Regenerative Medicine: Navigating the Uncertainties

APPENDIX TO
VALUE PROJECT FINAL REPORT

March 2012

Technology Strategy Board
Driving Innovation

Contents

Summary

A key approach taken by the VALUE project was to use current data from exemplar regenerative medicine products, coupled with insights and experiences of drug developers actively participating in the consortium, to inform the project research and development of final outputs.

A selection of product case studies representative of the main categories of regenerative medicines were prepared using a standard format to provide an information resource for work package activities. A selection of these case studies is provided in this Appendix as they also represent a valuable resource to product developers.

The four product categories identified for case study development were:

1) Non-medicines Lead: Karen Hodgkin, Cell Medica Ltd

2) Autologous Products Leads: James Blann, TiGenix and Paul Ripley, Quy Biosciences Ltd

3) Allogeneic Products Lead: Tim Allsopp, Neusentis Neusentis (Pfizer)

4) Other Products Lead: Patrick Ginty, Loughborough University

As the project evolved, information flow became more dynamic and information gathering was widened to draw on data as required from additional products*.

Case Study Leads Contact Info

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* *It should be noted that the case studies for VALUE partner products contained in this Appendix are comprehensive and backed up by the first hand experiences of the authors whereas information gathered from public domain sources on the additional products contained herein is subject to change and sometimes difficult to verify.*

Case Study Product Category 1: Non-medicines

Cell Medica Ltd: Cytovir CMV (CMV-specific T-cells)

Brief Product Description:

CMV-specific T-cells are naturally occurring immune cells which can be selected using non-manipulative techniques. The cells are given to haematopoietic stem cell transplant recipients to reconstitute the patients' immunity to cytomegalovirus (CMV). Cells are selected from the same donor who provides the stem cells for the transplant; i.e. this is a patient-specific allogeneic product. The cells have received a classification from both the MHRA and EMA as non-medicinal i.e. not a medicinal product or ATMP. As such they are available commercially in the UK to specialist transplant centres.

Target Indications and Markets:

Key Q: Clinical indications

CMV-specific T-cells are indicated in the prevention or treatment of CMV infection post-haematopoietic stem cell transplant (HSCT).

The allo-HSCT procedure has been in practice for more than 40 years ago and is often utilised in connection with the treatment of leukaemia patients refractory to chemotherapy. These patients receive high dose myeloablative chemotherapy to kill the cancerous blood cells, but this procedure leaves the patient without a functioning immune system. The allo-HSCT procedure allows reconstitution of the patient's immune system through transplant of donor haematopoietic stem cells. (The donor is closely matched with respect to HLA type.) The allo-HSCT procedure also enables a graft vs. leukaemia (GVL) effect which is an important factor in curing the patient.

Following the allo-HSCT procedure, the patient typically recovers innate immune function (neutrophils, granulocytes) within a few weeks, but full functionality of the adaptive immune system which is critical to control viral infections may require 3-12 months. During this time, the patient is highly vulnerable to infections in particular from latent viruses which are either present in the patient prior to the allo-HSCT or introduced to the patient following transplant of the donor stem cells. Infections are a significant cause of morbidity and mortality in the allo-HSCT patient group.

CMV is a herpes virus which infects 60% to 90% of humans on a latent basis. Primary infection may be asymptomatic and is easily controlled by the adaptive immune response in healthy individuals. The immune response necessary to clear an intracellular viral pathogen is driven mainly by cytotoxic CD8+ and CD4+ T cells which, through their T cell receptors, are able to recognise viral antigens expressed on the surface of infected cells. Following primary infection, long lasting immunity to CMV is established by the generation of memory T cells which control the virus on an antigen-specific basis. In immunosuppressed CMV seropositive patients who lack protective CMV-specific memory T cells, reactivation of the virus can lead rapidly to systemic infection and death.

Key Q: Geographical target market

The regulatory treatment of the cells means that they are available currently in the UK and additional European countries can be added following local manufacturing authorisations. Discussions are underway to clarify the regulatory position in the USA.

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

There are no other cell based products on the market for the treatment of CMV infection post-transplant. Ganciclovir (oral form, valganciclovir) and foscarnet are the two main commercially available drug competitors.

Key Features of Business Model:

Key Q: big pharma, SME, IP company, virtual company

Cell Medica is a clinical stage cellular-therapeutics company engaged in the development and delivery of cellular immunotherapy treatment strategies for infectious disease and cancer. The Company's lead clinical application, referred to as Virus-Specific Immune Reconstitution (VSIR), involves the transfer of donor-derived virus-specific T cells into a patient in order to prevent infections following allogeneic haematopoietic stem cell (bone marrow) transplant. The company is a small to medium-sized enterprise employing 14 people (as of March 2012).

Key Q: Target Exit Strategy

The company is privately owned and is currently at Series A funding stage.

Key Q: Other products in portfolio

The company can utilise similar cell selection methodology to isolate additional pathogen-specific T-cells which may be useful in treating other infections affecting transplant recipients and wider patient groups. Currently adenovirus, EBV and the tumour antigen WT1 are under study.

Key Q: Define any relationships with clinical KOLs

The Scientific advisory team for the company comprises the following individuals.

Prof. Stephen Mackinnon
Head of Haematology, Royal Free Hospital
Professor of Medicine, University College London

Prof. Paul Moss
Professor of Haematology,
University of Birmingham Cancer Research Studies,

Prof. Charles Pusey
Director of Research & Develop., Hammersmith Hospital
Professor of Medicine, Imperial College

Prof. Stanley Riddell
Professor of Medicine
Fred Hutchinson Cancer Research Center

Prof. Cliona Rooney
Professor, Cell and Gene Therapy
Baylor School of Medicine

Prof. Gavin Screaton
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Professor of Medicine, Imperial College

Prof. Hans Stauss
Head of Clinical Immunology, Royal Free Hospital
Professor of Clinical Immunology, University College London

Dr Mark Lowdell
Director of Cellular Therapeutics Laboratory
Royal Free Hospital

The Chief Investigator for the company's clinical studies is Dr Karl Peggs, UCL, London

Regulatory Strategy/Status:

Key Q: Target approval routes

Directly selected CMV-specific T-cells have been classed as 'Not an Advanced therapy medicinal product' by the MHRA (2007) and the EMA (2010).

Key Q: Clinical data and time to approval

No clinical data required for regulatory approval

Phase 1 information:

1) **Walter EA, Greenberg PD, Gilbert MJ, Finch RJ, Watanabe KS, Thomas ED, Riddell SR. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. New England Journal of Medicine 1995;333(16):1038-44**

CMV disease in immunocompromised patients correlates with a deficiency of CD8+ cytotoxic T lymphocytes specific for CMV. We evaluated the safety and immunologic effects of immunotherapy with clones of these lymphocytes in recipients of allogeneic bone marrow transplants. Clones of CD8+ cytotoxic T cells specific for CMV proteins were isolated from the blood of bone marrow donors. Fourteen patients each received four intravenous

infusions of these clones from their donors beginning 30 to 40 days after marrow transplantation. The reconstitution of cellular immunity against CMV was monitored before and during the period of infusions and for up to 12 weeks after the final infusion. The rearranged genes encoding the T-cell receptor served as markers in evaluating the persistence of the transferred T cells. No toxic effects related to the infusions were observed. Cytotoxic T cells specific for CMV were reconstituted in all patients. In vitro measurements showed that cytotoxic activity against CMV was significantly increased ($P < 0.001$) after the infusions in 11 patients who were deficient in such activity before therapy. The level of activity achieved after the infusions was similar to that measured in the donors. Analysis of rearranged T-cell-receptor genes in T cells obtained from two recipients indicated that the transferred clones persisted for at least 12 weeks. Cytotoxic-T-cell activity declined in patients deficient in CD4+ T-helper cells specific for CMV, suggesting that helper-T-cell function is needed for the persistence of transferred CD8+ T cells. Neither CMV viraemia nor CMV disease developed in any of the 14 patients. The authors concluded that the transfer of CMV-specific clones of CD8+ T cells derived from the bone marrow donor is a safe and effective way to reconstitute cellular immunity against CMV after allogeneic marrow transplantation.

Phase 2 information:

Ongoing study

CMV: ASPECT (**C**yto**m**egalo**v**irus:**A**lternate **D**onor **S**tudy of **P**re-**E**mptive **C**ellular **T**herapy) is a prospective Phase 2 study to investigate the efficacy and safety of pre-emptive CMV Adoptive Cellular Therapy in patients receiving allogeneic haematopoietic stem cell transplant from an unrelated donor.

Patients will be HLA- matched unrelated donor T cell-depleted allogeneic HSCT recipients where donor and recipient are CMV seropositive.

The primary objective is to determine the efficacy of pre-emptive CMV-specific adoptive cellular therapy following T cell-depleted allogeneic HSCT with respect to reconstitution of CMV-reactive T cells. Secondary objectives are:

- to evaluate the safety of CMV-adoptive cellular therapy with respect to GvHD;
- to evaluate the feasibility of selecting CMV-adoptive cellular therapy from G-CSF mobilised peripheral blood;
- to measure the in vivo expansion of CMV-reactive T cells post infusion of ACT;
- to evaluate the potential clinical benefit of pre-emptive CMV-specific adoptive cellular therapy following T cell depleted allogeneic HSCT as measured by reduction in anti-viral drug therapy and the total number of in-patient days (total days in first 170 days post-single positive PCR result) and health care outcome as assessed by EQ-5D.

The primary endpoint is the peak number of circulating CMV-reactive T cells within the first two months, after single positive CMV PCR result (or post ACT infusion). Secondary endpoints are:

- the earliest detection of CMV-reactive T cells in the peripheral blood;
- the incidence and severity of GvHD;
- the duration of CMV antiviral drug therapy (total days), number of reactivation episodes and total number of in-patient days. EQ-5D scores.

Patients will be randomised (2:1) to pre-emptive infusion with CMV-specific T cells selected by the streptamer selection technique plus standard CMV antiviral therapy vs. standard CMV antiviral therapy alone.

Twenty four patients will be randomised to treatment arm A (ACT + standard therapy) and 12 to treatment arm B (standard therapy alone).

Treatment with CMV-specific T cells will be administered as pre-emptive therapy upon first detection of CMV DNA if infusion criteria are met. CMV antiviral drug therapy will be initiated according to the following criteria:

- if there is a doubling of the CMV load seven days after initial detection of viral DNA and the viral load > 3000 copies/ml;
- if the absolute viral load is > 5,000 copies/ml;
- if there is evidence of CMV disease.

Therapy will be stopped when the viral load is below the level of quantification of the assay.

The initial drug of choice is ganciclovir/valganciclovir, with foscarnet given if cytopenia precludes administration of the ganciclovir/valganciclovir.

Nine centre trial in the UK (36 patients).

Commenced October 2010: ongoing

Clinical trial number NCT01220895

UK CRN #4816 CMV~ACE **Published information exists covering the ex vivo preparation of T-cell therapies and their use in patients. Citing eight key publications, Cell Medica can reference data on 99 patients and the clear messages of reduced viraemia, reduced disease, reduced need for antiviral drugs and no side effects.**

The key published clinical Phase 2 references are:

2) Einsele H, Roosnek E, Rufer N, Sinzger C, Riegler S, Löffler J, Grigoleit U, Moris A, Rammensee HG, Kanz L, Kleihauer A, Frank F, Jahn G, Hebart H. Infusion of cytomegalovirus (CMV)-specific T cells for the treatment of CMV infection not responding to antiviral chemotherapy. Blood 2002;99(11):3916-22

We adoptively transferred donor-derived CMV-specific T-cell lines into eight stem cell transplant recipients lacking CMV-specific T-cell proliferation. All patients, of whom one was infected by a CMV strain that was genotypically ganciclovir resistant, had received unsuccessful antiviral chemotherapy for more than four weeks. CMV-specific lines had been prepared by repetitive stimulation with CMV antigen, which increased the percentage of CMV-specific T cells and ablated alloreactivity completely even against patients mismatched for one to three HLA antigens. After transfer of 10^7 T cells/m^2 at a median of 120 days (range, 79 to 479 days) after transplantation, no side effects were noticed. Despite cessation of antiviral chemotherapy, the CMV load dropped significantly in all seven evaluable patients, with a maximal reduction after a median of 20 days (range, 5 to 31 days). In two patients with high virus load, the antiviral effect was only transient. One of these patients received a second T-cell infusion, which cleared the virus completely. At a median of 11 days after transfer, CMV-specific T-cell proliferation was demonstrated in six patients, and an increase in CMV-specific CD4(+) T cells was demonstrated in five patients. In six patients, 1.12 to 41 CMV-specific CD8(+) T cells/microL blood were detected at a median of 13 days after transfer, with an increase in all patients lacking CMV-specific CD8(+) T cells prior to transfer. Hence, anti-CMV cellular therapy was successful in 5/7 patients, whereas

in 2/7 patients, who received an intensified immune suppression at the time of or after T-cell therapy, only transient reductions in virus load were obtained.

3) Peggs KS, Verfuerth S, Pizzey A, Khan N, Guiver M, Moss PA, Mackinnon S. Adoptive cellular therapy for early cytomegalovirus infection after allogeneic stem-cell transplantation with virus-specific T-cell lines. Lancet 2003;362(9393):1375-7

Adoptive transfer of CMV-specific T cells offers the potential for reconstitution of viral immunity after allogeneic transplantation. However, the logistics of producing virus-specific T-cell clones has limited the application of cellular therapies. We treated 16 patients for CMV infection with polyclonal CMV-specific T-cell lines generated by short-term culture. Massive in-vivo expansions of CMV-specific cytotoxic T lymphocytes were observed, resulting in reconstitution of viral immunity. In eight cases antiviral drugs were not required, and subsequent episodes of reactivation occurred in only two patients. Our findings indicate that application of CMV-specific cell lines is both feasible and effective in a clinical environment.

4) Cobbold M, Khan N, Pourgheysari B, Tauro S, McDonald D, Osman H, Assenmacher M, Billingham L, Steward C, Crawley C, Olavarria E, Goldman J, Chakraverty R, Mahendra P, Craddock C, Moss PA. Adoptive transfer of cytomegalovirus-specific CTL to stem cell transplant patients after selection by HLA-peptide tetramers. Journal of Experimental Medicine 2005;202(3):379-86

SCT patients are immunosuppressed profoundly in the early posttransplant period, and reactivation of CMV remains a significant cause of morbidity and mortality. Adoptive transfer of donor-derived CMV-specific CD8+ T cell clones has been shown to reduce the rate of viral reactivation; however, the complexity of this approach severely limits its clinical application. We have purified CMV-specific CD8+ T cells from the blood of stem cell transplant donors using staining with HLA-peptide tetramers followed by selection with magnetic beads. CMV-specific CD8+ cells were infused directly into nine patients within 4 h of selection. Median cell dosage was 8.6 x 10(3)/kg with a purity of 98% of all T cells. CMV-specific CD8+ T cells became detectable in all patients within 10 d of infusion, and TCR clonotype analysis showed persistence of infused cells in two patients studied. CMV viraemia was reduced in every case and eight patients cleared the infection, including one patient who had a prolonged history of CMV infection that was refractory to antiviral therapy. This novel approach to adoptive transfer has considerable potential for antigen-specific T cell therapy.

5) Micklethwaite K, Hansen A, Foster A, Snape E, Antonenas V, Sartor M, Shaw P, Bradstock K, Gottlieb D. Ex vivo expansion and prophylactic infusion of CMV-pp65 peptide-specific cytotoxic T-lymphocytes following allogeneic hematopoietic stem cell transplantation. Biology of Blood & Marrow Transplantation 2007;13(6):707-14

CMV reactivation and infection post-allogeneic hematopoietic stem cell transplant continue to cause morbidity and mortality. Current pharmacologic therapies are limited by side effects. Adoptive transfer of ex vivo generated CMV-specific T cells has the potential to restore immunity, prevent CMV, and circumvent the need for pharmacologic therapies. We have generated donor-derived CMV-specific cytotoxic T cells using dendritic cells pulsed with the HLA-A2 restricted nonapeptide NLVPMVATV (NLV) derived from the CMV-pp65 protein. These cytotoxic T cells have been given prophylactically to nine recipients aged 4 to

65 years on or after day 28 post-allogeneic hematopoietic stem cell transplant. Only 2/9 recipients received T cell depletion in vivo or in vitro. There were no immediate adverse reactions to the infusions. During 97-798 days of follow-up, two recipients developed CMV reactivation; neither developed CMV disease or required pharmacotherapy. Three recipients developed acute GvHD after infusion. Two recipients died, one from thrombotic thrombocytopenia purpura secondary to cyclosporine, one from complications of GvHD. A transient increase in numbers of CMV-specific T cells demonstrated by NLV-tetramer binding was seen in six recipients. Prophylactic adoptive transfer of NLV-specific T cells is safe and may be effective in preventing CMV reactivation.

6) Mackinnon S, Thomson K, Verfuerth S, Peggs K, Lowdell M. Adoptive cellular therapy for cytomegalovirus infection following allogeneic stem cell transplantation using virus-specific T cells. Blood Cells Molecules & Diseases 2008;40(1):63-7

Adoptive transfer of virus-specific T cells offers the potential for accelerating reconstitution of antigen-specific immunity and limiting the morbidity and mortality of viral infections following allogeneic haematopoietic stem cell transplantation. However, the logistics of producing virus-specific T cells and the risk of inducing GvHD secondary to the infusion of alloreactive clones have limited the application of cellular therapies. We report the results in patients of pre-emptive and prophylactic therapy with CMV-specific T cells. Cells were administered at early time points following transplantation (when the risk of GvHD is greatest) either prophylactically or following the detection of CMV DNA by a PCR-based surveillance technique. Massive in vivo expansions of CMV-specific cytotoxic T-lymphocytes (3 to 5 log) were observed in patients within days of adoptive transfer. Viral titres were decreasing within five days, in some patients the T-cell receptor CDR3 lengths of CMV-specific CTL expanding in vivo were identical to those of the transferred cells. A low incidence of late CMV reactivation was seen and no significant toxicities were observed. Our findings indicate that application of cell lines generated by either short-term in vitro cultures or by direct selection using gamma-capture, which allow expansion of both CD4(+) and CD8(+) virus-specific T cells, is both feasible and effective in a clinical environment. These simple in vitro methodologies should allow widespread application of adoptive transfer of virus-specific T cells.

7) Peggs KS, Verfuerth S, Pizzey A, Chow SL, Thomson K, Mackinnon S. Cytomegalovirus-specific T cell immunotherapy promotes restoration of durable functional antiviral immunity following allogeneic stem cell transplantation. Clinical Infectious Diseases 2009;49(12):1851-60

The profound immunodeficiency associated with allogeneic hematopoietic stem cell transplantation permits uncontrolled replication of latent human herpes viridae such as CMV. Morbidity and mortality associated with viral dissemination or its treatment are significant. Although ACT with virus-specific T cells offers the potential for accelerating pathogen-specific immune reconstitution, the risk of induction of graft-versus-host disease and the logistics of production of clonal T cell populations restrict application. We investigated the ability of CMV-specific mixed CD4(+) and CD8(+) T cell lines, generated by short-term ex vivo culture of donor lymphocytes with donor monocyte-derived dendritic cells pulsed with virus lysate, to restore antiviral immunity in 30 allogeneic transplant recipients at high risk of both uncontrolled viral replication and of graft-versus-host disease. There were no immediate toxicities and no excess of GvHD. Massive in vivo expansions of CMV-specific T lymphocytes occurred, temporally associating with periods of viral replication, suggesting that antigen exposure was necessary for optimal CMV-specific

immune reconstitution. The expanding populations maintained functional competence in ex vivo re-stimulation assays, promoting reconstitution of durable functional CMV-specific immunity and effectively preventing recurrent viral infection and late CMV disease. These data confirm the ability of cellular immunotherapy to hasten reconstitution of antiviral immunity following allogeneic transplantation, indicating that significant clinical benefits may be conferred in terms of reduction of secondary viral infection episodes, potentially reducing exposure to the toxicities of antiviral drugs.

8) Dong L, Gao ZY, Chang LJ, Liang Y, Tan XY, Liu JH, Yu XJ, Yang FH, Xie Y, Lu DP. Adoptive transfer of cytomegalovirus/Epstein-Barr virus-specific immune effector cells for therapeutic and preventive/preemptive treatment of pediatric allogeneic cell transplant recipients. Journal of Pediatric Hematology/Oncology 2010;32(1):e31-7.

This report describes a safe and effective therapy through adoptive transfer of donor CMV/Epstein-Barr virus (EBV) immune effector cells. The patients, from three to ten years of age, suffering from haematological diseases received haploidentical transplantation. All three patients developed varying levels of viraemia from days 13 to 31 and two patients developed CMV-interstitial pneumonitis or interstitial inflammation after transplantation. Tapering down the dose of immunosuppressives together with intensive antivirus therapy and escalated infusions of donor-derived CMV/EBV immune effector cells effectively controlled virus-related diseases. All three patients survived and remained CMV/EBV-free 14 to 16 months after transplantation.

Phase 3 information: one on-going clinical study (Wellcome Trust funded)

CMV~IMPACT

CMV~IMPACT (**C**yto**m**egalo**v**irus ~ **I**mmuno**p**rophylactic **A**doptive **C**ellular **T**herapy study) is a multicentre, prospective, controlled, open-label randomised Phase 3 study of prophylactic ACT for CMV following T cell-depleted allogeneic HSCT from a sibling donor. Because multiple methods for T cell depletion are available, and differences between them will likely have an effect on immune reconstitution, the study is restricted to patients receiving alemtuzumab-containing conditioning protocols. The study compares 'best-available' standard anti-viral monitoring and therapy alone, with 'best available' anti-viral monitoring and therapy plus prophylactic ACT with cells selected by either the gamma catch or multimer selection techniques. Patients are randomised to:

- standard best available antiviral drug therapy alone
- immunoprophylactic (Day 27) ACT prepared using Multimer Selection or Gamma Catch Selection in combination with standard best available antiviral drug therapy

The study tests the hypothesis that CMV-specific ACT based upon a prescribed T-cell dose/kg recipient body weight, can augment the impaired CMV immune function post-transplant and reduce the number of recurrent reactivations in patients following a primary reactivation event (and thereby reduce the requirement for antiviral drug therapy) without causing an increase in GvHD.

Individual groups will be compared for duration of antiviral therapy and number of reactivation episodes, plus GvHD incidence. Similar analyses will be performed for ACT versus no therapy .

The study subjects are sibling T cell-depleted allogeneic HSCT recipients where donor and recipient are both CMV seropositive. The primary objective is to evaluate the potential clinical benefit of prophylactic CMV-specific ACT following T cell-depleted allogeneic HSCT for reducing recurrent CMV reactivation. Secondary objectives are:

- to evaluate the effect of ACT on GvHD incidence;
- to evaluate the effect of ACT on the duration and number of episodes of antiviral drug therapy;
- to evaluate the effect of ACT on immunological endpoints;
- to evaluate the feasibility of centralised production and distribution of an ACT product.

The primary endpoint is the number of patients experiencing a recurrent episode of CMV reactivation after primary reactivation. Secondary endpoints are:

- incidence and severity of GVHD;
- duration of antiviral drug therapy (total days) and of viraemia (total days);
- incidence of CMV disease;
- laboratory evidence of reconstitution and persistence of CMV-specific immunity.

The number of recurrent CMV reactivations requiring treatment has been chosen as the primary endpoint because it represents a well-defined and clinically relevant measure of the potential therapeutic benefit of ACT to accelerate immune reconstitution in immunosuppressed patients following allogeneic HSCT. In addition, the total number of treatment days for recurrent reactivations will be considered as a secondary endpoint. Due to the requirement to delay immunoprophylactic ACT until following clearance of alemtuzumab, it is unlikely that ACT will have an effect on primary reactivation; hence the study is powered to detect reduction in subsequent (recurrent) reactivation episodes requiring antiviral drug therapy.

A minimum of 70 patients will be recruited across two arms:

Current status 14 UK centres open;

NCT 01077908 CMV IMPACT (clinical trials.gov)

UK CRN #5742

Key Q: Approval status

The product is commercially available in the UK currently (MHRA classification, 2007). Approval in other EU countries forthcoming on receipt of manufacturing authorisation as EMA have classed directly-selected cells using the streptamer technology as ‘not a medicinal product’ (2010).

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

The product may need to be both more cost-effective and efficacious than the current standard of care (ganciclovir and foscarnet) in order to be reimbursed. Transplants are commissioned by specialised commissioning groups. No tariff exists currently but the London SCG has taken the lead in developing a tariff for BMT.

Key Q: Nature of Product

Cell Medica selects naturally occurring CMV-Specific T-cells from a donor blood product using Stage Therapeutics Streptamer selection kit. The resulting cells are dosed at a maximum target dose of 5x10e4/kg (CD3+). The product is patient specific and the donor is the same as the one selected to donate the patient's initial stem cell transplant. Donor and patients are consequently highly MHC matched. Streptamers are MHC specific and currently 7 streptamers are available which covers approximately 80% of the population. Cells can only be selected from CMV seropositive donors (CMV latency approximately 60% in Europe).

Key Q: Make or Buy?

Cell Medica manufactures Cytovir CMV itself in the UK and does not plan to contract out this production.

