancreas. This could potentially liberate patients with type 1 diabetes from the need to administer insulin, but outstanding issues remain with immunosuppression to avoid transplant rejection, sustaining long-term treatment responses and obtaining sufficient donors. Cellonis Biotechnology, Ixion Biotechnology and ViaCyte are among the companies investigating this area.

Another major target for SC research and development (R&D) is the central nervous system, particularly neurological conditions. BrainStorm Therapeutics and NeuroGeneration are focusing on Parkinson's disease. Neuralstem is developing human neural cells from fetal tissue with putative neuroprotectant effects. ReNeuron, also using fetally derived neural cells, has initiated a clinical trial of ReN001 in post-ischaemic stroke victims. Other companies that have reached clinical trials include: Stem Cell Therapeutics, with NTx-265 intended to regenerate functional brain matter following a stroke; and StemCells, which has initiated a Phase I trial in neuronal ceroid lipofuscinosis (Batten disease) using human neural cells. As one of the leaders in this sector, StemCells is also targeting therapies for Alzheimer's disease and age-related macular degeneration (AMD).

### Pluripotent cells: the game-changer?

ESCs have received the most media attention in the past, but the field has faced several setbacks, due partly to federal funding restrictions in the United States. Geron abandoned its first-in-class ESC trial in 2011, citing cost reasons. The European Court of Justice's Brüstle ruling has threatened ESC patenting in Europe, although the German Federal Court of Justice upheld the patent's validity in December 2012.

Nevertheless, promising ESC research continues, with University College London (UCL) and Pfizer as well as Advanced Cell Technology exploring treatments for retinal diseases. AMD is a key target with early indications that photoreceptor damage can be reversed by implanting differentiated ESCs. Stemedica Cell Technologies are also conducting early trials in AMD with 'ischaemic tolerant' retinal pigment epithelial SCs.

Approval for ESC therapies remains a long-term prospect, however. iPSCs are also not a realistic near-term treatment option owing to their relative genomic instability and the fact that their recent emergence means that they have yet to be fully characterized. However, data on iPSCs are rapidly being amassed, and they will probably become widely used in disease modelling and drug discovery assays in the near future.

### Market outlook

In 2011, the SC therapies market was valued at $2.7 billion, consisting almost entirely of revenues from the well-established BMT segment. Furthermore, stem cell biobanking and ancillary products were estimated to be worth $2.6 billion. SC therapies are advancing across a broad and diverse front, and the total market is expected to expand to $8.8 billion by 2016 (compound annual growth rate: 10.6% 2011–2016)[1] (FIG. 1). Investment in the sector is increasing, although much of the interest remains relatively covert. Among the high-profile collaborations are Pfizer's deal with Athersys, involving milestone payments of up to $105 million. Novartis has a drug discovery alliance with Epistem, whereas Astellas Pharma has invested in Cytori's SC programmes. Increasing vindication of R&D in the sector in the form of new approvals will increase its visibility and spur further investment: in the near term this is likely to come from novel haematopoietic SC transplantation options as well as cardiovascular and autoimmune MSC therapies. In the long term, SCs have great promise for wider applications in regenerative medicine, including organ regeneration and replacement.

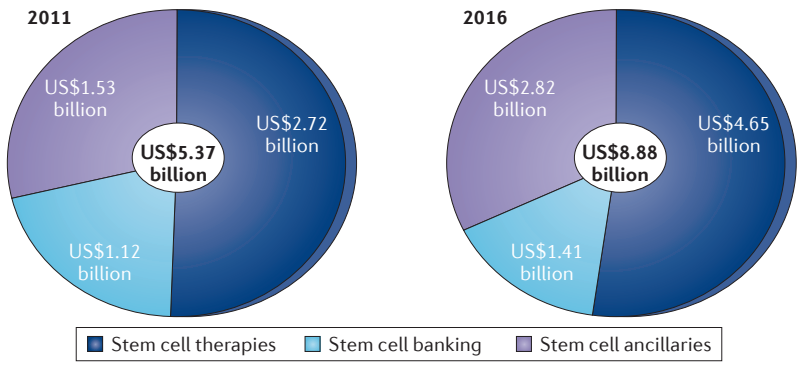


Figure 1 | **Stem cell market.** Projected revenues 2011–2016. Source: Visiongain.

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**Competing interests statement**
The authors declare no competing financial interests.