Key Value Steps:

1. Non-clinical data not required
2. Ability to leverage completed published academic clinical data
3. Regulatory classification of product means the cells are commercially available.

Sources:

Cell Medica website:
http://www.cellmedica.co.uk/index.html
Selection Kit supplier
http://www.stage-celltherapeutics.com/auswahl/home.php

Background papers:

Rauser G, Einsele H, Sinzger C, Wernet D, Kuntz G, Assenmacher M, Campbell JD, Topp MS. Rapid generation of combined CMV-specific CD4+ and CD8+ T-cell lines for adoptive transfer into recipients of allogeneic stem cell transplants. Blood 2004;103(9):3565-72

Chakrabarti S, Mackinnon S, Chopra R, Kottaridis PD, Peggs K, O'Gorman P, Chakraverty R, Marshall T, Osman H, Mahendra P, Craddock C, Waldmann H, Hale G, Fegan CD, Yong K, Goldstone AH, Linch DC, Milligan DW. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. Blood 2002;99(12):4357-63

Einsele H, Rauser G, Grigoleit U, Hebart H, Sinzger C, Riegler S, Jahn G. Induction of CMV-specific T-cell lines using Ag-presenting cells pulsed with CMV protein or peptide. Cytotherapy 2002;4(1):49-54

Aubert G, Hassan-Walker AF, Madrigal JA, Emery VC, Morte C, Grace S, Koh MB, Potter M, Prentice HG, Dodi IA, Travers PJ. Cytomegalovirus-specific cellular immune responses and

viremia in recipients of allogeneic stem cell transplants. Journal of Infectious Diseases 2001;184(8):955-63

Cwynarski K, Ainsworth J, Cobbold M, Wagner S, Mahendra P, Apperley J, Goldman J, Craddock C, Moss PA. Direct visualization of cytomegalovirus-specific T-cell reconstitution after allogeneic stem cell transplantation. Blood 2001;97(5):1232-40

Watanabe N, Kamachi Y, Koyama N, Hama A, Liang J, Nakamura Y, Yamamoto T, Isomura M, Kudo K, Kuzushima K, Kojima S. Expansion of human CMV-specific cytotoxic T lymphocytes to a clinical scale: a simple culture system using tetrameric HLA-peptide complexes. Cytotherapy 2004;6(5):514-22

Reusser P, Fisher LD, Buckner CD, Thomas ED, Meyers JD. Cytomegalovirus infection after autologous bone marrow transplantation: occurrence of cytomegalovirus disease and effect on engraftment. Blood, 1990;75(9):1888-94

Meyers JD, Reed EC, Shepp DH, Thornquist M, Dandliker PS, Vicary CA, Flournoy N, Kirk LE, Kersey JH, Donnall Thomas E, Balfour HH. Acyclovir for Prevention of Cytomegalovirus Infection and Disease after Allogeneic Marrow Transplantation. N Engl J Med 1988;318:70-5

Clinical trials:
http://www.clinicaltrials.gov

Investor websites:
http://www.imperialinnovations.co.uk/index.php
http://www.wellcome.ac.uk/Investments/index.htm

Case Study Product Category 2: Autologous

Quy Biosciences Ltd.: MS-Ten

Brief Product Description and Indications:

Cultured and minimally-passaged mesenchymal stem cells of bone marrow origin for the treatment of tendon injuries. The product is autologous, i.e. it is implanted after culture and characterisation into the tendon of the patient from which the cells were derived.

Target Indications and Markets:

Key Q: Clinical indications

MS-Ten is indicated for the treatment of degenerative and acute lesions of the Achilles tendon. Further indications, such as rotator cuff injury (shoulder) are planned.

Key Q: Geographical target market

Initial studies are planned for the UK. While the initial market may be the EU, the USA clearly represents the largest market and is included in the development/regulatory plan. A USA subsidiary and a USA-based laboratory will be essential for both registration and commercialisation of the MS-Ten worldwide.

Further market research is projected.

Key Q: Competition

The technology is based on an equine model. Competitors in the equine and canine arena exist and might be expected to move into the human market.

A number of companies are offering now a “Named Patient” service for a variety of similar and dissimilar indications, with or without evidence of efficacy, and these are potential competitors.

Key Features of Company Business Model:

Key Q: Structure

Quy Biosciences Ltd. Is an SME with a working Board and a very small number of technical/administrative employees. Other services are contracted in as necessary.

The single “product” is applicable to other comparable indications. The company is based on a similar indication which is marketed to equine veterinary surgeons for the treatment of (principally) superficial digital flexor tendon (SDFT) injury. Extensive experience in the equine field has been amassed, with almost 2,000 horses successfully treated to date.

Other products are bought-in or in-licensed, such as platelet-enriched plasma from Pall Corporation, and hoof patches (patent held by the Royal Veterinary College; royalties paid on sales).

Key Q: Future strategy/Exit strategy

Development is contingent on the availability of funding, and the company is open to Venture Capital or partnership, e.g. perhaps with big pharma. Other models are being considered (see later)

Key Q: Portfolio

Apart from possibilities in the veterinary area, MS-Ten is a single "product" which nevertheless can be extended to other indications

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

Current investors are small enthusiastic shareholders. They are looking for increased value in their shares, which is likely to come ultimately from acquisition. MS-Ten development is likely to require additional funding from VCs who also look towards acquisition, or possibly partnership with e.g. big pharma.

Ways of financially exploiting the IP with respect to potential competitors are being explored.

Grants for aspects of development are currently being used and are being continually explored.

Key Q: Relationships with clinical KOLs

The company is building relationships with specialist clinicians, principally with a view to their involvement in clinical trials, but also with a view to the provision of a "Hospital Exemption" service.

Regulatory Strategy/Regulatory Status:

Key Q: Target approval routes

The company is focused on obtaining (initially) EU registration as a CBMP. The company has discussed its IMPD, draft specification and Phase 1 trial protocol with MHRA/EMA, and its regulatory route is clear. "Validation" (a so-called Phase 0) is a prerequisite and will comprise the current work on cultural and testing method development, technology transfer to a GMP facility, and "real-time" validation of the entire procedure.

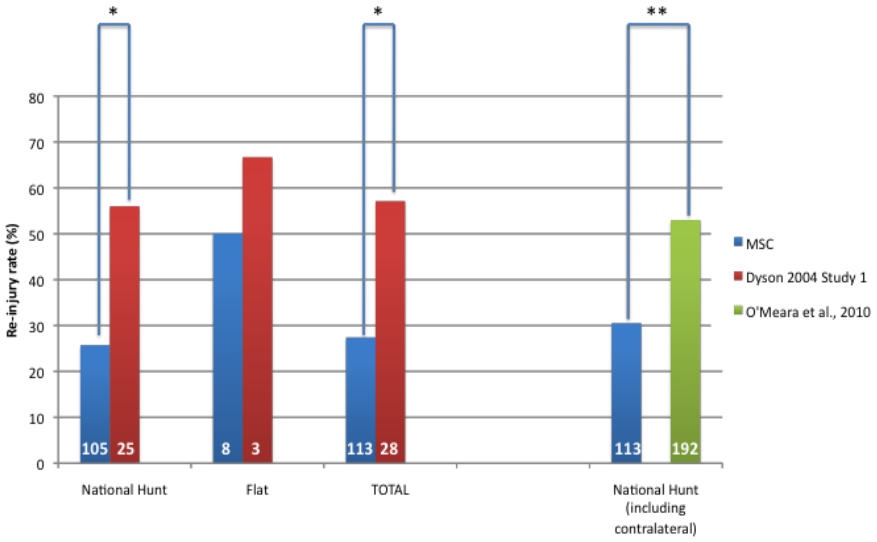
Key Q: Clinical data and time to approval

The extensive experience in equines provides "proof of concept", and directly relevant safety and efficacy data significantly superior to that normally available for new human products/indications.

Validation and Phase 1 (first-in-man) estimated to take a minimum of 18 months. Phase 2/3 will take c. 2 years with regulatory approval 2016.

Key Issue: These are minimum timings and are dependent on adequate financial support. Can investment and intra-company support maintain this length of development? Demonstration of efficacy at Phase 1 marks a milestone which would attract further investment.

Figure 1. Re-injury rate of National Hunt racehorses with tendon injuries following treatment with autologous MSC therapy (blue) or other conventional treatments (red or green)



From Godwin et al (2012)

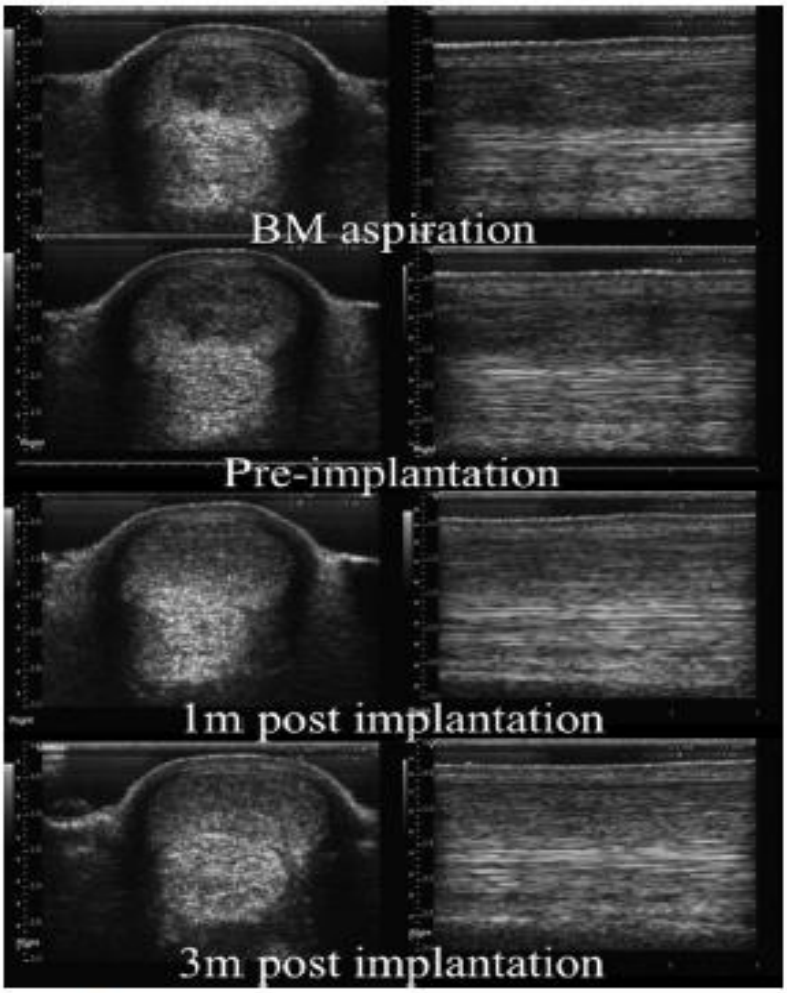


Fig 2: The ultrasonographic appearance of a superficial digital flexor tendon lesion after treatment with 2×10^6 mesenchymal stem cells. Note the rapid filling-in of the lesion and the absence of apparent adverse effects.

Reimbursement Strategy/Reimbursement Status:

Key Q: Requirements for reimbursement

Reimbursement will be contingent on demonstration of efficacy in controlled trials at Phase 2/3. Achilles and rotator cuff injuries have a high social cost and cost/benefit analysis will be important.

A number of KOLs have expressed interest in use of the product under the Hospital Exemption Scheme. This cannot proceed before completion of the 'first in man' study (see above).

Q: Can Hospital Exemption use provide significant income?

On completion of a 'first in man' safety study MS-Ten could be provided at selected clinics on a hospital exemption basis and would provide some limited income.

Manufacturing and Supply Strategy:

Key Q: Nature of product

(Living) autologous cultured cells. "Finished product" with a very limited life.

Key Q: Make or buy?

The product is made to Quy SOPs at a limited number of contracted specialist laboratories.

Production has been helpfully discussed with NHS BT (Simon Ellison). Their analysis of the manufacturing and supply issues is attached as Appendix 1

Publications:

AWAD, H.A. et al., (2003). Repair of patellar tendon injuries using a cell-collagen composite. J. Orthop. Res., 21, 420-431

DUDHIA, J., BECERRA, P., VALDES, M.A., NEVES, F., HARTMAN, N.G., FISKE-JACKSON, A., SMITH, R.K.W. (2011) British Society for Matrix Biology Spring 2011 meeting abstract

GODWIN, E. E., YOUNG, N. J., DUDHIA, J., BEAMISH, I. C. and SMITH, R. K. W. (2012), Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Veterinary Journal, 44: 25–32

GUEST, D. J., SMITH, M. R. W. and ALLEN, W. R. (2008), Monitoring the fate of autologous and allogeneic mesenchymal progenitor cells injected into the superficial digital flexor tendon of horses: Preliminary study. Equine Veterinary Journal, 40: 178–181.

GUEST, D. J., SMITH, M. R. W. and ALLEN, W. R. (2010), Equine embryonic stem-like cells and mesenchymal stromal cells have different survival rates and migration patterns following their injection into damaged superficial digital flexor tendon. Equine Veterinary Journal, 42: 636–642.

SMITH, R.K.W., KORDA, M, BLUNN, G.W. & GOODSHIP, A.E. (2003). Isolation and implantation of autologous equine mesenchymal stem cells from bone marrow into the superficial digital flexor tendon as a potential novel treatment. Equine Vet. J., 35 (1) 99-102.

SMITH, R.K.W. & WEBBON, P.M. (2005). Harnessing the stem cell for the treatment of tendon injuries : heralding a new dawn? Br. J. Sports Med. 39, 582-584

SMITH, R.K.W. (2008) Mesenchymal stem cell therapy for equine tendinopathy. *Disabil. Rehabil*. 30: 1752-1758

SMITH, R.K.W. (2009). Principles of stem cell therapy in the horse – the science behind the technology. Pferdheilkunde 24 (4) 1-4.

SMITH, R.K.W., DUDHIA, J., YOUNG, N., BEAMISH, I., FISKE-JACKSON, A., BECCERRA, P., VALDES, M., NEVES, F. HARTMAN, N., GOODSHIP, A. Effects of stem cell treatment in naturally occurring tendon and ligament injuries in horses. (2011) World Conference on Regenerative Medicine 2011 keynote lecture abstract.

TAYLOR, S.E., SMITH. R.K.W., CLEGG, P.D. (2007). Mesenchymal stem cell therapy in equine musculoskeletal disease: science, fact of clinical fiction? Equine Vet. J., 5, 39.

YOUNG, N.J., DUDHIA, J., GOODSHIP, A.E., SMITH, R,K,W. (2010) Mesenchymal Progenitor Cell Therapy for Tendon Regeneration. Paper no. 280. 56th Annual Meeting of the Orthopaedic Research Society

Other papers on a comparative assessment of a series of equine cases, and a controlled study comparing repair of tendons, and stem cell fate in treated and untreated horses, are in press or under preparation.

Key Value Steps: Identified:

1. IP is secure and considerable investment is being made to render the Patents more exclusive.
2. Extensive database of usage in almost 2,000 horses
3. Convincing evidence of safety and efficacy in controlled trials in horses.
4. Route to regulatory approval is established, although formal validation of the cultural process and trials in man has yet to start.
5. Availability of funding support.
6. Completion of “Phase 0” validation phase and product definition and specification.
7. Approval for the Phase 1 trial
8. Completion of Phase 1; approval for Phase 2/3.
9. Market approval; EU/USA.

Key External Interactions:

State any key interactions with members of the supply / value chain.

- Dialogue with MHRA established and route to MA defined.
- Discussions with clinical KOLs initiated
- Discussions with potential manufacturers/suppliers initiated (e.g. NHS BT)
- Relation to market providers (e.g. NHS, BUPA etc.) and to investment expertise is being established.

Sources:

Quy/VetCell website:
www.vetcell.com

Research papers referenced above

Further information:
Medicines – Case Study review – Autologous Supply Chain – Quy (prepared by Simon Ellison/Richard Schofield of NHS BT)

	Now	5-10 years	10-15 years
Ordering Characteristics			
1. Frequency of purchase	100-150 orders per annum in the equine market (UK only)	Looking at Human mkt - 500 increasing to 2000 per year per indication	Human Market will reach a plateau probably at approx 5000/year and decrease once allogeneic stem cells become available
2. Purchasing effort	Easy – Two phase purchase - place call to lab, take sample and dispatch via Royal Mail. Kit provided by lab. Requires training for taking of samples – explanation of product is complex.	Probably very little competition, methodology unlikely to change	Some competition in market place. Availability of sample kits and ease of use may be important in choice of lab to send kit to. Competition from allogeneic stem cell products will kick in during this period.
3. Rapidity of consumption	One-off requirements (or very few repeats)	One-off	One-off
4. Significance of purchase	High – ability to continue or recover fitness levels is important Significant value if can rehabilitate race horse	For humans the repair will possibly replace other more expensive treatments in terms of replacing need for surgery Similar value to "equine patients" if professional sportsman can be returned to fitness	May become an 'elective' procedure to improve under-performing or sub-standard tendons.
5. Waiting time	14-21 days in lab, 2-3 days in transit	Will be same for human treatment but experience for patient will depend on hospital waiting lists	Optimisation of process will reduce wait.
Product Characteristics			
6. Replacement rate	Zero	Zero	Zero
7. Gross margin	Medium – current price to vets around £800. Cost for culture £300	£8-10k per patient	Reducing with volume and competition

8. Adjustment	Will need to be translated into GMP process and clinical studies completed	For human version the benefits of the approach over existing treatments will need explanation and demonstration	
9. Searching Time	Zero – treatment centres aware of service	Will need sales and marketing operation	
10. Unit value	Medium-High - £800 per item for FG. Initial sample has no commercial value	High one off cost but low "lifetime" cost	
11. Product complexity	3 part process. First is to take sample of bone marrow from patient. Second is to culture the stem cells from the sample and the third is to implant stem cells back into damaged region in the patient	3 part process. First is to take sample of bone marrow from patient. Second is to culture the stem cells from the sample and the third is to implant stem cells back into damaged region in the patient	
12. Product life-cycle stage	Introduction phase	Rapid growth	Early maturity
13. Volatility of demand	Seasonal variation due to performance event seasons for horses	Steady all round demand	
14. Perishability	Limited shelf life for initial sample (48hrs) and cultured implant (48hrs). Sampling Kits need no special conditions		
Market Factors			
15. Target market	Speciality: Equine. Human trials UK market	Speciality: Human and other veterinary markets (Canine CCL) Growth in other regions	Speciality
16. Rate of technological change	Low	High as new innovative treatment that will replace pharmaceuticals and allograft	Unknown
17. Intensity of competition	Low	Low	Low - Medium
18. Geographic concentration of market	Mkt lies within 24 hrs transport of processing centre		Optimisation and developments in cryo storage may extend geographic reach

Regenerative Medicines – Case Study review – Autologous Supply Chain – Quy Distribution Channel.

Product Characteristics

The key characteristic of the Quy tendon therapy is the requirement to take and subsequently deliver a sample of bone marrow to the cell expansion facility. This implies both an inbound and outbound distribution channel requirement.

Sampling kits to obtain and preserve the inbound sample are distributed by Quy and therefore a need to ensure clinical centres are stocked with these kits is important. The sampling kits need no special conditions and can be dispatched via mail service.

Inbound samples are required to be kept cool and must reach the processing centre within 48hrs of being taken from the patient - this can be achieved by using validated cool boxes and utilising an overnight courier service.

The final product from expanded cells must also be kept cool (not frozen) and needs to be implanted within 24-48 hours of dispatch from the processing facility (it must be re-suspended in bone-marrow supernatant which has been kept frozen at the clinical centre from the time of sampling and re-constituted prior to implantation). The implantation procedure must be completed the day following receipt of the expanded cells from the processing centre.

The product is a one-off usage and no ongoing storage of collected samples required other than any regulatory requirements. Since there is no on-going repetition of treatment beyond the initial bone marrow aspiration and the final stem cell implantation there is no need for widespread clinical treatment centres.

The final product is relatively stable and the temperature/time limitations can bet met with in-expensive shipping containers and available courier options. This mitigates against the need for processing and treatment centres to be in close proximity.

Inbound samples are relatively inexpensive and loss of the sample would be inconvenient but not catastrophic. No special shipping management would be required in this example.

Outbound product from the processing sites to the treatment centres is more valuable – both in cost and in effect (the time taken in any need to re-sample, re-expand and re-ship would be a long and potentially complicated treatment). For outbound shipments consideration should be given to a higher level of shipment supervision, tracking and traceability.

Market Characteristics

The target market for these products is specialised (currently equine but if transferrable to human situations it would focus initially on sports injuries of a specific type [Achilles tendon] – this would expand to become available to a reasonable proportion of the estimated 20-30,000 patients per annum suffering from Achilles tendinopathy that is not responsive to physiotherapy.

The current product is used by approximately half of the specialist equine veterinary practices in UK. In humans it would be expected to follow a similar route with specialist sporting injury centres and orthopaedic hospitals being the centres offering the treatment.

The market must be within 24hrs of transportation from the processing centre to allow time for delivery and re-constitution in bone-marrow supernatant before re-implantation. On a national basis this would indicate one processing centre would be adequate. On an international basis the need for separate centres in each country should be explored versus the requirements for international transportation of these types of material and the time-lag effect this may cause. This in turn should be weighed against the market volume and cost of processing centres.

Competitive products are unlikely to enter the tendon and ligament market until allogeneic stem cell therapies become available with the exception of clinics that are offering hospital exemption treatments. Cost of entry versus size of market is likely to be a barrier to competitors which also mitigates against intensive distribution or multiple processing facilities.

Ordering characteristics

Order volumes and frequency of purchase are relatively low and will continue to be low indicating that a single distribution point would be acceptable.

The significance of each purchase is high and therefore control of the product from source to treatment centre is important indicating that a single point of distribution would be preferred.

The sampling process and implantation process requires to be closely followed, monitored and supervised by the processing centre. This further indicates a centralised, single step distribution channel.

Cost estimations

Transportation of goods is commonly expected to consume around 3-6% of the selling price of a product. Anything above 8% would be considered high and focus attention in cost management. Above 10% would be considered significant and distribution would then be considered as a driver in the cost make-up.

For the equine treatment the sampling and transport costs are:

1. Sampling kit (£55)
2. Transport box (£20)
3. Shipping to lab (£35)
4. Outbound finished product (£35)

Total accumulated cost = £145 of which the shipping costs are £70. The market cost of the equine treatment is £750 therefore the shipping adds 9% to the treatment cost.

The expected market cost of this treatment for humans is in the region of £8000 per treatment thus in this example transportation costs would be less than 1% of the treatment cost.

Summary

There are no overriding requirements in environment or time controls for these products that would indicate specialist distribution methods should be deployed (outside of HTA requirements to “track and trace”) other than the effect of total loss of the final product or the failure of the finished product due to failure in the environment/time control. The use of ‘validated’ packaging does not protect against failure and may not be sufficient to reveal that failure has occurred – product may have gone over temperature for a significant period of it’s journey – unless temperature logs have been used in the transportation. These would

add significantly to the cost unless recovered. The 'cost' of non-delivery or failure (and the probability of it occurring) should be weighed against the added cost of environment logging and increased supervision of the shipment in deciding any final distribution channel.

This product would be best suited to a supply chain that: -

- Is able to economically manage the process from patient-manufacturing-patient with minimal risk.
- Can manage the risk of loss/failure of product within agreed parameters
- Can track and trace the cells/tissue at all logistical points

TiGenix NV: ChondroCelect®

Brief Product Description:

ChondroCelect® is a cell-based medicinal product centrally approved in Europe as the first and currently only ATMP with a generic description of: "Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins." It has been developed as part of TiGenix' focus on regenerating motion for damaged and osteo-arthritic joints and is intended for the repair of the articular cartilage of the femoral condyle.

Target Indications and Markets:

Key Q: Clinical indications

ChondroCelect® is indicated for the repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present.

Key Q: Geographical target market

The primary market is Europe where ChondroCelect® is currently available in the UK, Benelux, Germany, Austria, Spain and Finland. It is soon to be available in, Portugal and France. Clarity on the regulatory pathway for the US market was obtained during a meeting in March 2010 at which the FDA requested an additional study before the filing of a Biologic License Application (BLA) and invited TiGenix to seek Special Protocol Assessment.

The European Medicines Agency (EMA) had also asked for an additional confirmatory study as a part of the requested risk management plan. This request was in the form of a post-approval commitment.

The protocol for this European confirmatory study, for which the design was agreed upon in a scientific advice meeting with the EMA, was presented during the meeting to the FDA. The initial feedback on the proposed protocol was positive and it is likely that the outline of the study can also be used for the US. TiGenix will interact with the regulatory agencies to assess the possibility for alignment of the protocol for it to fit the combined purpose of the confirmatory trial in Europe and the additional study in the US, and decide on the steps forward from there.

Gil Beyen, CEO of TiGenix, made an interesting comment at the time of the press release in March: "*This request for an additional study highlights the general difficulty to bring innovative products to market. The path will be longer than anticipated, but we believe that our 8 years of clinical trial experience with ChondroCelect® will help us to remain at the forefront of the field.*"

In the US only one cell-based product has obtained a Biologics License to date, and this occurred in 1997.

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

The market for the treatments of full-thickness (ICRS grade 3-4) defects is highly fragmented and immature. Current treatment options comprise a range of surgical treatments and conventional ACI-based therapies. Consequently, obtaining accurate data that provide a detailed breakdown of market share by product or treatment type is very difficult. However, the Company believes that ChondroCelect®'s validated efficacy, ease of use and novel

mechanism of action should enable the product both to capture market share from existing surgical treatments and to grow the current cell-based therapy market significantly.

In the U.S., only one cell-based ACI product, Carticel®, from Genzyme (Cambridge, MA), has obtained FDA approval. In 2000, the indication for Carticel® was narrowed to second-line treatment, for use in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure. Several other companies in the United Sates are making efforts to enter the cartilage repair market. ISTO Technologies (in partnership with Zimmer), HistoGenics and Prochon are reported to be in Phase 2 of clinical development. To the best of the Company's knowledge, no Phase 3 clinical trials have been started with cell-based products for cartilage repair in the US. The development and validation of an acceptable potency assay is a key requirement by the FDA in order to be allowed to start Phase 3 efficacy studies.

In Europe, where the barriers to entry for ACI services and cell-based products historically have been relatively low, different companies are active in the field. Examples include Verigen, which was acquired by Genzyme in 2005, Codon, CellGenix, Tetec, FAB, BioTissue, ArthroKinetics and Cellmatrix. Given the new regulatory framework for Advanced Therapy products, most of these companies are unlikely to remain in the market after 2012 unless they can demonstrate clinical efficacy in randomized controlled trials. As far as the Company is aware, only Genzyme has performed a randomized controlled Phase 3 trial in view of obtaining central market approval by the end of 2012. Tetec was said to have started, but no confirmation has been obtained.

Alternative competition may come from cell-free products that also target the cartilage repair market, which will generally be brought to market through the medical device regulatory route. This route is less rigorous than the pharmaceutical or medicinal products regulatory route that TiGenix is following. Different smaller companies such as BioTissue and ArthroKinetics are attempting to bring one-step, cell-free products to the market through the CE-marking route in Europe. Also larger orthopaedic groups such as Depuy (a Johnson & Johnson company) have initiated research projects and are performing clinical trials with cell-free products. Other competitors in this space, especially for the smaller lesions, are Smith & Nephew and Kensey Nash which target the repair of (smaller) cartilage defects with osteochondral plugs.

Key Features of Business Model:

Key Q: big pharma, SME, IP company, virtual company

TiGenix NV is an SME employing approximately 75 people, that has used significant private investment and an IPO (listed on the NYSE Euronext in March 2007, at €5 per share, opening at €5.89 and closing at €5.62 and currently at less than €1 per share) to raise sufficient funds to develop, manufacture and commercialise its lead product, as well as to fund the acquisition of Cellerix and to continue its R&D efforts to develop a product pipeline. The company has raised in excess of €88Million since its incorporation on February 21st, 2000.

Key Q: Target Exit Strategy

The company is publicly listed and has raised significant funds from a large variety of investors to develop a solid platform for product development as well as establish a strong core commercial team to bring its lead product, ChondroCelect®, to market. It now has a commercial core team in place and is well positioned to develop the market for ChondroCelect® as well as to continue to develop its pipeline stem-cell platform products. The company's products in development stage include Cx601 for the treatment of complex perianal fistula in Crohn's disease patients; and Cx611 to treat rheumatoid arthritis. Its

products in preclinical stage comprise Cx621 and Cx911 for autoimmune disease; and Cx603 and Synovial MSCs for osteoarthritis.

TiGenix is a biomedical company that focuses on 'Living Medicines'. The Company is exploiting the power of Regenerative Medicine to develop durable treatments, validated through controlled clinical trials, for damaged and osteoarthritic joints, as well as developing a strong stem-cell based product pipeline. The Company's lead product, ChondroCelect® for cartilage regeneration in the knee, is the first cell-based product that has successfully completed the entire development track from research, through clinical development to central European registration as a medicinal product. Based in Leuven, Belgium, TiGenix is listed on Euronext Brussels after a successful IPO in March 2007.

At that time the Company was, and today still is, the first and only company that has demonstrated positive Phase 3 results in a randomised controlled clinical trial for a cell-based product for cartilage repair, that has subsequently led to a central market authorization as an ATMP from EMA.

On October 6, 2009 ChondroCelect® received central European Marketing Authorisation as the first Advanced Therapy Medicinal Product (ATMP) under the new Advanced Therapies Regulation. On June 26, 2009, the Company had already received a positive opinion from the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) on its European Marketing Authorisation Application (MAA) for ChondroCelect®.

The Company is now in the process of commercialising the product in selected European markets, and is preparing the confirmatory study which will allow filing for regulatory approval in the U.S. Further leveraging its experience in developing, manufacturing and registering cell-based products, the Company is developing a portfolio of products that address specific musculoskeletal and auto-immune problems and that can be the basis for realising the Company's ambition to develop a leadership position in the new and promising field of Regenerative Medicine.

Regenerative Medicine holds the promise to be the next evolution of medical treatments. In 2006, the U.S. Department of Health and Human Services wrote "This new field holds the realistic promise of regenerating damaged tissues and organs in vivo (in the living body) through reparative techniques that stimulate previously irreparable organs into healing themselves. (…) This revolutionary technology has the potential to develop therapies for previously untreatable diseases and conditions. (…). Beyond the obvious health benefits of Regenerative Medicine, this technology is desperately needed to combat rising healthcare costs". Also the European authorities have recognised the importance of this new field. On the website of the EMA (http://www.emea.europa.eu/htms/human/advanced_therapies/intro.html) one can read: "Advanced therapy medicinal products (ATMPs) are medicinal products for human use, and are based on gene therapy, somatic cell therapy or tissue engineering. They offer groundbreaking new treatment opportunities for diseases and injuries of the human body".

Western societies are characterised by ageing populations that place an increasing emphasis on high quality of life and life-long mobility, and, as such, musculoskeletal problems represent a large and growing unmet medical need. Current therapies do not provide satisfying, long-term durable repair and the Company therefore believes there is a need for more effective, regenerative treatments aimed at durable restoration of the function of damaged and diseased tissues.

TiGenix' lead product, ChondroCelect®, uses the patient's own cells as a basis for a quality-controlled medicinal product for cartilage regeneration. The Company has identified a

specific set of genetic markers to identify potent cartilage-forming cells. These cells have demonstrated the ability to form stable cartilage when implanted *in vivo*. This is believed to be critical for the durable repair that is needed to prevent degeneration of the joint. Cartilage defects that have not been properly treated are more likely to lead to osteoarthritis (OA).

Regulatory changes in both Europe and the U.S. have greatly raised the efficacy threshold and burden of proof required for the approval of cell-based therapies. From its incorporation, the Company anticipated such an increasingly strict regulatory framework for new cell-based therapies and so developed ChondroCelect® as a medicinal product according to the principles of 'evidence-based medicine'. With a product that was the first to generate positive data from controlled Phase 3 clinical trials for this indication, and that was the first cell-based product to obtain central European Marketing Authorisation, TiGenix has demonstrated to be well positioned to capitalise on this changing regulatory environment. From December 30, 2008 onwards, a new regulatory framework has applied to ATMPs across the European Union. With the new ATMP regulation in place, all manufacturers of cell therapy, gene therapy and tissue engineered products will, after a transition period, have to meet the same standards of clinical validation and product quality as regulated by the EMA.

The pipeline development and partnering activities of the Company are focused on optimising the delivery methods of the cell products, and on broadening the product offering to other joints and other musculoskeletal tissues. The principal approach to further increase the ease of use of ChondroCelect® is through the combination with a biological cell carrier (membrane or scaffold) aimed at enabling arthroscopic or minimally invasive implantation of the cells (ChondroCelect-3D). Through further improvements of the cell culture methods the Company is investigating to further enhance the potency of its cell-based products. This opens the possibility of addressing larger cartilage defects and of treating more advanced and osteoarthritic joint surface lesions. The development of a proprietary stem cells platform aims at broadening the product offering to other musculoskeletal tissues and to move to allogeneic approaches in the area of auto-immune diseases. In addition, the Company's researchers are investigating new targeted therapies that can be used to modulate certain biological pathways. The Company also constantly evaluates opportunities to acquire businesses and technologies that it believes may be complementary to its business activities.

The Company believes its competitive strengths are:

• **A clear focus on a major unmet medical need.** TiGenix has a clear and singular focus on Regenerative Medicine approaches to treat joint disorders and OA, which are among the largest and fastest growing disease areas in Western societies, and represent major unmet medical needs. (Lidgren L (2003), The bone and joint decade 2000-2010, Bull.World Health Organ 81: 629.)

• **Demonstrated ability to develop cell-based products.** Starting from a strong scientific base, focused on the identification and characterisation of cell populations with specific biological functions, and building on state of the art clinical validation processes, including the successful completion of a randomised Phase 3 clinical trial, TiGenix has demonstrated its ability to bring a novel cell-based product 'from Bench to Bedside'.

• **First centrally approved ATMP product in Europe.** TiGenix' lead product, ChondroCelect®, is the first cell-based product that applied for central regulatory approval in Europe as a medicinal product. It was the first to receive a positive opinion from the EMA, and the first approved ATMP in Europe.

• **First product in the market - Commercial core team in place**. In anticipation of the launch of its lead product, and recognizing the importance of direct contact with the first prescribers of this innovative product, TiGenix established a high-level commercial core team consisting of experienced people with medical, scientific and commercial backgrounds, and with experience in pharmaceutical products as well as medical devices. With the acquisition of Cellerix, TiGenix now has a very strong product pipeline that can be developed and subsequently commercialised.

• **In-house cell manufacturing capability**. Recognizing the importance of efficient production of cell-based products for commercial success, the Company has since its start focused on manufacturing excellence. The in-house competence base is believed to be an important asset to develop a leadership position in the field of Regenerative Medicine.

• **Key opinion leader support**. The evidence-based approach TiGenix has followed throughout the development of ChondroCelect® has been appreciated by leading orthopaedic surgeons. The composition of the Company's scientific and clinical advisory board is a reflection hereof.

• **Innovative treatments in the pipeline.** TiGenix' in-depth know-how of the biology of stable cartilage formation and the signaling pathways associated with OA forms the basis of the ChondroCelect® product platform. In combination with the Company's proprietary stem cell technology, it offers the potential to broaden the product portfolio to the treatment of other joints and other musculoskeletal tissues, such as meniscus, and diseases of the auto-immune system, for which applications are currently being examined by the Company.

• **Solid intellectual property.** TiGenix has built a strong intellectual property portfolio consisting of patents and trade secrets surrounding the Company's genetic markers, cell culture methods and stem cell technology. The Company's core patents have been granted in Europe and the U.S., while several others are pending. This portfolio is further extended through the acquisition of Cellerix.

• **Experienced management team.** TiGenix' management team contains a strong mix of highly experienced professionals with a track record in the biomedical and pharmaceutical fields. The team has shown its ability to deliver by bringing the Company's lead product to the market, and in doing so has built up a unique expertise in the field of Regenerative Medicine.

All the above points to a sound business strategy where the company continues to demonstrate the appetite for success in the field of regenerative medicine, seeking to grow through innovative product development and technology acquisition to expand into a solid leadership position regenerative medicine company.

Key Q: Other products in portfolio

Further to ChondroCelect® the company also has an off-the-shelf scaffold called ChondroMimetic, which is a collagen based implant for the repair of smaller traumatic osteochondral lesions. Through the acquisition of Cellerix there are now several products in development stage including Cx601 for the treatment of complex perianal fistula in Crohn's disease patients; and Cx611 to treat rheumatoid arthritis. Its products in preclinical stage comprise Cx621 and Cx911 for autoimmune disease; and Cx603 and Synovial MSCs for osteoarthritis. With the development of this pipeline, TiGenix is now ideally placed to continue to play a leadership role in the regenerative medicine industry.

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

The Company was incorporated on February 21, 2000 for an unlimited duration. Since its incorporation, the Company raised approximately €88.1 million in equity financing. In the first years, the Company raised approximately €1 million in seed financing. In September 2003, the Company closed a second financing round of €12 million. During this round, four institutional venture capital (VC) companies invested in TiGenix (ING België NV, Auriga Ventures II FCPR, Fagus NV and Capricorn Venture Fund II NV).

In November 2005, TiGenix completed a third financing round of €16 million, with both existing and new investors. In this round, international investors from the United States of America (U.S.) (HSS Ventures Inc.) and Japan (ITX Corporation) were among the new investors. In March 2007, the Company listed on Euronext Brussels through an Initial Public Offering (IPO), raising a total of €46 million. In June 2009, the Company raised another €5.4 million through a private placement to secure the financing of its additional production facility. On December 15, 2009, a sixth financing round of €7.7 million was completed through a private placement, further details of which are provided below. In addition to the equity financing described above, a contribution in kind was performed on November 30, 2009, at the acquisition of OrthoMimetics. In 2011 TiGenix concluded a share swap acquisition of the Spanish company Cellerix, generating a further €33Million. Other sources of funding include technology grants by the Flemish government in 2000 (€992,465, which was fully paid), 2003 (€585,990, of which €574,899 was paid) and 2008 (€1,800,000, to be paid in the course of 2009, 2010 and 2011), a European FP7 grant in 2008 (€1,156,500, part of which was paid in the course of 2008 and part of which will be paid in the course of the following years), as well as various soft loans, income from licenses and research collaborations. As mentioned, the Company is listed on Euronext Brussels since March 22, 2007. Its current market capitalization amounts to approximately €63 million.

DETAILS ON THE ADMISSION TO TRADING OF THE PRIVATE PLACEMENT SHARES

Issuance of the Private Placement Shares

The meeting of the board of directors of December 9, 2009 resolved upon a capital increase within the framework of the authorised capital by way of a contribution in cash through the issuance of maximum 10% of the outstanding number of shares, i.e. 2,866,186 new shares, subject to the condition precedent of subscription to and confirmation of the capital increase. During its meeting of December 10, 2009, the board of directors decided to issue 2,204,300 new shares at an issuance price of €3.50 per new share, resulting in a capital increase of €7,715,050 (issuance premium included). On December 15, 2009, the realization of the capital increase for an amount of €7,715,050 (issuance premium included) through the issuance of the Private Placement Shares was confirmed.

The board of directors did at the occasion of the issuance cancel the preferential subscription right of the existing shareholders in accordance with Article 603 juncto Article 596 of the Belgian Company Code.

Issuance price of the Private Placement Shares

The issuance price of the Private Placement Shares (fractional value plus issuance premium) at which the Private Placement Shares were subscribed to within the framework of the Private Placement amounted to €3.50 per Private Placement Share.

This issuance price was determined by the board of directors of the Company upon advice of the lead managers and on the basis of a book-building procedure, in which only qualified institutional investors could participate, and taking into account various relevant qualitative

and quantitative elements, including but not limited to the number of shares requested, the size of the orders received, the quality of the investors submitting such orders and the prices at which the orders were made, as well as the market conditions at that time.

Purpose of the Private Placement

The principal purposes of the Private Placement were to support the Company's growth and to increase the Company's capitalisation and financial flexibility.

The Company intended to use the net proceeds of the Private Placement for research and development, clinical trials, sales and marketing, working capital, capital expenditure, acquisitions if and when they present themselves, and other general corporate purposes.

Key Q: Define any relationships with clinical KOLs

The scientific advisory board is made up of the following:

Name	**Institute**	**Position**
Frank Luyton, MD., PhD.	Katholieke Universiteit Leuven (Belgium)	Professor of Rheumatology
August Verbruggen, MD., PhD.	University of Gent (Belgium)	Professor of Rheumatology
Stefan Lohmander, MD, PhD.	University of Lund (Sweden)	Professor of Orthopaedic Surgery
Hari Reddi, PhD.	Univ. of California at Davis (US)	Prof. Ortho., Director of Centre for Tissue Engineering
Richard Coutts, MD, PhD.	University of California, San Diego (US)	Professor of Orthopaedic Surgery
Daniel Grande, PhD.	North Shore University Hospitals, Long Island (US)	Director of Orthopaedic Research

The clinical advisors to the Company include:

Name	**Institute**	**Position**
René Verdonk, MD, PhD	Universiteit Gent (Belgium)	Professor Orthopaedic Surgery
Johan Vanlauwe, MD	Katholieke Universiteit Leuven (Belgium)	Orthopaedic Surgeon
Bert Mandelbaum, MD	Santa Monica Orthopaedic and Sports Medicine Group (US)	Orthopaedic Surgeon
Matthias Steinwachs, MD	Schultess Clinic, Zürich (CH)	Orthopaedic Surgeon
Nicholas Scaglione, MD	North Shore University Hospitals, Long Island (US)	Orthopaedic Surgeon
Daniël Saris, MD, PhD	University Medical Center Utrecht (NL)	Orthopaedic Surgeon

Key Q: Background on investors

Breakdown of shareholders by percentage (as of June 6, 2011):

Shareholder	Number of shares	% of outstanding shares
Genetrix Life Sciences AB	5,835,379	6.40%
CX EBIP Agreement SL*	1,905.144	2.09%
Subtotal of Genetrix group	***7,740,523***	***8,49%***
Novartis Bioventures LTD	5.534.905	6.07%
Roche Finanz AG	5.534.905	6.07%
Ventech SA	5.195.199	5.70%
Ysios Capital Partners SGECR	4.760.342	5.22%
LSP III Management BV	4.445.053	4.88%
Biopartners Capital SLU	2,977,440	3.27%
Navarra Iniciativas Empresariales SA	1,693,412	1.86%
Bankinter Capital Riesgo I FCR	1,457,732	1.60%
Suro Capital SA SCR	1,243,746	1.36%
Nerel SL	818,410	0.90%
JV Risk Technologies SL	728,861	0.80%
Inversora Bico SL	443,869	0.49%
A&G Global Sicav-Midleton Fund	147,949	0.16%
Capital Riesgo de la Communidad de Madrid SASC	128,661	0.14%
Individuals acting in concert with the above on the basis of a lock-up agreement	1,963,395	2.15%
Subtotal of shareholders acting in concert on the basis of a lock-up agreement	***44,814,402***	***49.18%***
Mijnen NV	3,000,000	3.29%
LRM NV	200,000	0.22%
Subtotal of LRM group	***3,200,000***	***3.51%***
ING Belgium NV/SA	4,471,682	4.91%
BNP Paribas	2,534,098	2.78%
Gemma-Frisius Fonds KU Leuven NV	1,852,958	2.03%
A. van Herk / O.G.B.B.A. van Herk BV	1,699,962	1.87%
Subtotal on the basis of transparency declarations	***58,573,101***	***64.28%***
Other **shareholders**	32,549,565	35.72%
Total number of TiGenix shares	***91,122,667***	***100%***

Regulatory Strategy/Status:

Key Q: Target approval routes

Regulation by governmental authorities worldwide is a significant factor in the development, manufacture, commercialisation and reimbursement of TiGenix' product portfolio. All of the Company's products will require marketing approval, or licensure, by governmental agencies prior to commercialisation. Human medicinal products are as a rule always subject to rigorous preclinical and clinical testing and approval procedures of the FDA in the U.S., EMA in Europe and similar Regulatory Authorities in other countries. Various governmental statutes and regulations also govern or influence testing, manufacturing, safety, labelling and record keeping related to such products and their marketing. State, local or other authorities may also regulate pharmaceutical manufacturing facilities. The process of obtaining such approvals and the subsequent compliance with the appropriate statutes and regulations require the expenditure of substantial amounts of time and money.

The Company believes that the key to success in cell- and tissue-based therapies is to excel in "evidence-based medicine". Only by proving efficacy in prospective randomised clinical trials and by demonstrating the health-related economic benefits in well-designed pharmacoeconomic studies, will it be possible to convince Regulatory Authorities of the overall benefits provided by the use of these products. Under "evidence-based medicine", it is no longer sufficient to solely demonstrate the safety of cellular products. Their efficacy and potency must also be demonstrated and validated. The Company anticipated this early on and so positioned its cell-based products as defined medicinal products.

Since cell-based therapies are a relatively new field, the regulatory framework for these products is still developing. When TiGenix started designing its first clinical trials for ChondroCelect®, no clear regulatory framework for cell-based products existed in Europe. The Company therefore used an FDA guidance document, describing the regulation of products for cartilage repair as biologics (guidance for products comprised of living autologous cells intended for structural repair (MAS-cells; Docket No. 95N-0200)).

TiGenix decided to set up a fully controlled, prospective randomised clinical trial in compliance with GCP requirements - deriving from Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use - as well as related implementation measures and applicable guidelines, thus anticipating the future regulatory requirements of the European Regulatory Authorities.

This regulatory anticipation has proven to be the right choice, as cell-based products are now clearly classified as biological medicinal products, also in Europe. From December 30, 2008 onwards, a new regulatory framework has been implemented, regulating the development and market access of all ATMPs including tissue-engineered, somatic cell therapy and gene-therapy products across the European Union ((Regulation (EC) No 1394/2007 of 13 November 2007, published on December 10, 2007.) The implementation of the ATMP regulation in Europe creates a regulatory environment for the above mentioned product categories that is similar to the one existing for biologicals, both in Europe and the US.

According to the 2009 report of the Millennium research group "implementation of the advanced therapies regulation will fuel growth in the emerging tissue engineering industry, propel innovation, and boost the competitiveness of the EU in the biotechnology market." (Millennium Research Group European Market for Orthopaedic Biomaterials, July 2009.)

Although the basic regulatory frameworks are now in place in Europe and the US, at present still little experience with such products exists, and consequently the regulatory framework will continue to evolve. An example of this is the still limited number of regulatory guidance documents providing practical guidance on product development and requirements. The Company will therefore continue to proactively address the regulatory environment and to contribute, as an experienced industry player in the field, to the shaping of future guidance documents.

For classic pharmaceutical and biological products, the pre-clinical and clinical development paths are broadly similar in Europe and in the U.S. Initially, pre-clinical studies (both *in vitro* and *in vivo*) are conducted to evaluate the mode of action (proof of concept/principle) and to establish adequate proof of safety. Upon successful completion of pre-clinical studies, regulatory authorities may grant approval for clinical trials, which are typically conducted in three sequential phases that may overlap. In Phase 1 clinical trials, which consists of the initial introduction of the pharmaceutical into healthy human volunteers, the emphasis is on testing for safety and adverse effects, dosage tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase II clinical trials consist of studies in a limited patient population to determine the initial efficacy of the pharmaceutical for specific targeted indications, to determine dosage tolerance and optimal dosage and to identify possible adverse side effects and safety risks. Once a compound shows evidence of effectiveness and is found to have an acceptable safety profile in Phase II clinical trials, Phase 3 clinical trials are undertaken to more fully evaluate clinical outcomes. In these Phase 3 trials, which are often referred to as registration, pivotal or confirmatory studies, the final product candidate is tested for its efficacy in a large trial setting in the relevant patient group(s). The product is usually tested in a blinded controlled randomised trial comparing the new product to an approved form of therapy. The goal of these studies is to obtain strict statistical evidence of the efficacy and safety of the new product compared to the control.

Given the specific nature of cell-based products, the clinical development paths are less standardized than for classic pharmaceutical or biological products. Phase 1 studies are often not relevant, in particular for autologous cell-based products, since cells often need to be directly implanted into a tissue defect only present in patients. As cellular therapy Phase 3 studies are very complex to organize, often limited numbers of patients can be enrolled, and follow up times can be very long, so that the design and execution of these large confirmatory trials might not always be possible to the classical extent. Upfront discussions and agreement with the regulatory authorities is an important criterion to success. It is also expected that new regulatory guidance will become available in the near future, more clearly describing the regulatory expectations.

Upon successful completion of the above-referred clinical trials, a company can submit an application for marketing authorisation to the relevant regulatory authority. After review of the application, the regulatory authority may grant marketing authorisation, deny the application or request additional information, including further clinical testing of the drug candidate. When granting marketing authorisation, a Regulatory Authority may impose upon the sponsor an obligation to conduct additional clinical testing, referred to as Phase IV clinical trials or post-approval commitments, to monitor the drug after commercialisation. Additionally, marketing authorisation may be subjected to limitations on the indicated uses for the drug.

U.S. – FDA approval process

The FDA was the first to adopt a regulatory framework for cell therapy products. With the exception of cell-based products for skin repair, most cell therapy products are regulated as biologics (medicinal products) by the Center for Biologics Evaluation and Research (CBER),

requiring product characterization and solid clinical validation in prospective randomised clinical trials.

The FDA generally requires the following steps for licensure of a new biological product:

- pre-clinical laboratory and animal testing, conducted to assess a product's biological activity, to identify potential safety problems and to characterize and document the product's manufacturing controls, formulation and stability;
- submission to the FDA of an Investigational New Drug (IND) application, which must become effective before clinical testing in humans can begin in the U.S.;
- obtaining approval of Institutional Review Boards (IRB) of research institutions or other clinical sites to introduce the biological drug candidate into humans in clinical trials;
- adequate and well-controlled human clinical trials to establish safety and efficacy of the product for its intended indications, conducted in compliance with the FDA's GCP requirements;
- compliance with all GMP regulations and standards;
- submission to the FDA of a biologics licence application (BLA) for marketing that includes adequate results of product quality testing, pre-clinical testing and results of clinical trials;
- FDA review of the BLA in order to determine whether the product is safe, effective and potent for its intended uses;
- FDA review and inspection of the product's manufacturing facility for being compliant with GMP requirements;
- in case of a positive review, granting approval of the BLA for commercial sale or shipment of the product. In case of non-approvability, request for additional studies or data.

Europe – Regulatory approval process

Although different terminology is sometimes used, the general approval process for medicinal products by the EMA in Europe is quite similar to the process in the U.S. described above.

Similar to the U.S., prior regulatory approval is required in EU Member States for conducting clinical trials on human healthy volunteers. Currently, in each EU Member State, relevant data is submitted in summarised format to the relevant regulatory authority in the Member State in respect of applications for the conduct of clinical studies (Phases I to IV). The regulatory authorities in the European Union typically have between one (1) and three (3) months from the date of receipt of the application to raise any objections to the proposed clinical trial and they often have the right to extend this review period at their discretion. The authorities may require additional data before allowing the studies to commence and could demand that the studies be discontinued at any time if there are significant safety issues. In addition to obtaining regulatory approval, clinical trials must receive Ethics Committee approval. The exact composition and responsibilities of the Ethics Committees differ from one EU Member State to another. In each EU Member State, one or more independent Ethics Committees (depending on whether the study is a mono-centre or multi-centre clinical trial) will review the ethics of conducting the proposed research.

Upon successful completion of final Phase 3 trials, the sponsor can submit a Marketing Authorisation Application (MAA) for the drug candidate. In Europe, three routes exist to obtain marketing approval for the product: national product application, mutual recognition or decentralized procedure including several EU countries, and the Central Procedure at the EMA granting a licence for the whole European Union and Norway, Iceland, and

Liechtenstein. It is compulsory for ATMP products, like ChondroCelect® or the future cell-based products of the Company, to be submitted through the central procedure at the EMA.

When TiGenix started its product development activities no uniform European regulatory framework or well-defined regulatory path existed for cell-based products. At that time, cell-based products were (wholly or partially) subject to various legislations. This has led to a situation where certain cell-based products could nationally be marketed under different legal status. The EU ATMP Regulation of 2009 now requires that all new cell-based products first need to receive central EU approval before they can be put on the market. ATMPs require now a marketing authorisation granted by the European Commission (the centralised procedure), with the EMA co-ordinating the marketing authorisation application, the scientific assessment and post-authorisation supervision.

Companies that already have tissue-engineered products on the market before December 30, 2008 will have until December 30, 2012 to meet the standards of the regulation. Any products not meeting the standards after the deadline will be no longer legally on the market. Meanwhile, these products can legally remain on the market on the basis of their former regulatory approval status.

Finally, it is worthwhile noting that cell-based products also have to comply with the European Cell and Tissue Directives (the so-called SANCO-Directives), describing the conditions and quality requirements which have to be applied when sourcing the cells intended for manufacturing of the cell-based medicinal product. Since these legal documents are EU Directives, they have been translated into the respective national laws of the different EU Member States. Locally different interpretations of the Directives have occurred during the national legal implementations, and this has now leads to a complex situation with respect to the respective national legislations. Differences in these national SANCO requirements do not preclude marketing of the products, but rather add-on complexity in complying with the all-over requirements in this already difficult regulatory field.

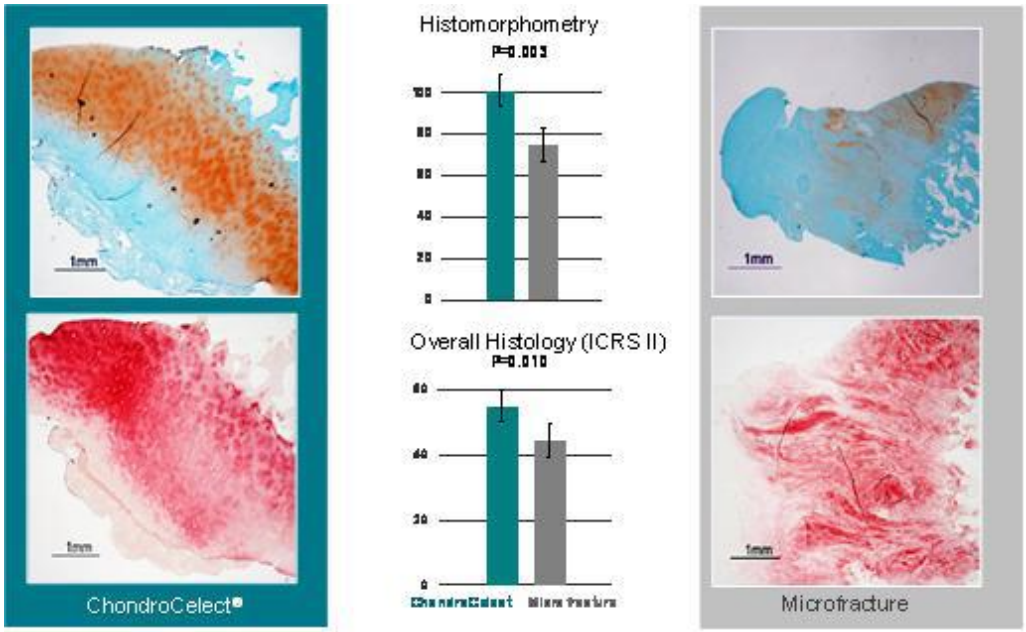
Key Q: Clinical data and time to approval

The efficacy of ChondroCelect® was studied in a Phase 3, multi-centre, randomized controlled trial, the TIG/ACT/01 study. ChondroCelect® was compared to microfracture in the repair of single symptomatic cartilage lesions of the femoral condyles of the knee.

Fifty-one patients were treated with ChondroCelect® and sixty-one patients with microfracture. Patients aged between 18 and 50 years, who had a single symptomatic cartilage lesion between 1 and 5 cm^2 of the femoral condyles met the inclusion criteria. Patients could be treatment-naïve or might have undergone previous arthroscopic or other surgical repair procedure(s). The median time since onset of symptoms was slightly longer in the ChondroCelect® group than in the microfracture group (2.0 years vs. 1.6 years). More patients in the ChondroCelect® treatment group, compared to patients in the microfracture group, had undergone previous knee surgery (88% vs. 77%). The primary analysis of the data, at 18 months post treatment, demonstrated that the primary objective of the TIG/ACT/01 trial was met:

(a) at 1 year following treatment, ChondroCelect® formed regenerated tissue that was superior to the repair tissue formed following microfracture as determined by histological analysis of biopsies taken 12 months after treatment (see figure below). The repair tissue formed by patients treated with ChondroCelect® was found to be less fibrous and to display features indicative of more durable hyaline-like cartilage;

Superior structural repair at 12 months



(b) at 6, 12 and 18 months clinical outcome was similar for both treatment groups with a slight advantage in improvement from baseline witnessed in patients treated using ChondroCelect®.

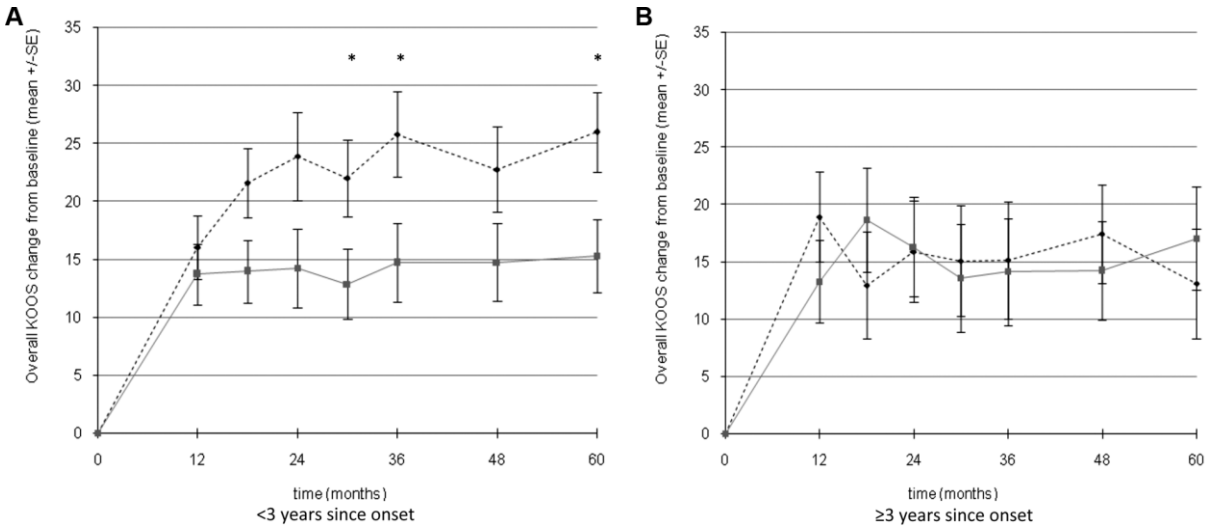
The later analysis of the longer term data (up to 36 months) demonstrated a continuous improvement in both treatment arms and a larger overall clinical benefit for the ChondroCelect® (CCI) group versus the microfracture group. The figure below presents the main clinical improvement from the baseline (i.e. the preoperative situation) for both treatment groups up to 36 months as measured by the Overall Knee Injury and Osteoarthritis Outcome Score (KOOS). The estimated benefit at 36 months, when using a mixed linear model with time as a categorical variable and considering the Compound Symmetry Heterogenous approach (CSH), was larger in the ChondroCelect® group than in the group of microfracture treated patients (P = 0.048). At this time point 39 patients were evaluated in the CCI arm and 43 were evaluated in the MF arm.

The failure profile also favoured the CCI arm, with 2 failures (treatment re-interventions) in the CCI group vs. 7 failures in the microfracture group. The re-interventions in the CCI group were caused by graft delamination or periost loosening. The treatment failures in the microfracture group generally had insufficient or inadequate cartilage repair.

No unexpected safety issues and no difference in safety profile were seen between the two treatment groups.

More subchondral bone issues were registered in the microfracture group. This could be an indicator of potential future failure after microfracture. Similar issues were described by Minas et al. in his publication on increased failure rate of ACI after previous treatment with marrow stimulating techniques. (Minas et al., *Am J Sports Med*. May 2009; 37(5):902-8.)

Overall Knee Injury and Osteoarthritis Outcome Score (oKOOS) change from baseline (means) graphs for subgroups with < 3-year onset (A) versus onset > 3 years (B). Dashed lines indicate characterized chondrocyte implantation (CCI) and solid lines indicate microfracture (MF). *P<.05 ANCOVA analysis.



The short-term results of the pivotal study were published in the American Journal of Sports Medicine (Saris et al., *Am J Sports Med*., Feb 2008;36(2):235-46.), a leading peer reviewed orthopaedic journal. This publication was honoured with the prestigious Hughston Award in July 2009, an award that is given by the American Orthopedic Society for Sports Medicine (AOSSM) to the most outstanding paper of the year published in the American Journal of Sports Medicine. The winning paper is chosen by a panel of AJSM editors and reviewers.

The 36 months data were also published in the same journal and expand on the results graphically depicted above. (Saris et al., Am J Sports Med., Oct/Nov 2009; 37(1):10s-19s)

The 60 month data largely corroborate the 36 month data (clinical outcomes graph above) and have been published in the AJSM (Vanlauwe J, Saris DBF, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five year outcome of Characterised Chondrocyte Implantation versus Microfracture for symptomatic cartilage defects of the knee – Early Treatment Matters. Am J Sports Med 2011; doi:10.1177/036354651142222), the highlights of which are that they confirm that clinical benefit at 24 months is maintained at the 5 year time point, indicating a durable therapy. The 60 month data also identifies which patient population best benefits from CCI: duration of symptoms is key. Patients whose time since symptom onset is < 3 years do have statistically significant and clinically relevant better outcome when treated with CCI versus Microfracture. In patients whose time since onset of symptoms was > 3 years, there was no difference between the two treatments. This is a clear indication that patients should be treated sooner rather than later, and is equally good news for patients, clinicians and payers, since for patients and clinicians it more clearly identifies the appropriate treatment algorithm for the pathology, and for payers it gives a finite patient population – CCI (Characterised Chondrocyte Implantation) should not be used in all patients. A further point of note is that in the patient group whose time since symptom onset is < 3 years, CCI represents what arguable could be described as a “cure” since when you look at the absolute values for the overall KOOS measure at baseline (pre-surgery score) and then look at the improvement at 5 years, the absolute value is within the range of a “normal healthy individual”.

The pivotal TIG/ACT/01 trial data have been complemented by supplementary information from an open label trial and other clinical programmes:

- an open label trial for the treatment of complex cases at the Belgian military hospital;
- an expanded access programme for the treatment of complex and salvage cases at three hospitals in Belgium;
- a compassionate use (named patient) programme in Benelux, Germany, and UK.

In total, more than 500 patients have been treated with ChondroCelect® to date.

In terms of time to approval, the TIG/ACT/01 trial started in 2002, and ChondroCelect® was granted its MA as an ATMP at the end of 2009. TiGenix was founded in 2000, and prior to the pivotal trial starting in 2002, had conducted various animal studies providing safety data and proof of concept that molecular markers could indeed be predictive of the capability to form hyaline cartilage. In essence the timeline from science to surgery for an ATMP can be likened to that of a pharmaceutical drug (approximately 15 years).

Key Q: Approval status

TiGenix is the first company that succeeded in obtaining central regulatory approval for a cell-based medicinal product in Europe, and ChondroCelect® is the first approved product under the new ATMP regulatory framework.

Taking into account the uncertain regulatory framework in Europe, TiGenix chose from the start to develop its products as medicinal products. The Company based its regulatory strategy for ChondroCelect® on the existing regulations in the U.S. expecting to follow a similar process in Europe. In addition and in anticipation of a changing European regulatory framework, the Company requested designation of the regulatory process for ChondroCelect® by the EMA Central Procedure. In June 2005, the EMA decided that ChondroCelect® could be considered as a cell therapy medicinal product. This designation made ChondroCelect® eligible for central review by the EMA and approval by the European Commission, thus providing direct access to all markets of the EEA countries.

The European Market Application dossier for ChondroCelect® was submitted to the EMA in June 2007. Germany and Finland were designed as the Rapporteurs (key reviewers) for the file. During the review process, the Company had several explanatory meetings with the EMA scientific committees, as could be expected for such a novel type of medicinal product. Early 2009, ChondroCelect® was granted official ATMP status, making it fall completely under the new 2009 ATMP Regulation. In June 2009, ChondroCelect® received a positive opinion from both EMA Committees deciding on the file, the Committee for Advanced Therapies (CAT) and Committee for Medicinal Products for Human Use (CHMP), respectively. This positive opinion served as the basis of the official legal market authorisation of ChondroCelect® by the European Commission which was obtained in October 6, 2009. In light of post-approval commitments TiGenix will ensure follow-up of the efficacy and safety of the ChondroCelect® product in post-approval studies.

In the U.S., the Company filed an IND application for ChondroCelect® in 2005, allowing it to discuss the ChondroCelect® development with the FDA (CBER) in view of submitting a Licence BLA. The Company has had multiple interactions with CBER for reviewing the existing product and clinical data, and for discussing the Agency's regulatory expectations and requirements.

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

Europe

Pricing and reimbursement are not harmonised in Europe and fall within the exclusive competence of the national authorities, provided that basic transparency requirements described in Directive 89/105/EEC of December 21, 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems are met. As a consequence, reimbursement mechanisms by private and public health insurers vary from country to country. In public health insurance systems, reimbursement is determined by guidelines established by the legislator or a competent national authority. In general, inclusion of a product in reimbursement schemes is dependent upon proof of the product's efficacy, medical need, and economic benefits of a product to patients and the healthcare system in general. Acceptance for reimbursement comes with cost, use and often volume restrictions, which again vary from country to country.

Today, there is no general reimbursement for ACI products in Europe, mainly due to a lack of robust data from clinical trials.

The ChondroCelect® pricing and reimbursement track will differ from the route conventional ACI therapies have taken until now, since ChondroCelect® will follow the pricing and reimbursement track for medicinal products and/or novel therapies. Several countries have established processes to reimburse novel therapies, but the stakeholder and decision-making pathways vary significantly between countries. Similar to pharmaceutical products, a pricing and reimbursement dossier must be submitted to the national authorities. Based on the clinical data and health-economic studies, TiGenix has developed a detailed Core Value Dossier to prepare these applications and the negotiations with the national reimbursement agencies and private payers.

In Germany, TiGenix has submitted and obtained in early 2009 a “New Diagnostic and Therapeutic Procedures” (“Neue Untersuchungs- und Behandlungsmethoden” or NUB) agreement from InEK (Institut für das Entgeltsystem im Krankenhaus), which makes ChondroCelect® eligible for reimbursement as an innovative therapy before the attribution of a new DRG (Diagnose Related Group) code and tariff. Out of the 546 NUB applications for 2009, the ChondroCelect® application was one of only 87 which received a positive ruling by IneK. The individual hospitals which submitted a NUB application for ChondroCelect® can now negotiate budgets with their local Krankenkassen (sick funds) to cover reimbursement for ChondroCelect®, a process which usually takes several months.

In the UK, TiGenix has successfully been utilizing the “pass-through payment” mechanism in the NHS where PCT’s have the capability to fund ChondroCelect® for individual patients on an ad hoc basis. In the private sector, eight of the largest insurance companies have now agreed to fund ChondroCelect® for individual patients, again on an ad hoc basis. These decisions to fund are based upon clinical need, product indication, and an independent health-economic analysis which puts the cost per QALYG of treating with ChondroCelect® rather than microfracture below the level that NICE would ordinarily describe a product/therapy as cost-effective.

For each of the other target markets, TiGenix has developed pricing & reimbursement strategies and plans, where possible in discussion with the local authorities. The files are being finalized for submission according to the plan that has been established.

U.S.

In the U.S., only one cell-based product for cartilage repair is on the market. This product, Carticel® from Genzyme (Cambridge, MA), is said to be reimbursed by 85% of the payers. The target population for ACI are persons between 18 and 55 years, for which worker compensation plans and private insurers are the main payers. Also Medicare, the federal healthcare programme for the elderly and disabled, initiated reimbursement of ACI in 2005. Genzyme has obtained a special reimbursement code (HCPCS J-code 7330) for the Carticel® product. The current in-market price for Carticel in Medicare is US$18,285 and the National Average Payment (Ingenix, HCPCS Level II Updateable 2006) for commercial reimbursement of the cells is US$29,625. In order to ease the administrative burden on facilities, Genzyme contracted with US Bioservices, a specialty pharmacy that manages the full reimbursement process for Carticel®.

Over the past years the Company has, with the assistance of a US reimbursement expert, engaged in a dialogue with key decision makers at different payers in order to identify unique preferences and concerns by payer type and to obtain insight in the perceived value drivers, reimbursement barriers and price elasticity for ChondroCelect®. Based on this information, the Company will create its pricing and reimbursement strategy and infrastructure before the launch of the product in this market.

Status: the product is available in the UK, Benelux, Germany and Austria, and is soon to be available in France, Spain, Portugal and the Nordics. It is not currently available in the US.

Manufacturing and Supply Strategy:

Key Q: Living cell product?

Efficient manufacturing is of strategic importance within the Company as it utilises some of the Company's core know-how. TiGenix considers cell culture technologies and related operations as a core competence based on which the success of the Company as a leader in Regenerative Medicine is being built.

Already in 2002 the Company established its own central CEF, located at the University Hospital in Leuven, Belgium. Since its establishment, the CEF has produced over 500 ChondroCelect® batches. The CEF is GMP certified for the commercial manufacturing of ChondroCelect®. In anticipation of the growing demand for ChondroCelect® and the expansion of the product pipeline, TiGenix has secured additional production capacity in Europe. After carefully evaluating a number of options, taking into consideration technical, logistical, regulatory and financial criteria, TiGenix has selected a building of 2,400 m² on the Chemelot Campus, near Maastricht, the Netherlands, to locate its second CEF. The site is centrally located in TiGenix' key European markets, in a region that is strong in distribution and (bio)logistics and that is highly committed to develop as a transnational knowledge centre in life sciences and Regenerative Medicine.

TiGenix B.V. has subsequently entered into a long term lease agreement for the building and is in the process of designing and building the clean rooms, quality control labs and supplementary areas. It is anticipated that the additional capacity will be fully operational during 2012.

In a ChondroCelect®-treatment procedure, logistics are an important success factor for which TiGenix has worked out a standardised procedure. To this end, the Company has installed a support desk at its head office that manages all logistics arrangements. Transportation of biological samples (patient biopsies) and final products (ChondroCelect®) are handled by selected ISO 9001 certified courier services. The biological samples and

ChondroCelect® are packed in sterile and tamper proof packaging, and conditioned at the appropriate temperature.

A cartilage biopsy is harvested in the operating theatre and placed into a custom designed transit box. A TiGenix certified courier then transports the temperature controlled biopsy box to the CEF in Belgium (currently) where the chondrocytes are enzymatically digested from the cartilage and then cultured to create the ATMP ChondroCelect®. The ChondroCelect® is then transported back to the hospital, again by TiGenix certified courier, where it is implanted autologously, at a timepoint of the surgeon/patient's choice between 9 and 13 weeks.

Key Q: Make or Buy?

This is an obvious one for TiGenix since the company was founded with the expertise of cell-culture and expansion at its core.

Publications:

ChondroCelect® Specific Publications:

Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, Luyten FP. Characterized Chondrocyte Implantation Results in Better Clinical Outcome at 36 Months in a Randomized Trial Compared to Microfracture. Am.J.Sports Med 2009;37(Supplement 1):10s-19s.

Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y, Vandekerckhove B, Almqvist KF, Claes T, Handelberg F, Lagae K, van der BJ, Vandenneucker H, Yang KG, Jelic M, Verdonk R, Veulemans N, Bellemans J, Luyten FP. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med. 2008;36:235-246.

Vanlauwe J, Saris DBF, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five year outcome of Characterised Chondrocyte Implantation versus Microfracture for symptomatic cartilage defects of the knee – Early Treatment Matters. Am J Sports Med 2011; doi:10.1177/0363546511422220.

Vanlauwe J. et al. Clinical Outcomes of Characterised Chondrocyte Implantation. Cartilage 2011; doi:10.1177/1947603511430325.

Dell'Accio F, De Bari C, Luyten FP 2001 Molecular markers predictive of the capacity of expanded human articular chondrocytes to form stable cartilage in vivo. Arthritis Rheum. 44: 1608-1619.

Dell'Accio F, De Bari C, Luyten FP 2003 Microenvironment and phenotypic stability specify tissue formation by human articular cartilage-derived cells in vivo. Exp.Cell Res. 287: 16-27.

Dell'Accio F, Vanlauwe J, Bellemans J, Neys J, De Bari C, Luyten FP 2003 Expanded phenotypically stable chondrocytes persist in the repair tissue and contribute to cartilage matrix formation and structural integration in a goat model of autologous chondrocyte implantation. J.Orthop.Res. 21: 123-131.

Publications on ACI as a field, but relevant to ChondroCelect®:

Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased Failure Rate of Autologous Chondrocyte Implantation After Previous Treatment With Marrow Stimulation Techniques. Am.J Sports Med. 2009.

Rubak JM, Poussa M, Ritsila V. Effects of joint motion on the repair of articular cartilage with free periosteal grafts. Acta Orthop Scand. 1982;53:187-191.

Coletti JM, Jr., Akeson WH, Woo SL. A comparison of the physical behavior of normal articular cartilage and the arthroplasty surface. J Bone Joint Surg.Am. 1972;54:147-160.

NICE. The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints. NICE. 2005

Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, Jobanputra P, Waugh N. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. Health Technol.Assess. 2005;9:1-98.

Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. Osteoarthritis Cartilage. 2009.

Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J.Orthop.Sports Phys.Ther. 1998;28:88-96.

Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual.Life Outcomes. 2003;1.

Derrett S, Stokes EA, James M, Bartlett W, Bentley G. Cost and health status analysis after autologous chondrocyte implantation and mosaicplasty: a retrospective comparison. Int.J.Technol.Assess.Health Care. 2005;21:359-367.

Minas T. Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. Am.J.Orthop. 1998;27:739-744.

Key Value Steps:

1. Pre-clinical data sufficient to demonstrate technology difference and market space (2000)
2. Data shows COGS can be controlled during clinical trials and post launch (2002-2010)
3. Phase 3 data sufficient for ATMP application (June 19, 2007)
4. ATMP Authorisation and Market Launch (October 6, 2009)
5. General Reimbursement gained. (Ongoing. 2010 is ad hoc, goal is to move to routine)

Key External Interactions:

The only key external interactions are those with the scientific and clinical advisory boards, and the investors.

Sources:

TiGenix website:
www.tigenix.com
Company prospectus, Financial Reports and Press Releases.
Clinical and cost-effectiveness paper references provided above.

Cardio3Biosciences: C3BS-CQR-1 (C-CURE®)

Brief Product Description and Indications:

Autologous bone marrow-derived cells treated with the "Cardiopoietic cocktail" and re-injected into the heart. The product indicated for chronic heart failure.

Implanted cells proliferate, engraft and terminally differentiate into new autologous heart muscle cells which behave identically to those lost in infarction without carrying the risk of rejection. The product has an indirect effect through the beneficial effect of factor excreted by the transplanted cells on the host's own resident cardiac stem cells.

Target Indications and Markets:

Key Q: Clinical indications

C-CURE is indicated for the treatment of chronic heart failure where degeneration or loss of myocardial tissue has occurred.

Key Q: Geographical target market

The Phase 2 study has been conducted in Belgium, Serbia and Switzerland. The technology is licensed from a clinic in the USA and it has to be assumed that the target market is international, with EU the initial target for regulatory approval.

Key Q: Competition

There are other companies active in this potentially highly lucrative area, T2Cure for instance. Cardio3Biosciences aims to be the first to obtain (regulatory) approval (in EU?/USA?)

Key Features of Company Business Model:

Key Q: Structure

Cardio3Biosciences was founded at Louvain-la-Neuve in Belgium in 2007, licensing, in accordance with the Bayh-Dole Act (USA), the technology from the Mayo Clinic, Rochester, Minnesota (MN), USA. The Mayo clinic received an equity position and rights to receive royalties, shared with the inventors, Drs Tenzic and Behfar at Mayo. No royalties have been paid to date.

It has 45 employees and an in-house manufacturing facility. There is a management team of 8.

Q: License or IP? Manufacturing know-how?

Key Q: Future strategy/Exit strategy

The company appears to be quite well-funded (€3.3M) with a burn-rate of €0.4M/month. Mention is made of an IPO and appears to be attracting investment rather than acquisition.

Q: Timing of IPO?

Key Q: Portfolio

Cardio3Biosciences have 2 "proteins", C3BS GQR-1 for the treatment of acute myocardial infarction (AMI), and C3BS GQR-2 for AMI/Heart failure;

a Medical Device, C-Cath, for intramyocardial injection, in their pipeline. GQR-1 is scheduled to enter Phase 2 trial at the end of 2011, GQR-2 enters an animal testing phase in 2012. CE mark application for C-Cath is projected for 2012.

Also an allogeneic product C3BS-AQR-1, which is currently under tests in a pig model.

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

Cardio3 BioSciences raised €37.5M since inception of which €22.8M was in equity. The last financing round (Series C) took place in October 2010 and was based on the 3-month safety and feasibility data of the C-Cure Phase 2 trial. All proceeds are fully dedicated to clinical trials and the development of the pipeline of product candidates and research programmes.

The Company has been awarded non-dilutive financial support (in the form of recoverable cash advances and subsidies) from the Walloon Region for a total of €14.7M. Cardio3 Biosciences intends to continue to apply for public funding to fund certain of its development and research programmes. So far, all of the clinical, research and development programs are financed up to 70% by regional funding.

The current capitalization table as of 31 October 2010 is on a non-fully diluted basis:

Mayo Clinic	27%
Founders	20%
Management	3%
Investors	50%

The financial investors of Cardio3 BioSciences are UMBRELA Investments, TOLEFI SA, SRIW TECHNO SA, AVION SA, GRIFOLS SA, HUNZA Ventures II, LIFE SCIENCES RESEARCH PARTNERS (Désiré Collen), Barco Trading Limited and private investors.

Q: The company benefits from regional funding. Is this localisation a potential drawback?

Key Q: Relationships with clinical KOLs

Dr. Josef Bartunek, Associate Director of the Cardiovascular Center in Aalst, Belgium (Co-Principal Investigator of the Phase 2 trial)

Professor Andre Terzic, lead regenerative medicine specialist at Mayo Clinic, Rochester, MN, USA., and Co-Principal Investigator of the Phase 2 trial.

Regulatory Strategy/Regulatory Status:

Key Q: Target approval routes

Not stated. CTA made to "appropriate national authorities". It is likely that the rather small Phase 2 trial relied on national approval since the study was carried out in Serbia, Belgium and Switzerland.

Phase 3 recruitment is under way and is believed to include USA.

Key Q: Clinical data and time to approval

Six-month data are available from the Phase 2 trial and are being used to apply for a Phase 3 study (2011) for which recruiting is currently underway..

Cardio3 Biosciences aims to be the first company with an approved SC product for the treatment of ischaemic heart disease.

Reimbursement Strategy/Reimbursement Status:

Key Q: Requirements for reimbursement

Cardio3Biosciences is looking to appropriate regulatory approval.

Manufacturing and Supply Strategy:

Key Q: Nature of product

(Living) autologous cultured cells in a solution containing growth factors. The "Finished product" shelf-life is not stated. There may be a freezing step.

Key Q: Make or buy?

Cardio3Biosciences have their own in-house GMP facility. They produce the product using a "high cell density bioreactor" and are moving towards production in fully automated closed reactors. Manufacturing sites are planned in North America, EU and Asia.

Publications:

Cardio3 BioSciences presented detailed data from the Phase 2 clinical trial of C3BS-CQR-1 (C-Cure(R)), its novel stem cell therapy for ischemic cardiomyopathy, at the 60th annual American College of Cardiology in New Orleans, USA, 2011.

Key Value Steps: Identified:

1. Secure licensing system based on technology developed in USA.
2. Statistically significant results obtained in a small (24 controls, 21 treated) Phase 2 trial.
3. Recruitment started for a Phase 3 study. 45 patients enrolled so far.
4. Manufacturing technology developed. Maybe proprietary/IP protected. Closed automated system offers GMP advantages.
5. Regional funding may or may not be an advantage
6. Dependence on Investor pipeline.
7. Dialogue with regulatory authorities probably established but strategy internationally unclear
8. Completion of Phase 3; MA application(s), reimbursement strategy

Key External Interactions:

State any key interactions with members of the supply / value chain.

- Limited clinical KOL base at present
- EMA and FDA on board?
- Marketing and reimbursement strategy unclear
- Good relations established with investors

Sources:

http://www.c3bs.com/fr/about-us/whoarewe.html

http://www.c3bs.com/images/stories/pdf/EN_C-Cure-6-month-Data-Release-final.pdf

http://www.google.co.uk/url?sa=t&source=web&cd=39&ved=0CFgQFjAIOB4&url=http%3A%2F%2Fwww.les-benelux.org%2Flevel2a%2Fdocuments%2FChristianHomsy.pdf&ei=6vizTZDKNI64hAfUqZnkDw&usg=AFQjCNGWXVZRZg2H3llWwR5GeRUE-kXjuQ

Note: latter is a very useful power-point presentation from Cardio3Biosciences' CEO.

t2cure GmbH: t2c001

Brief Product Description and Indications:

Bone marrow material is obtained from the iliac crest under local anaesthesia. The mononuclear cell fraction is purified from the bone marrow aspirate by Ficoll gradient centrifugation at a central GMP-compliant manufacturing facility. For cardiac diseases, BMCs are then injected into the coronary arteries via catheter without further in vitro cell propagation. The same principle is applied in the peripheral setting, where BMCs are injected via a catheter into the arteries of the limbs.

Target Indications and Markets:

Key Q: Clinical indications

t2c001, the lead product/indication, is indicated for the treatment of acute myocardial infarction. Other indications, for which Proof of Concept studies only are available, are chronic heart disease (with or without shock-wave therapy), and peripheral arterial diseases, with focus on thromboangiitis obliterans.

Key Q: Geographical target market

T2cure's activities are currently confined to the University of Frankfurt-am-Main and selected medical clinics in neighbouring regions of Germany

Key Q: Competition

There are other companies active in this potentially highly lucrative area, Cardio3Biosciences for instance is proceeding to a MA for similar indications. Subject to IP constraints, which do not seem to be strong, there is little to stop other companies offering a similar service.

Protection may be offered by the acquisition, from Innovectis, the technology arm of Frankfurt University, of patents based on the characterisation of SCs to establish their likely potency.

Key Features of Company Business Model:

Key Q: Structure

t2cure was founded as a private company in 2006 by Prof. Andreas M. Zeiher and Prof. Stefanie Dimmeler, academic researchers at Frankfurt University. They appear to be the only Directors. The company is run by 5 key executives. There is no information on the company's website on number of staff and services are probably contracted out.

Q: How is the IP protected (see below)?

Key Q: Future strategy/Exit strategy

I presume the company intends to expand by making arrangements with a growing number of clinics which will provide the service.

Key Q: Portfolio

t2cure do not have separate products, rather the same principle (density gradient concentrated BM-derived SCs) are used for a number of different indications. The lead indication is acute myocardial infarction, where a Phase 2 study has been completed.

The other indications are chronic heart disease, with or without shock wave therapy; dilated cardiomyopathy and peripheral artery disease. All these have completed "Proof of Concept" studies, described as Phase 1 / 2.

T2cure acquired (reported on 25/11/2008) a family of patents and patent applications from Innovectis, the technology transfer arm of Frankfurt University, covering a technology that allows for the rapid characterization of the potency of bone marrow-derived cells in the treatment of cardiovascular diseases. Potency testing is of course a key criterion for batch release, and thus for market approval, of stem cell-based therapies.

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

t2cure is privately financed with Entrepreneurs Fund BV, Amsterdam, as lead investor.

Report from Bloomberg's Business Week:

On 12/1/2010, miRagen Therapeutics Inc. entered into a licensing agreement with t2cure GmbH that provides miRagen Therapeutics with exclusive rights to the technology and intellectual property related to the in vivo-use of discoveries made by the University of Frankfurt and licensed by t2cure regarding microRNA 92. microRNA 92 (miR-92) is a regulator of neoangiogenesis as part of ischemic disease, which may be relevant to peripheral arterial disease and other cardiovascular disorders. t2cure retains the rights to use modulators of miR-92 for ex-vivo treatment of cellular therapeutics. Financial details of the agreement were not disclosed. Within the miR-92 family is an endothelial cell-enriched miRNA known as miR-92a. miR-92a appears to target mRNAs corresponding to several pro-angiogenic proteins. miRagen believes miR-92a serves as a therapeutic target in the setting of ischemic disease, and intends to explore its function during other vascular disorders, including atherosclerosis. miRagen plans to expand the preclinical exploration of miR-92a inhibition in ischemic cardiac injury in the near term.

Key *Q: Relationships with clinical KOLs*

The following clinics in Germany offer t2cure's service:

Prof. Dr. A. M. Zeiher
Klinikum der Johann-Wolfgang Goethe-Universität
Frankfurt

Prof. Dr. Dr. Jürgen Haase
Kardiocentrum Frankfurt an der Klinik Rotes Kreuz
Frankfurt

Prof. Dr. Volker Schächinger
Klinikum Fulda AG
Fulda

Dr. Hubertus von Korn
Krankenhaus Hetzelstift
Neustadt

There are also relationships with DRK - Blood Donor Service - Baden-Württemberg-Hessen gGmbH, and Innovectis GmbH, the technology arm of Frankfurt University.

Regulatory Strategy/Regulatory Status:

Key Q: Target approval routes

24/5/2010: Orphan drug status acquired FDA and EU.

25.5.2010: t2c001 obtained certification from the Committee of Advanced Therapies (CAT) under the European Medicines Agency Advanced Therapy Medicinal Product (ATMP) regulations. This is stated to have been the first time the certification system was used in the European Union.

About 550 patients have received t2c001 to date.

Good safety and efficacy data are provided by a randomised double-blinded study (NCT 00279175) conducted at a number of centres in Frankfurt and Giessen, Germany, involving 204 patients. Statistically significant benefits were obtained in the study and a MRI sub-study, and they are fully reported in relevant journals. It is not known whether this study was fully GCP-compliant, and supplementation by a "Phase 3" study, to which 100 patients have already been recruited, is planned..

Key Q: Clinical data and time to approval

Q: What are t2cure's regulatory plans? What is the extent of their dialogue with EMA? What will happen if competition forces them to apply for a MA?

Reimbursement Strategy/Reimbursement Status:

Key Q: Requirements for reimbursement

The clinics below have all successfully concluded negotiations with health care payers or are currently entertaining such discussions.

Klinikum der Johann-Wolfgang Goethe-Universität, Theodor-Stern-Kai 7, 60590 Frankfurt.

Kardiocentrum Frankfurt an der Klinik Rotes Kreuz, Pfingstweidstr. 11, 60316 Frankfurt.

Klinikum Fulda gAG, Pacelliallee 4, 36043 Fulda.

Krankenhaus Hetzelstift, Stiftstraße 10, 67434 Neustadt.

K-J Maiwald from the HQ of the largest German private insurance company (Debeka) outlined in the journal "Regenerative Medicine" (2009) stated that he considers stem cell therapy post infarct as insurable, because "stem cell therapy is effective in basically all cases post acute infarct".

A number of other clinics in Germany are listed for information on incurring costs or applicable options for individual reimbursement: Hamburg (Asklepios Klinik Barmbek, and Medizinisches Versorgungszentrum), Bad Berka (Zentralklinik Bad Berka), and Suhl (SRH Zentralklinikum Suhl GmbH).

Manufacturing and Supply Strategy:

Key Q: Nature of product

(Living) autologous mononuclear cells concentrated from the patient's own bone marrow are implanted via a cannula into affected sites in the heart (or vein). There appears to be no cultural step and the cells are delivered almost immediately to the patient. The shelf-life will

be very limited. Currently, clinics offering t2cure's service are located close to the manufacturing site in Frankfurt.

Key Q: Make or buy?

The "product" is made for t2cure at a central GMP facility in Frankfurt.

Publications:

Assmus B, Rolf A, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Tillmanns H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Tonn T, Dimmeler S, Dill T, Zeiher AM, and Schächinger V (2010). Clinical Outcome 2 Years After Intracoronary Administration of Bone Marrow-Derived Progenitor Cells in Acute Myocardial Infarction. Circulation Heart Failure;3:89-96

Dill T, Schächinger V, Rolf A, Möllmann S, Thiele H, Tillmanns H, Assmus B, Dimmeler S, Zeiher AM, Hamm C (2009). Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: Results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac Magnetic Resonsance Imaging substudy. Am Heart J 157:541-7

Fischer-Rasokat U, Assmus B, Seeger FH, Honold J, Leistner D, Fichtlscherer S, Schächinger V, Tonn T, Martin H, Dimmeler S, Zeiher AM (2009): A pilot trial to assess potential effects of selective intracoronary bone marrow-derived progenitor cell infusion in patients with nonischemic dilated cardiomyopathy: final 1-year results of the transplantation of progenitor cells and functional regeneration enhancement pilot trial in patients with nonischemic dilated cardiomyopathy. Circ Heart Fail. Sep;2(5):417-23.

Burt RK, Loh Y, Pearce W, Beohar N, Barr WG, Craig R, Wen Y, Rapp JA, Kessler J. (2008): Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. JAMA. 299(8):925-36.

Erbs S, Linke A, Schächinger V, Assmus B, Thiele H, Diederich KW, Hoffmann C, Dimmeler S, Tonn T, Hambrecht R, Zeiher AM, Schuler G. (2007): Restoration of microvascular function in the infarct-related artery by intracoronary transplantation of bone marrow progenitor cells in patients with acute myocardial infarction: the Doppler Substudy of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. Circulation. 116(4):366-74.

Assmus B, Fischer-Rasokat U, Honold J, Seeger FH, Fichtlscherer S, Tonn T, Seifried E, Schächinger V, Dimmeler S, Zeiher AM (2007): Transcoronary transplantation of functionally competent BMCs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: results of the TOPCARE-CHD Registry. Circ Res.;100(8):1234-41

Lipinski MJ, Biondi-Zoccai GG, Abbate A, Khianey R, Sheiban I, Bartunek J, Vanderheyden M, Kim HS, Kang HJ, Strauer BE, Vetrovec GW (2007): Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. J Am Coll Cardiol. 50(18):1761-7

Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surma EK, Al-Mallah M, Dawn B. (2007): Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. Arch Intern Med.;167(10):989-97

Schächinger V., S. Erbs, A. Elsässer, W. Haberbosch, M. Hambrecht, H. Hölschermann, J. Yu, R. Corti, D.G. Mathey, C.W. Hamm, T. Süselbeck, B. Assmus, T. Tonn, S. Dimmeler, A.M.

Zeiher (2006): Intracoronary Bone Marrow-Derived Progentor Cells in Acute Mycardial Infaction. N. Engl. J. Med. , 355, 1210-1221.

Schächinger V., S. Erbs, A. Elsässer, W. Haberbosch, R. Hambrecht, H. Hölschermann, J. Yu, R. Corti, D.G. Mathey, C.W. Hamm, T. Süselbeck, N. Werner, J. Haase, J. Neuzner, A. Germing, B. Mark, B. Assmus, T. Tonn, S. Dimmler, A.M. Zeiher (2006). Improved clinical outcome after intracoronary administration of bone-marrow.derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur. Heart J., 27, 2775-2783.

Assmus B, J. Honold, M.B. Britten, U. Fischer-Rasokat, R. Lehmann, C. Teupe, K. Pistorius, H. Martin, N.D. Abolmaali, T. Tonn, S. Dimmeler, A.M. Zeiher (2006): Transcoronary Transplantation of Progenitor Cells after Myocardial Infarction. N. Engl. J. Med, 355, 1222-1232.

Bartunek J, M. Vanderheyden, B. Vanderkerckhove, S. Mansour, B. De Bruyne, P. De Bondt, I. Van Haute, N. Lootens, G. Heyndrickx, W. Wijns. (2005): Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promote cardiac recovery after recent myocardial infarction. Circulation, 112 (Suppl I), I178-I183.

Schächinger V., B. Assmus, M.B. Britten, J. Honold, R. Lehmann, C. Teupe, N.D. Nasreddin, T.J. Vogl, W.-K. Hofmann, H. Martin, S. Dimmeler, A.M. Zeiher. (2004): Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction. J. Am. Coll. Cardiol. 44, 1690-1699.

Wollert K.C., G.P. Meyer, J. Lotz, S. Ringes-Lichtenberg, P. Lippolt, C. Breidenbach, S. Fichtner, T. Korte, B. Hornig, D. Messinger, L. Arseniev, B. Hertenstein, A. Ganser, H. Drexler. (2004): Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet, 364, 141-148.

Britten M.B., N. Abomaali, B. Assmus, R. Lehmann, J. Honold, J. Schmitt, T.J. Vogl, H. Martin, V. Schächinger, S. Dimmeler, A.M. Zeiher (2003): Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI). Circulation, 108, 2212-2218.

Assmus B, V. Schächinger, C. Teupe, M. Britten, R. Lehmann, N. Döbert, F. Grünwald, A. Aicher, C. Urbich, H. Martin, D. Hoelzer, S. Dimmeler, A.M. Zeiher (2002): Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). Circulation; 106: 3009-3017.

Strauer B.E., M. Brehm, T. Zeus, N. Gattermann, A. Hernandez, R.V. Sorg, G. Kögler, P. Wernet. (2001): Intracoronare, humane autologe Stammzelltransplantation zur Myokardregeneration nach Herzinfarkt. Dtsch. med. Wschr., 126, 932-938.

Dill T, Schächinger V, Rolf A, Möllmann S, Thiele H, Tillmanns H, Assmus B, Dimmeler S, Zeiher AM, Hamm C (2009). Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging substudy. Am Heart J. Mar; 157(3):541-7.

Key Value Steps: Identified:

1. 550 patients treated with t2cure001 for the lead indication, but there is no reporting of a study intended for regulatory submission.
2. Further indications have been studied in the clinic and are stated to be at Proof of Concept stage.

3. Recruitment started for a Phase 3 study with t2c001. c. 100 patients enrolled so far.
4. IP protection may be offered by potency/characterisation licensed in from Innovectis (also based at Frankfurt University).
5. Possibility of revenue generation from IP licensing deal with MiRagenics Inc.
6. Revenue stream being generated from provision of service with contracted clinics local to Frankfurt.
7. Low dependence on investor pipeline?
8. Regulatory strategy unclear, may be forced to initiate MA application.

Key External Interactions:

Limited clinical KOL base at present

Contacts with researchers and potential licence/IP opportunities through Frankfurt University's technology arm

Orphan drug status (FDA and EU), and CAT Certification obtained, but relationship with EMA and the MA process not clear.

Limited investor base

NOTE: This Company's model appears to be the establishment of a revenue stream based on extending clinical use, while gradually acquiring IP and study data. It remains to be seen whether the company has the resources to move to a MA if this is required by competition or regulatory pressure.

Sources:

http://www.t2cure.de/about_t2cure/overviewmission/

Assmus B, Rolf A, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Tillmanns H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Tonn T, Dimmeler S, Dill T, Zeiher AM, and Schächinger V (2010). Clinical Outcome 2 Years After Intracoronary Administration of Bone Marrow-Derived Progenitor Cells in Acute Myocardial Infarction. Circulation Heart Failure;3:89-96

Dill T, Schächinger V, Rolf A, Möllmann S, Thiele H, Tillmanns H, Assmus B, Dimmeler S, Zeiher AM, Hamm C (2009). Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: Results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac Magnetic Resonance Imaging substudy. Am Heart J 157:541-7

Case Study Product Category 3: Allogeneic

Pluristem Therapeutics Inc: PLX-PAD

Background:

Pluristem Therapeutics Inc. (NasdaqCM: PSTI; DAX: PJT) is a clinical stage biotechnology company developing and manufacturing standardized cell therapies derived from the human placenta. Pluristem's PLX (PLacental eXpanded) cell products are expanded using the company's patented proprietary technology. The scalable technology offers cell therapies that are readily available for the treatment of critical limb ischemia (CLI) as well as other diseases and require no tissue matching prior to administration. Pluristem has a strong patent portfolio, a 45-person research and development team, company owned GMP certified manufacturing and R&D facilities of over 20,000 square feet, strategic relationships with major research institutions and a seasoned management and board.

Brief Product Description and Indications:

Pluristem's lead product candidate, PLX-PAD, is in clinical trials in multiple sites in the U.S. and Europe for patients suffering from critical limb ischemia (CLI), the end-stage of peripheral artery disease (PAD). Other earlier stage development indications are intermittent claudication; neuropathic pain; wound healing; orthopaedics, IBD, ischemic stroke, BM-transplantation & MS.

The PLX cells are mesenchymal-like adherent stromal cells (ASCs) derived from full term placenta. The cells are expanded in the company's proprietary bioreactor system, which provides a three dimensional (3D) microenvironment that enables full control over the manufacturing process, large-scale growth of these cells and batch to batch consistency. PLX cells are immune privileged and possess immune-modulatory properties.

Open-label, dose-escalation Ph-1 Safety study. Small number of patients (21) treated so far but top line results were promising. The interim data demonstrated that PLX-PAD is safe, well tolerated and effective. Trials in US/Germany met primary end points. No immune response in patients injected. All patients received HLA-nonmatched PLX-PAD cells. No specific sensitization to PLX-PAD cells observed.

2 territories: US - Duke University Hospital, Baptist Princeton Hospital, Center for Therapeutic Angiogenesis, Birmingham, USA. 12 patients with Rutherford Category 4-5 Critical Limb Ischemia. Two dosage groups (6 patients per dose) – single and double administration. Intramuscular administration in 30 locations above and below the knee. Clinical follow up – 3 months. Long term follow-up – 12 months. Safety Endpoints:

- Amputation incidence at three (3) months post treatment
- Death incidence at three (3) months post treatment
- Rehospitalization incidence at three (3) months post treatment
- Adverse events
- Immunological reactions
- Efficacy Parameters

Qualitative:

- Wagner Score (wound)
- Visual Analog Score (pain)
- King's College Score (quality of life)

Quantitative:

- Ankle-brachial index (ABI)
- Toe-brachial Index (TBI)
- Transcutaneous Oxygen Pressure (TcPO2)

German site:Franziskus-Krankenhaus Institute of Berlin (supported by the Charité-Universitätsmedizin Berlin). Open label, Dose escalation, 15 patients with Rutherford Category 4-5 Critical Limb Ischemia. Three doses (3 patients in the low dose, 6 patients in the intermediate and high dose). Intramuscular administration in 50 locations above and below the knee. Clinical follow up – 3 month. Long term follow-up – 24 months.

Safety Endpoints:

- Adverse events
- Safety laboratory values and ECG findings
- Immunological reaction
- Tumorigenesis
- Efficacy Parameters

Other criteria as for US sites.

A total of twenty-one patients, representing 77% of the cohorts required to complete the Phase 1 dose-escalating studies in the U.S. and Germany, have been dosed with PLX-PAD. This includes fifteen patients dosed in Germany, representing the complete patient enrolment in that country.

These Phase 1 studies were designed to evaluate the safety of PLX-PAD in patients with CLI. Both trials have currently met their primary safety endpoints. Additionally, the administration of PLX-PAD cells did not induce an immune response in any of the patients dosed, demonstrating that injection of PLX-PAD cells is well tolerated.

Target Indications and Markets:

Key Q: Clinical indications

The Paul-Ehrlich Institute approved 2 Phase 2 Clinical protocol synopses:

1) A Multinational, Multicenter, Randomized, Double-blind, Placebo Control, Parallel Study to Assess the Clinical Safety and Efficacy of Intramuscular (IM) Injection of Allogeneic placental derived ASC's (PLX-PAD Cells) for the treatment of patients with Symptomatic Critical Limb Ischemia. Fontaine class III-IV; Rutherford category 4-5.

2) A Multinational, Multicenter, Randomized, Double-blind, Placebo Control, Parallel Study to Assess the Clinical Safety and Efficacy of Intramuscular (IM) Injection of Allogeneic placental derived ASC's (PLX-PAD Cells) for the treatment of patients with Symptomatic Severe Intermittent Claudication. Fontaine class IIb; Rutherford category 3.

Q: What dose of cells will be used?

Q: How many centres and will the recruitment rate be adequate – indicated Ph2 as ~150 and Ph3 as ~400?

Q: Will the studies be sufficiently powered to generate meaningful data?

Key Q: Geographical target market:

US->EU-> RoW

Approximately 1.1 million people in the U.S. suffer from CLI, reflecting the aging population and the increasing prevalence of diabetes, SAGE GROUP (September 2005).

In 2008, approximately 2.8 million people in Western Europe have CLI and that this number is projected to grow to 3.4 million by 2020. SAGE GROUP (October 2008).

PAD and CLI Markets: The prevalence of PAD has usually been cited at 8-12 million people in the US. However, data from other sources suggests that the total number could be as high as 20 million patients. PAD increases significantly with age, as prevalence among the 65 and older age group is 12%-20%. (*Spronk, S, et al. Cost-effectiveness of new cardiac and vascular rehabilitation strategies for patients with coronary artery disease*).

Q: Assuming clinical success what is the likely proportion of the relevant markets that this product is likely to reach?
Q: What are the assumptions behind this forecast?

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

In market - PAD/PVD:

Antithrombotic drugs

Lipid lowering agents

Revascularization

Cell therapies:

Aastrom – going into Ph3 after successful multi centre Ph2 with autologous therapy (TRC). Other clinical stage autologous, less quality e.g. ALdagen, Baxter, Beike, BioHeart. Unknowns are Harvest Technologies, MultiGene Vascualr systems, TCA, Theravitae.

Many companies with allogeneic MSC-like somatic cell therapies or EPC-based therapies have pre-clinical data – best of the bunch Pervasis (tissue constructs for AV shunts, large vessel repair), ATHS.

Nothing marketed for CLI.

Q: Are cell therapies likely to be superior to non-cell therapeutics and what is needed for this product to distinguish itself from the competition?

Key Features of company business model

Key Q: big pharma, SME, IP company, virtual company

SME with a solid case of characterizing the cells and, in particular, the cells seem very scalable - claim to target production cost for 1 M cells of $1. They seem to have a solid IP position at this time. No royalties liability (other than Israeli government). Ownership of the IP: in 2007 they acquired from the “Weizmann Institute of Science” and the “Technion- Israel Institute of Technology” all the patents related to the technology. 15 granted patents; 39 applications.

Q: Not sure how the IP is different or conflicts with that of their competitors, particularly Celgene also working on placental derived cells?

Q: Is this a business model suitable for large pharma?

Key Q: target exit strategy

Already listed. Not favoured scenario for pharma venture investment. Collaborative R&D with pharma most likely prospect as their IP is their product is their livelihood. Possible that individual exclusive licensing in DA could be a possibility.

Q: Is exit for them to be a major acquisition?

Key Q: Other products in portfolio

Not much else product –wise. Processing IP, know how, trade secrets etc

Q: Do they need to diversify their business model?

Sources of finance & other key external relationships:

Key Q: Sources of finance; what do they want back?

No royalties due to licenors. The company has also received approval for a government grant in the amount of $2.5 million from the Office of the Chief Scientist at the Ministry of Industry, Trade and Labor of Israel, as government participation in R&D expenses for the period March 2010 to February 2011. This is the fifth consecutive year that Pluristem has received this grant. Company is burning $5-$6M a quarter funded by additional stock offerings.

Q: Will any acquirer be asked to repay the state aid?

Key Q: define any relationships with clinical KOLs

Carsten Tschope - Medical Clinic for Cardiology and Pulmology, Berlin Brandenburg School for Regenerative Therapies, Berlin, Germany.

Edwin M. Horwitz -Department of Pediatrics, Division of Oncology/Blood and Marrow Transplantation, Children's Hospital of Philadelphia, Pennsylvania, USA

Dr. Abraham Treves - a leading Israeli expert on hematopoietic stem cells (HSCs)

Dr. Avinoam Kadouri - CEO of Rainbow Biotechnologies Sarl and is considered one of the leading scientists in industrial biotechnology with a worldwide reputation

Prof. Ron Gonen, MD - In 2002 he was appointed Associated Professor at the Faculty of Medicine, Technion – Israel Institute of Technology

Jacob Michael Rowe, MD, F.A.C.P. - from University College and University College Hospital in London.

Prof. Arnon Nagler - received his certification in Internal Medicine from the Israel Board of Internal Medicine

Aristidis Veves, MD - the Research Director of the Joslin-Beth Israel Deaconess Foot Center and of the Microcirculation Lab, and Associate Professor at Harvard Medical School.

Brian Annex, MD - residency in internal medicine at Tuft's-New England Medical Center in Boston.

Regulatory Strategy/Status:

Key Q: Target approval routes and time to approval

Data to support the IND filing is published in CytoTherapy article. IND approval was granted within a month. Pre-clinical data was generated in collaboration with the Department of Pediatrics, Division of Oncology/Blood and Marrow Transplantation, Children's Hospital of Philadelphia, Pennsylvania, USA. Placental-derived adherent stromal cells (ASC) were studied in a standard limb ischemia model of male Balb/c mice. The intramuscular (i.m.) administration of PLX-PAD in the model significantly improved blood flow (BF) (P_0.0008), increased capillary density (P_0.021), reduced oxidative stress (P_0.034) and reduced endothelial damage (P_0.004), while increasing limb function versus the administration of a phosphate-buffered saline (PBS) control vehicle in the affected limb.

It has taken longer for the company to receive permission from the Paul Ehrlich Institute for the clinical trial in Germany as PLX-PAD was the first allogeneic cell product given to humans in Germany.

Q: Regulatory agencies do not mandate any unique clinical trial parameters for cell therapies – discuss?

Q: How robust is the IND package to enable bridging into other indications?

Q: Will the regulators require acute toxicity studies for i.v. delivered product for other indications?

Q: How acceptable will be the regulatory package for other EU countries?

Key Q: Approval status

Q: What other data will be needed in support of IND/EMA filings?

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

Q: Are the healthcare cost savings and the costs to produce a successful treatment suitable for consideration for reimbursement?

Q: What are the assumptions associated with this estimate?

Manufacturing & supply Strategy:

Key Q: living cell product?

ASC are isolated from full-term human placentas. All placentas obtained by Pluristem are received from a maternity ward following scheduled Caesarean sections under approval of the Israeli Ministry of Health Helsinki Committee. All placenta donors sign an informed consent before donor screening and testing are performed. The placentas are transported from the medical centre to Pluristem under controlled conditions: they are placed in a sterile plastic bag and then into a Styrofoam box with ice packs, and delivered to Pluristem.

At Pluristem the placentas are placed in a quarantine area until released for use by quality control (QC) and quality assurance (QA). Placenta-processing initiation occurs 54 h following the Caesarean section. The production of PLX-PAD is performed in a state of- the-art clean room facility according to good manufacturing practice (GMP) regulations. The facility and utility systems provide a 125-m2 clean room production area, a QC laboratory, a storage room and cold storage areas.

The production process is composed of several major steps that include receipt of the placenta, recovery and processing of ASC, growth of the cells in tissue culture flasks [two-dimensional (2-D) cultures] and harvest and storage of the cells in liquid nitrogen as 2-D cell stock (2DCS). The 2DCS is considered to be an in-process intermediate product and is tested for sterility, mycoplasma, immunophenotype and viability. Upon meeting 2DCS release specifications, the appropriate amount of 2DCS is thawed, washed and seeded onto carriers in bioreactors for further expansion in three-dimensional (3-D) culture. The process is not automated.

After 1-2 weeks of growth in the bioreactors, the cells are harvested and cryopreserved in liquid nitrogen as PLX-PAD. During the manufacturing process an in-process control (IPC) is established based on FDA guidelines. PLX-PAD are manufactured and released under a QC program including IPC testing and a battery of product-release tests and specifications, such as visual appearance, viability, immunophenotype, mycoplasma, endotoxin, sterility and an in vitro potency assay.

In-house processing. No further details known on plans for multi site manufacture and distribution.

Ability to achieve patient volume for CLI is critical as COGs for both allogeneic and autologous therapies increase with lower volumes.

They will need to reformulate and supply for non-CLI indications and i.v. delivery. Beyond cost impact, specialized delivery poses the greatest risk to adoption when the prescriber is uncomfortable and may need to refer. A complex RoA may limit adoption of the cell therapy unless the product profile is demonstrably superior to any alternatives. A specialized device may further hinder adoption given the added cost and complexity.

Q: Will the need to reformulate the therapy for i.v. delivery pose a major risk to adoption of this as more production centres will be needed?

Key Q: make or buy?

Q: Continue to make or would costs of production be lowered if contracted out?

Publications:

1. Safety and biodistribution profile of placental-derived mesenchymal stromal cells (PLX-PAD) following intramuscular delivery. Ramot Y, Meiron M, Toren A, Steiner M, Nyska A Toxicol Pathol. 2009;37(5):606-16. Epub 2009 May 28

2. Placental-derived and expanded mesenchymal stromal cells (PLX-I) to enhance the engraftment of hematopoietic stem cells derived from umbilical cord blood Prather WR, Toren A, Meiron M. Expert Opin Biol Ther. 2008 Aug;8(8):1241-50. Review.

3. The role of placental-derived adherent stromal cell (PLX-PAD) in the treatment of critical limb ischemia. Prather WR, Toren A, Meiron M, Ofir R, Tschope C, Horwitz EM Cytotherapy. 2009;11(4):427-34

4. Placental-derived and expanded mesenchymal stromal cells (PLX-I) to enhance the engraftment of hematopoietic stem cells derived from umbilical cord blood. Prather WR, Toren A, Meiron M. Expert Opin Biol Ther. 2008 Aug;8(8):1241-50. Review

5. Pluristem Therapeutics, Inc Prather W. Regen Med. 2008 Jan;3(1):117-22.

Key Value Steps:

1. Matching proposed production costs.
2. What does their data look like post 6 months?
3. Adequately powered, successful Phase 2 data on efficacy.

Key External Interactions:

However, by leveraging an existing cold-chain for distribution, most of the significant hurdles might be overcome

Assumptions made

- CLI is a high disease severity
- CLI is moderate disease acuity
- Addressable population is low
- Physician receptivity is moderate
- Treatment options are limited
- Unmet need is therefore high

Sources:

Published material and non-confidential slide material

Case Study Product Category 4: Other

Cytori Therapeutics: Celution®800/CRS

Brief Product Description:

The Celution®800/CRS is a medical device that automates and standardizes the extraction, washing, and concentration of autologous Adipose-Derived Regenerative Cells (ADRCs), which can then be redelivered to the same individual in a single surgical procedure. In addition, the Celution® device can wash adipose tissue and mix it with the processed ADRCs to create a cell-enriched graft for immediate re-implantation into the same patient. The Celution® device is a sterile, closed system that is computer controlled and automated. The adipose tissue is processed using a sterile single use consumable set (Celution®805/CRS) and a proprietary enzyme solution that is designed to release stem and regenerative cells from adipose tissue (CELASE™ 835/CRS).

Target Indications and Markets:

Key Q: Clinical indications

As a device, the intended use of the Celution® System will vary dependent upon regulatory clearances, clinical market demand and the compatibility of the system and its by-products for that intended use. The company are currently targeting two major clinical areas; cardiovascular disease (myocardial ischemia and myocardial infarction) and reconstructive surgery e.g. for breast cancer patients.

Key Q: Geographical target market

Despite being a US-based company, Cytori have thus far only gained regulatory approval for the EU for the Celution® System (CE marked in the EU). It is estimated that nearly 50% of their sales come from Japan, with the remainder from the UK, Italy, Spain and Germany. However, the company have other products with regulatory approval in the US and are currently planning to carry out clinical studies under an IDE in order to support a regulatory application to gain market approval for Celution®. The company are also targeting Eastern Europe, with Russia being the most significant target market for the product in that region.

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

Breast Reconstruction

Lipo-modelling is currently a commonly used technique in breast reconstruction surgery. Fat is removed from the abdomen or thighs of the patient before being injected into the area in need of reconstruction e.g. after wide local excision procedure. Lipo-modelling is a surgical intervention carried out using the patients' own tissues (autologous) and there is no commercial involvement in the process as a result. It is also associated with unpredictable results due to variable graft retention. The major alternatives to this are more complex reconstructive surgery or the surgical implantation of a breast implant containing either silicone or saline, although implants are seen as unsuitable to address post-breast conservation therapy (BCT) in most cases.

Chronic Myocardial Ischemia and Acute Myocardial Infarction

Chronic Myocardial Ischemia (CMI) (ischemic heart disease) is one of the biggest causes of death in the Western world. There are numerous drugs used to treat CMI in its early stages,

which then as the disease progresses, will lead to the requirement for surgical interventions such as angioplasty and coronary artery bypass surgery. When the disease has progressed beyond the use of these surgical procedures, a heart transplant is the only chance of survival for patients. However, drug-based treatments are limited, surgical interventions are often unsuccessful / merely delaying the inevitable and heart transplants procedures are limited by either a lack of suitable donors or patient rejection. A lack of suitable drug and surgical treatments has resulted in an increasing number of cellular therapeutics being taken in clinical development for the treatment of CMI (table 1). However, none of these cell therapy products are close to market, as all are regulated as section 351 HCT/Ps and there are no pivotal Phase 3 trials yet underway.

Table 1 Current cell therapy products in clinical development for the treatment of CMI

Company	**Product**	**Regulatory Route**	**Stage of Development**
Aldagen	ALD-201 (autologous bone marrow derived stem cells that have high levels of ALDH activity)	IND-BLA	Phase 1 complete Phase 2 in planning
Aastrom Biosciences	Autologous bone marrow derived stem cells (mesenchymal and hematopoietic)	IND-BLA	Phase 1 complete and Phase 2 in progress
Advanced Cell Technology	Autologous stem-cell derived myoblasts	IND-BLA	Phase 1 complete Phase 2 recruiting
Arteriocyte	ACY001 (autologous own bone marrow-derived hemangioblast stem cells)	IND-BLA	Phase 1 complete
Baxter	ACT34-CMI (adult autologous cellular therapy CD34+ stem cells)	IND-BLA	Phase 1 complete. Phase 2 recruiting

Treatment of an Acute Myocardial Infarction (AMI) is conventionally through restoration of the blood flow to the heart, thus limiting the damage to the myocardium and preventing further complications after a heart attack. Although many patients frequently survive AMIs, the damage caused to the myocardium during an attack shortens their lives. Conventional drugs and devices (e.g. pacemakers) have been used to restore heart function but they are limited to extending the life of patients for a finite period and heart transplants are not a viable solution for the reasons stated above. For this reason, many cellular products that seek to restore cardiac function by regenerating the tissue that is damaged during AMI are currently in development (Table 2). All of these products are in the early phases of clinical development. However, TGI 1200 (Bioheart) is the most interesting of these products as it too is a CE-marked medical device and essentially uses the same technology as the Celution® System (processing of adipose derived stem cells).

However, unlike the Celution® device this product has yet to undergo clinical studies to provide positive evidence of clinical utility. At present it is only CE Marked for research and investigational use.

Table 2 Current cell therapy products in development for the treatment of AMI

Company	**Product**	**Regulatory Route**	**Stage of Development**
Capricor	Intra-myocardial injection of autologous, cardiac-derived stem cells	IND-BLA	Phase 1 in progress
Osiris	Prochymal; intravenously infused allogeneic mesenchymal stem cells	IND-BLA	Phase 1 complete and enrolling patients for Phase 2
Angioblast Systems	A range of adult stem cell, peptide and gene therapy products.	IND-BLA	Mesenchymal pre-cursor cells are most advanced product Phase 2 studies underway
Bioheart	TGI 1200 Cell Isolation System for the isolation of adult stem cells used to treat AMI	CE mark in EU	Yet to undergo clinical studies

Q: Will the number of cellular products being developed for the same CV indications diminish the market for the Celution® System or will the necessity for most of them to gain regulatory approval as ATMPS / HCT/Ps allow Cytori to gain a significant share of the market before they can reach it?

Key Features of Business Model:

Key Q: big pharma, SME, IP company, virtual company

Cytori Therapeutics Inc. (San Diego, CA) is a small to medium-sized publically-listed company (NasdaqGM: CYTX $5.69 per share Feb 2011) that employs ~110 people, most of which are based in San Diego. The company was founded when two separate companies with complementary technologies' became one in 2005; Stem Source Inc. (owned IP on adipose derived regenerative cells technology) and MacroPore Biosurgery Inc (a medical device / materials biomaterials company). Despite being the main source of revenue, the focus of the business has moved away from the poly-lactic acid resorbable products manufactured by MacroPore Biosurgery and towards new technologies that combined the knowledge of both companies i.e. one that involved both cells and devices.

Thus, the business model for Cytori is to develop, manufacture and sell their products globally for use in regenerative medicine applications by seeking strategic partnerships and

utilising the medical device regulatory pathways. By using these device pathways, the company has sought fast market approval for what will be viewed as a disruptive technology, especially for those developing drugs and cellular therapies for cardiovascular indications.

Q: Will the business model depend upon successful market entry in the US and the willingness of clinicians to take on the risk of re-implanting the cells, despite their being no testing procedures for the identity of the cell population before re-implantation?

Key Q: Target Exit Strategy

The company has been floated on the stock market and raised significant funds from private investors suggesting that they are not anticipating a trade sale but plan to grow to take their products through the regulatory, reimbursement and adoption process with the help of key partners such as Olympus and GE Healthcare.

Key Q: Other products in portfolio

Cytori have several other products in their portfolio, which are geared to the preparation and removal of adipose tissue.

PureGraft

PureGraft is a product which allows the operator to prepare a fat graft in about 20 minutes. The PureGraft bag clears the lipoaspirate of blood, tumescent fluid, and free lipid in a closed, sterile system. The physician can be in complete control of the hydration of the fat graft by adjusting the length of time that the bag is allowed to drain during the final step. PureGraft has been given clearance by the FDA as a Class II medical device under the 510(k) pre-market notification system and the CE mark in Europe (both 2010).

Harvest instrument set

The harvest instrument set is a collection of autoclavable components provided by various manufacturers which have been packaged together by Cytori. This kit contains all of the instruments necessary for tissue collection and has been optimized for use with Cytori's tissue processing technology. This kit is used for the harvest of adipose tissue both for storage and banking as well as autologous fat transfer procedures.

Delivery instrument set

The Delivery Instrument Set is a collection of autoclavable components which are optimized for fat graft preparation and delivery. The kit contains unique accessories necessary for optimal PureGraft fat graft preparation and two Celbrush™ delivery tools.

StemSource™ cell bank

A StemSource™ cell bank will allow hospitals, stem cell storage companies, or tissue banking labs to process and cryopreserve a patient's own adipose-derived stem and regenerative cells when the cells are younger and more viable. StemSource™ cell banking services coupled with the real time Celution® clinical cell therapy may ultimately allow hospitals to provide a broad array of regenerative medicine services to patients.

The foundation of the cell bank is Cytori's FDA-approved Celution®900-MB System, which automates the processing of stem and regenerative cells from adipose tissue. This function facilitates the preparation and storage of the cells.

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

Olympus Joint Venture Details

- Olympus licensed its device-related technology to the Joint Venture and paid $30 million into to the Joint Venture for its 50% interest therein.
- Cytori exclusively licensed its therapeutic device technology, including the Celution® System and certain related intellectual property, to the Joint Venture with Olympus and received an initial $11 million payment and its 50% interest in the Joint Venture in 2005.
- Upon Cytori's receipt of a CE Mark for the first generation Celution® System, Cytori received a second $11 million milestone payment from the Joint Venture in 2006 and a further $1.5 million from Olympus for granting commercialization collaboration rights for the use of their technology for a specific therapeutic area outside of CV disease, in the same year.

Additional Investment and Green Hospital Supply

In addition to the payments received from Olympus described above, the company has continued to aggressively raise money through further strategic collaborations and selling shares to select investors. In August 2006, Cytori announced that it had entered into agreements to raise approximately $16.8 million through the sale of 2,918,255 shares of common stock to Olympus Corporation as well as new and existing institutional investors at $5.75 per share. Olympus has agreed to purchase a total of 1,913,043 shares. The purchase price was determined by Cytori's closing price on August 9, 2006. In February 2007, the company announced that it has entered into definitive agreements to raise a further $21.5 million through the issuance of 3.75 million shares at $5.74 per share.

In March 2007, Cytori announced that they had entered into a strategic equity agreement with Green Hospital Supply, Inc., one of the main medical equipment suppliers in Japan, who purchased 1.0 million shares of the Company's common stock at $6.00 per share ($6 million in total). In Feb 2008, Green Hospital Supply purchased a further 2 million shares of unregistered Cytori common stock at $6.00 per share ($12 million in total) and was granted a non-voting observer seat on Cytori's board of directors. In June 2008, Cytori secured a $15 million loan facility from GE Healthcare. In August 2008, Cytori raised $17 million from a private placement financing led by Olympus Corporation with participation from select institutional investors. In March 2009 Cytori announced that they had closed and received a further $10 million, through the sale of common stock to select investors (4,771,174 shares, at a purchase price of $2.10 per unit). In May 2009, Cytori Therapeutics Inc. announced that it has entered into definitive agreements to raise approximately $4.2 million through a private placement with select investors (1.86 million shares at a purchase price of $2.28 per share).

In June 2009, Cytori announced that they had entered into an equity agreement with Seaside 88, LP (Seaside). Under the terms of the agreement, Seaside has committed to purchase up to 7.15 million Cytori common shares, in a series of closings every two weeks in the amount of 275,000 shares each for a total of up to 26 purchases. The price paid at each closing was dependent upon the share price at that time (minimum of $2.50 per share). During this time the share price averaged ~$7.00 per share so the approximate amount raised over the 12 months was $17.857 million. In October 2010, Cytori announced that they had closed their public offering of 4,600,000 shares of common stock. All of the shares were offered by Cytori. Net proceeds from the sale of the shares, after underwriting discounts and commissions and other offering expenses, were approximately $19.3 million.

Finally, in December 2010 Cytori and Astellas Pharma Inc. announced that they have entered into a strategic equity agreement to evaluate the potential of adipose derived stem and regenerative cells for the treatment of serious illnesses for which there is no fundamental treatment. Astellas purchased approximately 1.43 million unregistered shares of Cytori common stock at $7.00 per share for net proceeds to Cytori of $10 million. As part of the agreement, Cytori granted Astellas the following additional rights; Two year right of first refusal for a worldwide research, development and/or commercialization partnership using Cytori's products and technologies in the treatment of liver disease; Non-voting observer seat on Cytori's board-of-directors; and Participation in a newly formed scientific advisory board.

In summary, Cytori have raised a significant amount of money (~$160M + $17M in loans) but have not yet made a profit. This will be largely dependent on FDA approval in the US and successful reimbursement in the EU, which are both dependent upon the strength of the clinical data currently being collected. Their share price has remained consistent for five years and investors have been very willing to get on board since the company gained its EU approval and the decision to focus on CV indications for which their main competition is still many years from the market due to a greater regulatory burden. Much of the investment has come from Japan, a tie in with the regulatory approval of their StemSource™ product in Japan and because of the potential for selling the Celution® System in the second biggest medical device market in the world.

Key Q: Background on investors

Olympus

Olympus was founded in Tokyo in 1919 with the declared purpose of manufacturing microscopes that would garner recognition in the global market. The company has a working capital of ¥48.3 billion and employs over 35,000 people worldwide. The company also has a separate arm for the manufacture of medical devices (Olympus Medical Systems Corp) with a working capital of ¥1 billion and more than 2500 employees.

Green Hospital Supply

Green Hospital Supply is one of the biggest medical device suppliers in Japan. Formed in Osaka in 1993, the company has a working capital of ¥5.7 billion and employs over 1,500 people across Japan.

Astellas Pharma

Astellas Pharma Inc., located in Tokyo Japan, is a pharmaceutical company with approximately 16,000 employees worldwide. The organization is committed to becoming a global category leader in Urology, Immunology & Infectious Disease, Neuroscience, DM Complications & Metabolic Diseases, and Oncology.

Seaside 88 Advisors LLC

Seaside 88 appears to be a private equity firm based in Palm Beach, Florida. There is little or no information on them available in the public domain.

Key Q: Define any relationships with clinical KOLs

One of the most important clinicians associated with Cytori is Eva Weiler-Mithoff of the Glasgow Royal Infirmary, Weiler-Mithoff became the lead investigator for the RESTORE-2 trial, in which the Celution® System was used in post-lumpectomy patients to restore lost volume and correct soft tissue defects. In December 2009, Weiler-Mithoff attended the San Antonio Breast Cancer Symposium and announced positive 6 and 12-month data for the procedure and is seen as the one of the key figures in the success of the trials so far.

Regulatory Strategy/Status:

Key Q: Target approval routes

Cytori are currently carrying out clinical trials to increase the number of indications covered by the CE mark and to support adoption into the EU market. The company were hoping to gain 510k clearance for the Celution® device in the US but due to a lack of suitable predicate devices (such is the novelty of the device), the company are now following the pathway for Class III medical devices (Pre-Market Approval (PMA)). This requires the company to collect clinical data to show sufficient safety / efficacy to gain regulatory approval in both the CV and reconstructive surgery applications. The company are currently in discussions with the FDA regarding clinical studies in the US.

Q: Will any subsequent change in the regulations regarding the use of enzymatic cellular manipulation result in greater clinical data requirement? Also, would these changes apply given the fact that Celution® is regulated as a medical device and not a medicinal / biological product?

Key Q: Clinical data and time to approval

The company are carrying out three clinical studies to support the safety and efficacy of ADRCs for three indications in order to support reimbursement and adoption in Europe.

<u>Cardiovascular Trials</u>

Note: All of the CV trials are being carried out with a second generation version of the Celution® System. This system contains a second enzyme which prevents the clumping of cells with the aim of enhancing the delivery of the cells through the narrow catheters that are used in the CV applications.

Name of trial: APOLLO-01 (48-patient, double-blinded, placebo controlled).

Indication: Acute Myocardial Infarction (heart attack).

Full title: A Randomized Clinical Trial of **A**di**PO**se-Derived Stem ce**LL**s in the Treatment of Patients With ST-Elevation my**O**cardial Infarction - The APOLLO Trial.

ClinicalTrials.gov ID: NCT00442806

http://www.clinicaltrials.gov/ct2/show/NCT00442806?term=apollo-01&rank=1

Primary endpoint: Safety; as determined by Major Adverse Cardiac and Cerebral Events (MACCE) over 6 months.

Secondary endpoint: Feasibility - Assessment of cardiac function via functional and imaging studies including MRI, SPECT, and Echocardiography over 6 months.

Study Details and Timeline: Cytori's APOLLO-01 trial is a safety and feasibility study in Europe to evaluate the use of ADRCs as a treatment in heart attack patients. Within 24 hours of experiencing heart attack symptoms, a patient's own ADRCs are extracted and injected into his/her coronary artery. Enrolment is complete, and patients will be followed and evaluated for three years. The last patient enrolled in the study is expected to finish study participation by April of 2012. Subjects who have coronary artery disease and have suffered a ST-elevation acute myocardial infarction will be evaluated for eligibility in this study. Eligible subjects will undergo standard treatment after admission to the hospital and will then undergo liposuction under local anaesthesia, after which ADRC's will be isolated from the lipoaspirate. According to randomisation subjects will receive either ADRC's or placebo.

This two-centre study is taking place in the Netherlands (Erasmus University Medical Centre, Rotterdam) and Spain (Hospital General Universitario Gregorio Maranon, Madrid). The PI for the studies is Patrick Serruys, MD, PhD (Erasmus University Medical Centrum, Rotterdam). The study commenced in January 2008 and is due to be completed by April 2012.

Name of trial: PRECISE-01 (36-patient, double-blinded, placebo controlled).

Indication: Chronic Myocardial Ischemia.

Full title: A Randomized Clinical Trial of adi**P**ose-de**R**ived st**E**m & Regenerative *C*ells **I**n the Treatment of Patients With Non reva**S**cularizable isch**E**mic Myocardium - The PRECISE Trial.

ClinicalTrials.gov ID: NCT00426868

http://www.clinicaltrials.gov/ct2/show/NCT00426868?term=precise-01&rank=1

Primary endpoint: Safety - Determined by Major Adverse Cardiac and Cerebral Events (MACCE) over 36 months.

Secondary endpoint: Feasibility - Assessment of cardiac function using a variety of functional and imaging studies including MRI, SPECT and Echocardiography over 36 months.

Study Details and Timeline: The purpose of this study is to establish safety and feasibility of utilizing Adipose Derived Stem & Regenerative Cells (ADRCs) in patients who have areas of myocardium that are not revascularizable and have demonstrated reversible ischemia. Cytori's PRECISE-01 trial is a safety and feasibility study in Europe to evaluate the use of ADRCs in chronic ischemia patients that cannot be treated with other means. A patient's own ADRCs are extracted and then injected around the injured, oxygen-deprived areas of his/her heart through a catheter. Enrolment is complete, and patients will be followed and evaluated for three years.

The last patient enrolled in the study is expected to finish study participation by April of 2012. Meanwhile, data from six months of study participation for all patients will be analyzed in 2010. This data will provide information on safety and feasibility of the use of ADRCs in this patient population. This four-centre study is taking place in the Netherlands (Erasmus University Medical Centre, Rotterdam and the University of Utrecht Medical Cente, Utrecht), Spain (Hospital General Universitario Gregorio Maranon, Madrid) and Denmark (Rigshospitalet University Hospital, Copenhagen). The PIs for the studies are Francisco J Fernández-Avilés, MD, PhD, FACC, FESC Hospital G.U. Gregorio Maranon and Emerson C Perin, MD, PhD of theTexas Heart Institute.

Interim data (6 months)

The following was reported in May 2010:

1. Liposuction and cell injection were safe in these severely compromised patients, with no serious adverse events (arrhythmia or major adverse cardiac events).
2. MVO2 showed a statistically significant improvement from baseline to six-months in the cell treated group as compared to placebo. *MVO2 is a clinically relevant prognostic factor in heart disease and is commonly used as a contributing measure to stratify patients for heart transplant.*
3. The results showed absolute increase (improvement) in MVO2 by 0.6 mL/kg/min in the treated group versus 2.8 mL/kg/min decrease (worsening) in the placebo group from baseline to six-months, based on matched-pair analysis. This difference was statistically significant ($p < 0.05$). This analysis excludes two patients whose follow up MVO2 results were not available.

4. For the entire cohort of patients, mean MVO2 improved from 16.6 mL/kg/min at baseline to 17.2 mL/kg/min at six-months in cell-treated patients, and worsened from 19.0 mL/kg/min to 15.5 mL/kg/min in the placebo group.
5. METS (metabolic equivalent), a measure of the patient's aerobic capacity, improved by 0.2 points from baseline to six-months in the cell treated group compared to a decrease of 0.8 points from baseline to follow up in the placebo group based on matched-pair analysis; the difference was statistically significant ($p < 0.05$).
6. The percent of left ventricle infarcted, the portion of the heart not receiving blood to support pumping, decreased (improved) by 3.0% in the cell treated group compared to an increase (worsening) of 5.2% in the placebo group, an absolute difference of 8.2%.
7. Improvements in New York Heart Association Functional Class, which classifies the severity of heart disease on a scale of one to four, were observed in 63% of patients treated with cells as compared to observed in 33% of patients in the placebo group.

Improvements were also reported at the 12 month and 18 month stages. These data were used to successfully extend the list of indications that were allowable under the original CE mark.

Recent Development

In January 2011, Cytori Therapeutics received approval from The Netherlands to initiate a pivotal European trial, named ADVANCE, to investigate adipose-derived stem and regenerative cells (ADRCs), processed by the Celution One System, in the treatment of patients with acute heart attacks. This is the first country and trial-centre approval for ADVANCE.

Name of trial: ADVANCE (360-patient, double-blinded, placebo controlled).

Indication: Acute Myocardial Infarction (heart attack).

Study Details and Timeline: The primary endpoint of the trial is reduction in infarct size as measured by cardiac magnetic resonance imaging (MRI). ADVANCE will use the Celution One, our next generation device manufactured by Olympus-Cytori Joint Venture. The Celution One System draws on the same core technology and scientific innovation as the Celution®800 System, which is currently approved in Europe for breast reconstruction, certain aesthetic procedures and specific types of wounds. Additional country and trial-centre approvals are anticipated throughout Europe during the first half of 2011. One of the goals of the trial is to expand the Celution® System CE Mark to include acute heart attack claims and to provide economic data to justify its implementation and reimbursement.

<u>Reconstructive Surgery Trials</u>

Name of trial: RESTORE-01 (11-patient, uncontrolled).

Indication: Breast reconstruction after partial mastectomy

Full title: A Clinical Evaluation Of Adipose Derived **R**egenerative Cells In The Treatment Of Patients With Br**E**ast Deformities Post **S**egmental Breast Resec**T**ion (Lumpectomy) With **O**r Without **R**adiation Th**E**rapy.

ClinicalTrials.gov ID: None

Primary endpoint: Safety

Study Details and Timeline: This 11-patient trial was used to show safety when separating and processing ADRCs using the Celution® System for autologous transplantation. The study was completed in 2007 and provided the basis for a larger European trial (RESTORE-2).

Name of trial: RESTORE-02 (70-patient, uncontrolled, open label).

Indication: Beast reconstruction after Lumpectomy

Full title: A Clinical Evaluation Of Adipose Derived **R**egenerative Cells In The Treatment Of Patients With Br**E**ast Deformities Post **S**egmental Breast Resec**T**ion (Lumpectomy) With **O**r Without **R**adiation Th**E**rapy. A Phase IV Post Market Study.

ClinicalTrials.gov ID: NCT00616135

http://www.clinicaltrials.gov/ct2/show/NCT00616135?term=restore-2&rank=1

Primary endpoint: Efficacy - Patient and physician satisfaction with functional and cosmetic results. Improvement in overall breast deformity measured at 12 months compared to baseline.

Secondary endpoint: Change in breast volume and shape at 6 and 12 Months compared to baseline. Improvement in skin pigmentation abnormalities at 6 and 12 months compared to Baseline. Improvement in overall breast deformity at 6 Months compared to Baseline.

Study Details and Timeline: The study was conducted after the granting of the CE mark for the Celution® System in order to show the efficacy of autologous Adipose Derived Stem & Regenerative Cells (ADRCs) when transplanted into in post-mastectomy / lumpectomy patients. The study commenced on in June 2008 and completed in March 2010.

This four-centre study is taking place in the UK (Glasgow Royal Infirmary, Glasgow), Spain (Hospital General Universitario Gregorio Maranon, Madrid), Belgium (Jules Bordet Institute of Cancer, Brussels) and Italy (Università degli Studi di Firenze, Florence).

Interim data (6 months)

The study reported a high degree of patient (73%) and physician (82%) satisfaction at the interim six-month observation period with the overall outcome after a single treatment in difficult to treat breast reconstruction patients. On a scale of zero to five (five is extremely satisfied and zero is extremely dissatisfied), mean patient satisfaction scores improved from 2.8 at baseline to 3.9 at six-month follow up. Mean physician satisfaction scores improved from 3.1 to 4.1. For the 32 patients, there was a mean age of 52 years and a mean defect volume estimated by the investigators of 106 milliliters in 33 treated breasts (one patient had both breasts treated).

General anesthesia was used in most patients (32 out of 33 during liposuction and 20 of 33 for re-injection). In 24 patients, a single donor site was used, in eight patients two sites, and in one patient, three sites were used for liposuction. The abdomen was the preferred site for harvest of the graft (28 of the total 43 harvest sites). One operative complication was reported. A patient on anticoagulation therapy had a postoperative hematoma that resolved without continuing harm to the patient. Patient and physician satisfaction scores are based on pre-operative versus post operative assessment of symmetry, scarring, pigmentation and overall breast deformity.

Key Q: Approval status

The Celution® System is approved as a medical device for reconstructive applications in the EU. Clinical studies carried out under an Investigational Device Exemption are required for the device to be approved by the FDA under a Pre-Market Approval (Class III).

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

Cytori are targeting the UK as its first European market in which they are seeking coded reimbursement, this is despite the UK being dominated by the socialised medicine approach (publically funded healthcare). This has largely been dictated by the different approach taken by the NHS and private healthcare providers. The NHS are viewed to take a more diligent approach to use of the device where as Cytori are concerned that less regulated private clinics may not use the device correctly, which could potentially have a negative effect on adoption of the technology. NICE is currently reviewing lipofilling as an interventional procedure. Note: Cytori had nothing to do with the NICE review. I believe this was prompted by the increasing use of lipofilling in the NHS.

Cytori are also of the belief that there is sufficient flexibility in the UK system that will allow the product to reach the market, as codes are in place for products such as this. The product has currently been sold to 6 NHS units in the UK with another 7-8 units currently preparing and submitting business plans for the acquisition of the Celution® System. In total, 50 units have been sold in the EU so far at a cost of £60,000 per unit and £1700 per procedure (based on the use of consumables that must change after every procedure).

In order to gain reimbursement, Cytori have geared their clinical studies towards collecting data that will satisfy the many payers and clinical / cost effectiveness assessments that are required throughout Europe and the US. This is despite having regulatory approval in the EU, as the CE mark did not require clinical data and does not yet cover all of the potential cardiovascular indications. The company are also targeting Germany, Italy, Spain and France.

Manufacturing and Supply Strategy:

Key Q: Living cell product?

Despite the fact that the Celution® System is used to process autologous cells for therapeutic indications, the product itself is a medical device and thus avoids the more rigorous GMP requirements and manufacturing processes associated with complex biologics such as cellular products.

Key Q: Make or Buy?

Without a viable cell component Cytori could manufacture the Celution® System without the level of regulatory and technical burden that comes with having a complex biological component e.g. sterile GMP manufacture. In addition, this has allowed the company to use the tried and tested infrastructure that exists for medical devices including the distribution and supply networks that are already in place. Without the need for a highly sophisticated bio-manufacturing process, Cytori has been able to manufacture the Celution® System in-house with the exception of some small components that are produced by contract manufacturers.

Cytori have used strategic partnerships with other, larger organisations in order to expand their product pipeline and utilise the production and commercial know-how of those with more resource / market knowledge at their disposal.

GE Healthcare

A partnership with GE Healthcare was set-up in order to gain market entry for the Celution® System in select European countries. GE Healthcare will commercialise the Celution® System in translational medicine and stem cell banking in combination with Cytori's StemSource™ cell bank product. According to Cytori CEO Christopher J. Calhoun, "GE

Healthcare will immediately broaden our access to customers in Europe and should greatly expand our Celution® System installed base. We will benefit from their existing hospital relationships and their established regenerative medicine sales infrastructure in countries where we currently do not commercialize the Celution® System. Ultimately, our mutual goal is to broaden the relationship after we are able to better assess the market opportunities across several therapeutic indications and geographic regions." Note: The contract with GE has been revised and they no longer cover the surgical indications.)

The partnership provides GE Healthcare with exclusive commercialization rights for 18 months in the U.K., France, Germany, Norway, Finland, Denmark, Sweden, Austria, and Switzerland for the cosmetic and reconstructive surgery market, translational medicine, and stem cell banking. The same terms apply in Belgium, The Netherlands and Luxembourg for translational medicine and stem cell banking. GE Healthcare was granted a two year right of first refusal to sales and distribution rights in the United States and all remaining European countries.

Olympus

Cytori formed a 50:50 joint venture with Olympus, in order to develop and manufacture medical devices. Thus far, the main output from this partnership has been the manufacture and distribution of the Celution® System.

Highlights of the agreement included:

- Olympus licensed its device-related technology to the Joint Venture and pay $30 million to the Joint Venture for its 50% interest therein
- Cytori exclusively licensed its therapeutic device technology, including the Celution® ™ System and certain related intellectual property, to the Joint Venture and received an initial $11 million payment and its 50% interest in the Joint Venture
- Upon Cytori's receipt of a CE Mark for the first generation Celution® System, Cytori received a second $11 million milestone payment from the Joint Venture
- •The Joint Venture obtained exclusive rights to develop, manufacture, and supply the devices for all therapeutic applications solely to Cytori at a formula-based transfer price and Cytori maintained marketing rights to the devices for all therapeutic applications of adipose stem and regenerative cells

Green Hospital Supply

In March 2007, Cytori entered into a strategic equity agreement with Green Hospital Supply, Inc., one of the medical equipment suppliers in Japan. Green Hospital Supply purchased 3 million shares ($18 million worth in total) and was granted a non-voting observer seat on Cytori's board of directors. This move provided a Japan-wide supplier of Cytori's products, utilising the sound infrastructure that was already in place.

Publications:

Research and Pre-Clinical data

http://ir.cytoritx.com/releasedetail.cfm?releaseid=386309
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=439604
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=429809

Zhu, Min, Zhou, Zhengyu, Chen, Yan Schreiber, Ronda, Ransom, John T, Fraser, John K, Hedrick, Marc H, Pinkernell, Kai, Kuo, Hai-Chien. Supplementation of Fat Grafts With Adipose-Derived Regenerative Cells Improves Long-Term Graft Retention. *Annals of Plastic Surgery*: 64 (2) 222-228 (2010)

Hicok KC, Hedrick MH. Automated isolation and processing of adipose-derived stem and regenerative cells. *Methods Mol Biol.* 2011;702:87-105.

Lin K, Matsubara Y, Masuda Y, Togashi K, Ohno T, Tamura T, Toyoshima Y, Sugimachi K, Toyoda M, Marc H, Douglas A. Characterization of adipose tissue-derived cells isolated with the Celution® system. *Cytotherapy.* 2008;10(4):417-26.

Fraser JK, Schreiber R, Strem B, Zhu M, Alfonso Z, Wulur I, Hedrick MH. Plasticity of human adipose stem cells toward endothelial cells and cardiomyocytes. *Nat Clin Pract Cardiovasc Med.* 2006;3 Suppl 1:S33-7

Clinical data

APOLLO Trial

http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=544906
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=467678

PRECISE Trial

http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=386027
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=467680
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=530503

RESTORE-2 Trial

Weiler-Mithoff E, Pérez Cano R, Hedrick M, Lasso Vazquez J, Lehr A, Vranckx J, Milstein A. Single treatment cell-enhanced reconstruction after BCT: a proven technique. *San Antonio Breast Cancer Symposium* (2009).

http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=429810
http://ir.cytori.com/InvestorRelations/releasedetail.cfm?ReleaseID=480428

See *clinical data and time to approval* section above for further data.

Key Value Steps:

1. European approval (CE mark)
2. Positive 12-month clinical efficacy data for breast reconstruction indications
3. Partnership with GE Healthcare
4. Partnership with Olympus
5. Positive 12-month clinical efficacy data for cardiovascular indications
6. Clinical trial approval in the US
7. Approval by the FDA (PMA)

Key External Interactions:

Olympus, Green Hospital Supply and GE Healthcare – see manufacturing section.

Sources:

Most material from an Interview with John Ferris (European Business Development Manager, Cytori).

Cytori website:
www.cytori.com

Financial information:
http://finance.yahoo.com/news/Cytori-Enters-Strategic-iw-694893597.html?x=0&.v=1
http://www.reuters.com/finance/stocks/keyDevelopments?symbol=CYTX.O

Clinical data:
http://www.wired.co.uk/magazine/archive/2010/12/features/all-natural?page=3
http://www.cytori.com/Innovations/ClinicalTrials/ReconstructiveSurgery/RESTORE2INTERIMRESULTS.aspx

Investor websites:
Astellas Pharma Inc.
www.astellas.com/en
Green Hospital Supply
http://www.daiwair.co.jp/CIB/3360/english/index.html

Tengion Inc: Neo-Bladder Augment™

Brief Product Description:

The Tengion Neo-Bladder Augment™ is being developed for patients with neurogenic bladder, or dysfunctional bladder due to some form of neurologic disease or condition, for which treatment often requires an augmentation of the bladder in order to relieve high pressure and incontinence. Neo-Bladder is composed of autologous urothelial cells and smooth muscle cells cultured on a polyglycolic acid scaffold which is surgically attached to the dome of the bladder.

Target Indications and Markets:

Key Q: Clinical indications

Neo-Bladder has three clinical indications; (1) spina bifida (2) spinal cord injury and (3) urge incontinence. Phase 2 clinical trials have been carried out in patients with spina bifida and spinal cord injury.

Key Q: Geographical target market

The primary market is the US, with all current clinical development being carried out for FDA approval. The secondary target market is the EU, where there are plans to develop this products as an orphan drug.

Q: Is the US market large enough to justify the development / production costs of a product that has been given orphan status in the EU but not in the US?

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

There are no other cell or drug-based products on the market for the treatment of neurogenic bladder or dysfunctional bladder but there are surgical procedures available. The current best treatment is autograft of bowel tissue with 10-15,000 augmentations or replacements of a bladder every year in the US.

Q. Will the product be sufficiently cost-effective and efficacious to dislodge autograft as the best treatment?

Key Features of Business Model:

Key Q: big pharma, SME, IP company, virtual company

Tengion inc. is a small to medium-sized enterprise employing 65 people (as of March 2010), that has used significant private investment and an IPO (listed on the NASDAQ April 9th 2010; listed at $5 per share closing at $5.02 and currently at less than $3 per share) to raise sufficient funds to develop and manufacture its lead products and take them to market. The company owns significant IP (30 US patents) and 100 worldwide patents related to its product portfolio and platform technology.

Key Q: Target Exit Strategy

The company has already gone public and raised significant funds from a large variety of investors to develop a large product pipeline which suggests that they were originally not looking for a trade sale. However, as there has yet to be a product that has reached

approval or even Phase 3, it may be that a trade sale is the only way by which the investors may see some return.

Q: How will the investors see any return given the money spent and the lack of progress? i.e. no Phase 3 data or regulatory approvals.

Key Q: Other products in portfolio

There are 6 different products in the pipeline, covering Urologic, Renal, Gastrointestinal and Vascular applications. There are two lead products, Neo-Bladder Augment and Neo-Urinary Conduit. The latter is intended for the treatment of patients with bladder cancer and has become the focus of Tengion's strategy. According to a recent company statement, Tengion claim that "our Neo-Urinary Conduit leverages recent advances in our technology platform that enable us to produce this product candidate more quickly and efficiently, and less expensively, than our Neo-Bladder Augment, enabling us to address larger market opportunities".

Q: The large product pipeline makes this a business model more suited to big pharma but is this the most sensible strategy given the relatively small market for the lead product?

Sources of Finance and Relationships with KOLs:

Key Q: Sources of finance

Tengion has had three rounds of financing, raising $39 M in series A, $50 M in series B and 54$ M in series C. An additional $30M was raised through an IPO in 2010 = $173 M in total.

Series A funding included the following investors; Oak Investment Partners; Johnson & Johnson Development Corporation, HealthCap, and L Capital Partners and closed in 2005.

Series B funding included the previous investors and Bain Capital LLC and Quaker BioVentures and closed in 2006.

Series C funding included the previous investors and two new investors; Deerfield Partners and Safeguard Scientifics, and closed in 2007.

The key relationship amongst the investors is with Johnson and Johnson, as this provides a link to key resource and know–how in terms of business development, suppliers, distribution networks, etc.

Key Q: Background on investors

Oak Investment Partners is a multi-stage venture capital firm that has funded 481 ventures in a wide variety of technology sectors with a fund of ~$6 billion. They usually serve as lead or co-lead investor and invest $25-150 with a minimum equity stake of 20% in most cases. They invest 75% of their fund in later-stage growth companies and the remaining 25% in early-stage companies. Oak have also invested in Genzyme and Cephalon Inc.

The Johnson & Johnson Development Corporation (JJDC) is the venture capital subsidiary of Johnson & Johnson. JJDC is comprised of experts and leaders in the health care and technology venture communities who identify early market indicators, health care trends, and strategic investment opportunities. JJDC determines the success of an investment's performance not only in financial returns, but also in the viability of providing strategic growth options for Johnson & Johnson.

Health Cap Investments are a European-based venture capital firm that has funded 78 companies with 30 of those being start-ups. The firm have raised 5 funds as of 2010 with

the most recent being in the spring of 2006. The first four funds are now fully invested with the initial investment for Tengion coming from fund IV.

L Capital Partners is a $165-million fund looking to advance companies with the potential to take groundbreaking products to market. This is reflected in their portfolio of healthcare, technology and energy & environment companies. The firm is a multi-round investor that supports each company with a team of partners, principals and associates who have deep industry expertise and financial acumen.

Bain Capital Ventures is the Boston-based venture capital affiliate of Bain Capital, which has approximately $64 billion of assets under management worldwide. Founded in 1984, Bain Capital and its affiliates have made more than 300 investments. The firm's history of investing in early stage companies also dates back to 1984, having made over 125 venture-stage investments. In 2001, Bain Capital Ventures was formed as a separate arm of Bain Capital to focus exclusively on growth investments. Bain invest across a variety of industries including internet, business services and healthcare. They invest in early to late stage development companies with funds of $100k to $50 million.

Quaker Bioventures, as the name suggests, are a venture capital firm that invest solely in the life science industries. They typically invest between $5 million and $25 million with initial investments of anything between $2.5 million and $12 million. Quaker prefers to lead or co-lead financing rounds.

Deerfield Partners is a venture investor firm – no more information found.

Safeguard Scientifics is a venture capital firm that specialises in the life sciences sector. The company will deploy up to $25 million into early and late stage companies with a low regulatory risk and near-term revenue.

Key Q: Define any relationships with clinical KOLs

The most prominent name in the clinical community associated with Tengion is Anthony Atala M.D., who is the scientific founder and world-renowned scientist behind the Tengion technology platform. Other than Anthony Atala, the most complete Phase 2 clinical studies carried out with this product were done so by David B. Joseph, M.D., who is Professor of Surgery at the University of Alabama and Chief of Pediatric Urology at the Children's Hospital in Birmingham, Alabama. Dr Joseph is actively researching treatments for and associated with spina bifida making him the ideal choice for the Phase 2 clinical study detailed below. Other key members of the clinical community who advise and champion Tengion include Alan B. Retik, M.D., who is the Chief of Pediatric Urology & Surgeon in Chief, Children's Hospital Boston and Mark P. Schoenberg, M.D., Professor and Director of Urologic Oncology, Brady Urological Institute, Johns Hopkins.

Regulatory Strategy/Status:

Key Q: Target approval routes

Neo-Bladder Augment is regulated as a section 351 HCT/P / device combination product by the FDA (CBER with input from CDRH). This includes compliance with 21 CFR 1271 (GTP), 210 / 211 (GMP), 312 (IND), 600s (all biologics), 820 (GMP for devices). The product was given an orphan drug designation by the EMA in Europe in 2008 and would be regulated as an orphan under the advanced therapy medicinal product requirements, found in 2001/83/EC, EC/1394/2007 and all associated GMP and GCP requirements.

Key Q: Clinical data and time to approval

Neo-Bladder has partially completed two studies under an IND for its first two indications in the US.

Phase 1 information:

No Phase 1 trial carried out *or* no data available.

Phase 2 information:

Four centre trial in the US (estimated 40 patients (4 x 10)).

Trial one (commenced January 2007 and completed December 2009):

Clinical trial number NCT00419120 (Non-blinded, non-randomized trial). Subjects with neurogenic bladders secondary to spina bifida (aged 3 – 21 yrs only).

10 patients (6 female; average age 8.2 yrs) were implanted in four different centres during the Phase 2 trial.

Primary endpoint: Changes in bladder compliance as measured by urodynamics at 12 months

Secondary endpoints: Changes in bladder pressure and capacity at 6, 9, 12, 36 and 60 months and safety

6 patients showed some improvements after the procedure. Serious and non-serious adverse events were recorded. Two "safety events" were reported in patients 12 months after they had been treated with the "Neo-Bladder Augment". These issues are said to be resolved.

Trial two (commenced July 2007 and still ongoing):

Clinical trial number NCT00512148 (Non-blinded, non-randomized trial). Subjects with neurogenic bladder secondary to spinal cord injury (aged 18+).

10 patient study. No data available yet.

Cost: $39 million was raised to take this product and others through the non-clinical stage and submit the IND application. A further $50 million was raised before 2006 to carry out Phase 2 trials (starting in January 2007) and to continue developing other products.

Time to approval: Phase 2 trials are still ongoing after three years and plans for Phase 3 trials have been shelved. Best case scenario for approval would be 7-10 years from now (2010) based on length of Phase 2 trials and the requirement for Phase 3 trials, BLA preparation and review. Development work began in 2003 (7 years to Phase 2), indicating that the total time from pre-clinical to approval will be ~14-17 years.

Key Q: Approval status

The company are still assessing Phase 2 data and awaiting long-term data before preparing for pivotal Phase 3 trials. These studies have been delayed and there are clear indications that the Neo-Urinary Conduit (currently in PI for the treatment of patients with bladder cancer) will be accelerated ahead of the development of the Neo-Bladder Augment. Clinical trials for the Neo-Urinary Conduit are now underway, suggesting that this is the case.

Q: Are the clinical data sufficient for Phase 3? Trials have only been carried out on 10 patients according to all available sources.

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

The product may need to be both more cost-effective and efficacious than the current standard of care (autograft procedures) in order to be reimbursed. However, there are no reimbursement or cost-effectiveness data available for the US market.

UK reimbursement potential was assessed in a publication out of Prof. Richard Lilford's group at Birmingham University – see publications list. This paper used the predictive headroom method to assess the cost-effectiveness of a tissue engineered bladder (using QALYs) and concluded that a complete tissue engineered bladder (not Neo-Bladder Augment) may be sufficiently cost-effective to replace the current standard of care but this would be dependent on the size of the market and real-life development / production costs allowing the pricing to remain within the predicted headroom.

Status: the product is not available anywhere in the EU and is only available in the US as an investigational product.

Q: If a complete tissue engineered bladder may not to be reimbursed, is a product with a smaller market and reduced clinical utility (Neo-Bladder Augment) reimbursable?

Manufacturing and Supply Strategy:

Key Q: Living cell product?

Tengion's products all contain living autologous cells that are taken from a patient, expanded ex-vivo and replaced as the main component of a cell / scaffold construct. Cell biopsies are taken from patients at the designated trial centres before being transported to a single manufacturing site in Winston-Salem, NC where the cells are isolated (into urothelial and smooth muscle cells) and propagated with the whole process taking 5-7 weeks. The cells are then seeded onto a pre-fabricated polymer scaffold and the construct is taken back to the clinical study site for re-implantation.

Q: This sounds like a very costly and time-consuming process, especially if each patient sample is delivered individually. Can such an inefficient process be used on a larger commercial scale?

Key Q: Make or Buy?

Tengion have not used contract manufacturing facilities during the development of Neo-Bladder Augment and built two manufacturing sites. Site 1 (Winston-Salem, North Carolina) which has been used thus far, for the cGMP manufacture of the product, and site 2 (Pennsylvania) which has been designed and validated for Phase 3 and commercial production but which has remained unused as Phase 3 trials have not yet commenced.

Q: Was it a sensible to build a validated manufacturing site for Phase 3 / commercial production with no Phase 2 data available?

Publications:

State public domain publications of safety, efficacy and cost-effectiveness

Clinical safety and efficacy:

De Filippo R., Bertram T., Jayo M., Seltzer E. (2009, April 28). Adaptive Regulation of Regenerated Bladder Size After Implantation with Tengion Neo-Bladder Augment™ Early Clinical Outcomes and Preclinical Evidence. Presentation given American Urology

Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

Joseph D., Borer J., De Filippo R., McLorie G., Goldberg L., Tillinger M., Seltzer E. (2009, April 28). A Phase 2 Study - Tengion Autologous Neo-Bladder Augment™ (NBA) for Augmentation Cystoplasty in Subjects with Neurogenic Bladder Secondary to Spina Bifida. Poster presented at American Urology Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

Cost effectiveness:

Cost-effectiveness analysis at the development phase of a potential health technology: examples based on tissue engineering of bladder and urethra. McAteer H, Cosh E, Freeman G, Pandit A, Wood P, Lilford R. J Tissue Eng Regen Med. 2007 Sep-Oct;1(5):343-9.

Key Value Steps:

1. Pre-clinical data sufficient for clinical trials (IND) approval (2005)

2. Data shows that COGS can be controlled during clinical trials (2007 - ongoing)

3. Phase 2 data sufficient for commencement of Phase 3 (2007 - ongoing)

4. Market approval in US

Key External Interactions: (*state any key interactions with members of the supply chain/value chain*)

The only key external interaction is that with the clinical advisory board.

Sources:

Tengion website:
http://www.tengion.com/

Proof-of-concept research papers:
Phenotypic and functional characterization of in vivo tissue engineered smooth muscle from normal and pathological bladders. Lai JY, Yoon CY, Yoo JJ, Wulf T, Atala A. Journal of Urology, 168 (4), pp. 1853-1858, 2002.

In vitro biocompatibility evaluation of naturally derived and synthetic biomaterials using normal human bladder smooth muscle cells. Pariente JL, Kim BS, Atala A. Journal of Urology, 167 (4), pp. 1867-1871, 2002

Preparation of poly(glycolic acid) bonded fiber structures for cell attachment and transplantation. Mikos AG, Bao Y, Cima LG, Ingber DE, Vacanti JP, Langer R. J Biomed Mater Res., 27 (2), pp. 183-189, 1993.

Controlled fabrication of a biological vascular substitute. Stitzel J, Liu J, Lee SJ, Komura M, Berry J, Soker S, Lim G, Van Dyke M, Czerw R, Yoo JJ, Atala A. Biomaterials, 27 (7), pp. 1088-1094, 2006. Epub 2005.

Pre-clinical papers:
Bertram T., Christ G.J., Andersson K., Aboushwareb T., Fuellhase C., Soler R., Wagner B.J., Jain D., Ludlow J.W., Payne R., Jayo M.J. (2009, April 21). Pharmacologic Response of Regenerated Bladders in a Preclinical Model. Poster presented at the Experimental Biology Meeting, held in New Orleans, LA, April 18-22, 2009.

Seltzer E., Tillinger M., Jayo M., Bertram T. (2009, April 28). Role of Biomechanical Stimulation (Cycling) in Neo-Bladder Regeneration - Translational Basis for Clinical Outcomes.Ð¿Ñ—Ð…Poster presented at American Urology Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

De Filippo R., Bertram T., Jayo M., Seltzer E. (2009, April 28). Adaptive Regulation of Regenerated Bladder Size After Implantation with Tengion Neo-Bladder Augment™ Early Clinical Outcomes and Preclinical Evidence.Ð¿Ñ—Ð… Presentation given American Urology Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

Jayo, M. J., Jain, D., Ludlow, J. W., Payne, R., Wagner, B. J., Seltzer, E., McLorie, G. A., & Bertram, T. A. (2007, October 27). A regenerative neo-bladder construct in trigone-sparing cystectomized dogs: Long-term safety, continence, voiding, and urodynamics. Poster presented at the American Association of Pediatrics Section on Urology National Conference and Exhibition.

Clinical papers:
De Filippo R., Bertram T., Jayo M., Seltzer E. (2009, April 28). Adaptive Regulation of Regenerated Bladder Size After Implantation with Tengion Neo-Bladder Augment™ Early Clinical Outcomes and Preclinical Evidence. Presentation given American Urology Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

Joseph D., Borer J., De Filippo R., McLorie G., Goldberg L., Tillinger M., Seltzer E. (2009, April 28). A Phase 2 Study - Tengion Autologous Neo-Bladder Augment™ (NBA) for Augmentation Cystoplasty in Subjects with Neurogenic Bladder Secondary to Spina Bifida. Poster presented at American Urology Association 2009 Annual Meeting - Chicago, IL - April 25-30, 2009 (http://www.aua2009.org/).

Phase 2 trial data:
http://www.clinicaltrials.gov/ct2/show/NCT00419120?term=spina+bifida&rank=15
http://clinicaltrials.gov/ct2/show/NCT00512148?term=tengion&rank=5

Cost effectiveness paper:
Cost-effectiveness analysis at the development phase of a potential health technology: examples based on tissue engineering of bladder and urethra. McAteer H, Cosh E, Freeman G, Pandit A, Wood P, Lilford R. J Tissue Eng Regen Med. 2007 Sep-Oct;1(5):343-9.

Interview with Tengion CEO Steven Nichtberger.

Paving a path to regenerative medicine. *The Gray Sheet*, **33** (42) p18 (2007).

Tengion Presentation:
In vitro Analysis of Scaffold/Cell Products Tengion Autologous Neo-bladder Construct 6th - 7th December 2007. National Transportation and Safety Board (NTSB).

Investor websites:
http://www.safeguard.com/
http://www.lcapitalpartners.com/
http://www.baincapital.com/
http://www.oakinv.com/
http://www.jjdevcorp.com/
http://www.quakerbio.com/
http://www.healthcap.se/default.asp?page=docs/funds.asp

Altrika: Myskin™

Brief Product Description:

Myskin™ is an active wound healing product for application to burns, graft sites, diabetic foot ulcers and chronic wounds as part of a clinical wound management strategy. The product consists of autologous epidermal keratinocytes that have been cultured on a silicone sheet coated with a <100 nm thick layer of plasma polymerised acrylic acids (to support cell attachment and growth). The autologous keratinocytes are isolated from a small biopsy from the patient. The dermal and epidermal layers are separated enzymatically and the keratinocytes are gently scraped from the dermal-epidermal interface before being placed on the polymer coated silicone sheet.

Myskin™ is supplied as a 5cm diameter circular disc of surface area 19.6cm^2 (other formats may be supplied after consultation with Altrika). The product is individually packaged on a sterile, buffered, serum-free mixture of Dulbecco's Modified Eagle's medium (76%) and Hams F12 medium (23%) in an agar gel form. Myskin™ is applied at weekly intervals with the potential for 20 applications from a single biopsy, though anecdotal clinical evidence suggests that 12 are usually sufficient.

Target Indications and Markets:

Key Q: Clinical indications

Myskin™ is indicated for use on diabetic foot ulcers in standard care for the treatment of neuropathic full-thickness ulcers of at least four weeks duration, which have not responded to conventional treatment.

Myskin™ is also indicated for the treatment of burns in place of or in addition to skin grafting. Myskin™ can be applied over meshed skin grafts. Where skin grafts are taken in the treatment of burns or reconstructive surgery, Myskin™ can be used for re-epithelialisation of graft donor sites. The use of Myskin™ in venous leg ulcers in combination with standard therapeutic compression bandaging is being evaluated for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency. Myskin™ may also be effective on other non-healing.

Key Q: Geographical target market

Myskin™ is not licensed in any region although pilot clinical studies have been carried out in the UK. Myskin™ can only be supplied to qualified practitioners in the UK who can ensure there is adequate infrastructure to support a high standard of care. Provided care can be guaranteed and a biopsy is taken by a qualified surgeon then patients may be treated with Myskin™ outside of a clinical setting. Altrika is working with healthcare partner organisations to deliver the product to international markets. However, without an MA the product cannot enter into the European markets.

Key Q: What competitors are in the market already (or are seeking market approval) for same indication(s) and what is their stage of development?

The market for diabetic foot ulcers is likely to become extremely competitive in the next 5-10 years given the intention of both Advanced Biohealing and Organogenesis to gain market approval for Demagraft® and Apligraf® respectively. Both companies will require data from

a pivotal (Phase 3 trial) but are still more advanced than Altrika given the lack of infrastructure for commercial cell therapy manufacture.

The burns market may be a more realistic for Myskin™, should it receive a MA from the EMA as there are fewer cell therapies in the market. The current standard of care depends on the extent of the burns i.e. bandages and ointments may be suitable for some, where as skin grafting (all or auto) is required for more serious trauma.

Key Features of Business Model:

Key Q: big pharma, SME, IP company, virtual company

Altrika is a SME and wholly owned biomedical subsidiary of a high throughput materials company (Ilika Technologies Ltd) that commenced trading in 2010. Ilika is a company that invents, tests and selects materials that can be scaled-up for everyday commercial use. Ilika uses high throughput, or combinatorial, techniques which involve the rapid synthesis of a large number of different structurally related materials. Through Altrika, Ilika have an interest in the biomedical devices and therapeutics sector. Altrika acquired the assets from York Pharma in 2009 (who themselves acquired the assets from Celltran in 2008 for £70,000 plus royalty payments over 5 years) which included key personnel, IP and two laboratories regulated by the HTA and the MHRA in Sheffield. The IP was related to two products; Cryoskin™ and Myskin™. Ilika was listed on the London stock exchange (AIM: IKA) on the 14th of May 2010 (51p per share). Celltran was a spin-out company from the University of Sheffield that was placed into administration in 2008 before the acquisition by York Pharma.

Altrika is a vehicle to maintain and increase revenues from the Cryoskin™ and Myskin™ products, whilst developing its own regenerative and biomedical product range using its proprietary platform technology for the selection and synthesis of materials for biomedical applications. Altrika also offer a contract research service for companies wishing to synthesise and screen new materials for biomedical applications.

Key Q: Target Exit Strategy

The company has been floated on the stock market but the assets and IP have already been sold twice, as stated above. The current owners of the assets and IP (Altrika; Ilika) are attempting to take the product into other European markets but are encumbered by not having a MA for the product in Europe and will not be able to sell the product after December 2012 without one. This suggests that Altrika's main reason for the acquisition of the IP and facilities from York Pharma may be the value within that IP and the resultant product portfolio, rather than the Myskin™ product, which will require significant investment over a number of years if it is to achieve regulatory approval as an ATMP in Europe (see regulatory section).

Key Q: Other products in portfolio

Cryoskin™

Cryoskin™ is an active treatment for burns and hard to heal wounds, using viable donor cells to provide support for the healing process in the wound bed. The product consists of a frozen mono-layer of undifferentiated allogeneic keratinocytes attached to a medical grade silicone backing, perforated to allow movement of exudate. The cell layer produces a 'cocktail' of trophic factors, which along with cell to cell interactions, encourage and promote the growth of the patient's own cells to grow back at an increased rate. The cells are from a fully screened donor that has been specially selected for their ability to grow at a desirable and expected rate, and grow in serum and animal free media. They have been used to treat over 600 patients and are cultured in GMP accredited clean rooms. The sheets

are stored at -80°C for up to 6 months and are individually sealed in sterile packages designed to be taken straight to theatre. Although manufactured under a Manufacturer's Specials License from the MHRA, no license is required to store the product at an end-user site, allowing local storage within hospitals for immediate use. However, as is an unlicensed product, it is only provided directly to medical professionals and treatment centres on a named-patient basis.

Other products

There are 3 additional products in the pipeline; Lyphoderm™, a corneal bandage product and leukodepletion filters. The most advanced of these is *Lyphoderm™*, which consists of a total lysate derived from cultured human keratinocytes providing a natural complex of growth factor activity. In phase 2 clinical trials Lyphoderm™ provided evidence of efficacy in a large group of venous leg ulcer patients. It also offers a potentially effective treatment for chronic wounds and has overcome the logistical, delivery and storage challenges associated with many regenerative medicine products i.e. cell-based products / delivery. The Lyphoderm™ product was acquired by Celltran in 2006 when it merged with Belgian Biotechnology firm 'Innogenetics'.

Sources of Finance and Relationships with KOLs

Key Q: Sources of finance

Celltran raised £15 million to develop my skin and its development pipeline between start up in 2000 and administration in 2008. Much of this initial funding came from the White Rose Technology Seedcorn Fund and Sheffield University Enterprises Ltd, with further funding from Catalyst BioMedica (the commercial arm of the Wellcome Trust), the Yorkshire Funding Managers (YFM) Group, Biofusion, Partnerships UK plc, Vernon-Carus, South Yorkshire Investment Fund, Innogenetics NV and PUK Ventures.

The most significant investment in the company was in August 2005 when the company raised £2.7 million in a funding round led by Biofusion (the major shareholder at the time) to further develop the product portfolio. This funding round was boosted by the approval and launch of the Myskin™ product in the UK only a year before. However, a lack of progress as a result of limited cash flow and the impending requirement for a market authorisation for Myskin™ in Europe led to administration in 2008 before York Pharma acquired the assets of Celltran in the same year to save what was perceived as valuable IP and to keep the lead product (Myskin™) on the market. Only one year later York Pharma was placed into administration due to a lack of cash-flow and the IP and other assets were acquired by Ilika in 2010 (marketed through Altrika). Since 2010 Ilika, through Altrika, has been trying to generate further funding through for the Myskin™ product and the rest of the pipeline though internal financial restructuring.

Key Q: Background on investors

Biofusion (now fusion IP)

The Fusion IP model is to sign long term exclusive partnership agreements with leading research intensive universities for 100% of their future IP pipelines and the right to 100% of the equity in the resultant spin-out companies on incorporation. They then align the interests of the academic by giving them a significant shareholding in the spin-out company. This gives Fusion high quality IP from their university partners, their own commercial expertise and start-up funding, and enables them to turn world class research into valuable businesses.

The Yorkshire Funding Managers (YFM) Group

We have over 25 years experience of helping UK businesses create transformational growth. The group have teams specialising in various stages; from early-stage capital to MBOs and pre-IPO funding. They have committed investment funds of over £375m and provide between £100,000 and £10m of equity for companies in all sectors. The company utilises several funding models that are tailored to the size / status of the business, the level of risk and the potential benefit.

Technology Seedcorn Fund

The White Rose Technology Seedcorn Fund is an early stage seedcorn fund, which invests in exciting new technology emerging from the Universities of York, Leeds and Sheffield. The £9m Fund provides venture capital funding of up to £500,000 to enable the transition from promising research to commercial reality. They help growing companies with management input, advice and experience and bring an investor's viewpoint to bear at an early stage. The fund have made a number of investments in areas such as life sciences (vaccines, devices, diagnostics and therapeutics), engineering (e.g. sensors), software and energy. They look for opportunities with exciting growth potential, protectable IP and committed management teams where a seedcorn investment can make the opportunity standalone and/or attractive to later stage investors and trade partners.

Sheffield University Enterprises Ltd (SUEL)

SUEL was formed as Unisheff Ventures Ltd in 1984 to help the University of Sheffield commercialize intellectual property created by their research in a similar way to Fusion IP (see above). Since changing their name in 1998, they have assisted in the formation of over 75 companies spun-out from the universities of Sheffield and Cardiff and helped create more than 150 jobs nationwide. Although continuing to help universities with their exploitation process, they are now focussed using the skills, experience and attributes gained in assisting technology transfer to help more businesses outside the university sector.

Catalyst BioMedica

Between 1999 and 2003, Catalyst Biomedica, acted as the technology transfer subsidiary of the Wellcome Trust, securing many successes in relation to Trust intellectual property, concluding more than 60 licence agreements, and supporting 30 Development Fund projects that have led to more than a dozen new start-up companies. Following a review of the Trust's translation activities in 2003, the Wellcome Trust began integrating the activities of subsidiary, Catalyst BioMedica Ltd, into the main body of the Trust to create a new division whose primary objective is to translate biomedical research into tangible health benefits through support for applied research that has commercial potential.

Partnerships UK and PUK Ventures

Partnerships UK (PUK) was a public private partnership formed in 2000 out of HM Treasury. It was a joint venture that bridged the gap between public and private sectors, with a unique public sector remit to work with Central Government, Devolved Administrations and Local Authorities. Partnerships UK has since been closed and the associated businesses disposed of. This included PUK ventures, the venture capital arm of the business.

Vernon-Carus

Vernon Carus Is a Worldwide Leader In the Supply of Perioperative, Infection Control and Woundcare Products To Over 50 Countries Worldwide and Has Subsidiaries In Malta (For the Middle East Markets) and Australia. Details of their involvement with the Myskin™ product are unclear but they did reproduce the clinical datasheet that appears on the Altrika website.

No other information relating to this company in the public domain.

South Yorkshire Investment Fund

The South Yorkshire Investment Fund (SYIF) offer seedcorn finance, business loans and equity-linked investments from £15,000 to £2.5 million for businesses in or relocating to South Yorkshire.

Innogenetics NV

Innogenetics NV is an international biotechnology company that develops and markets diagnostic products to improve therapy management and patient health. Innogenetics develops and markets a range of diagnostic assays with a focus on molecular diagnostics and multiparameter testing. Its products are sold in over 90 countries through its 6 subsidiaries and a large number of distributors. Innogenetics merged with Celltran in 2006 in order to gain the IP related to their Lyphoderm™ wound healing product.

Key Q: Define any relationships with clinical KOLs

Myskin™ has not been used in a formal clinical trial as it was not classified as a medicine by the MHRA. Therefore there are no clear clinical KOLs that champion the Myskin™ product other than the lead authors on two clinically-focussed papers – see references section.

Regulatory Strategy/Status:

Key Q: Target approval routes

The Myskin™ product is currently regulated by the HTA under the EU Tissues and Cells Directive (2004/23/EC) as it was not defined as a medicinal product by the MHRA at the time of classification in 2003. This is likely to due to the product being autologous and not being sufficiently covered by the EU medicinal products for human use Directive (2001/83/EC) as the ATMP regulation (EC/1394/2007) had yet to be published by the EC. Therefore, it has been used in clinical trials (name trials) without the need for authorisation from the MHRA. The product was launched on the 28th of April 2004 has been on the market since despite the fact that the product now falls under the definition of an ATMP. However, in December 2012, any product that is classified as an ATMP will require a market authorisation (MA) from the European Medicines Agency (EMA) to remain on the market. Therefore, without sufficient clinical data being available it is unlikely that the product can remain on the market unless they can justify its use on the basis of clinical need i.e. there are no suitable alternatives.

Key Q: Clinical data and time to approval

One “formal” clinical study has been carried out with Myskin™ thus far with 7 additional patients being treated on an ad-hoc basis. The more formal trial was a pilot study in the UK to evaluate the clinical efficacy of Myskin™ to promote wound healing in patients with chronic neuropathic foot ulcers. Six diabetic patients with neuropathic ulcers resistant to conventional therapy were treated with weekly applications of autologous keratinocytes delivered on Myskin™ in addition to conventional therapy until wound healing was achieved. The results are summarised in Table 1 below.

Table 1 Results of a 6-patient efficacy trial using Myskin™ to treat chronic neuropathic foot ulcers

Patient	Age	Diabetes (type)	Diabetes duration (years)	Duration of ulcer(s)	Response to Myskin™
1	43	1	22	1. 4 years 2. 3 months 3. 4 weeks 4. 4 weeks	Decrease in size 10 applications before healing 6 applications before healing Decrease in size after 8 applications (treatment ongoing)
2	56	1	30	2 years	8 applications before healing
3	46	1	29	16 months	6 applications before healing
4	64	2	12	10 months	No response after 24 applications
5	65	2	15	2 years	Treatment discontinued after 3 applications due to MRSA infection
6	63	2	19	3 months	10 applications before healing

Summary

Complete healing was achieved in six out of nine ulcers in six patients, a reduction in ulcer size was achieved in one ulcer and no response was seen in one ulcer. Treatment was discontinued in one patient due to infection. Complete wound healing required between 6 and 17 applications over a period of 6-20 weeks. There were no recurrences in the healed ulcers after a follow-up of 6 months.

In addition to the pilot study, 7 patients with a range of non-healing wounds were treated were Myskin™, the results can be seen in Table 2.

Table 2 Results from 7 patients treated with Myskin™ for a variety of non-healing wounds

Patient	Age	Clinical condition	Response to Myskin™
1	28	Acute burn injury (28% BSA)	Accelerated re-epithelialisation following the application of Myskin™ Improved healing following the application of Myskin™
2	9	Acute burn injury (40% BSA)	Accelerated re-epithelialisation following the application of Myskin™ Improved healing following the application of Myskin™
3	81	Extensive chronic wounds (8 weeks duration) on both legs following partial skin graft failure after 28% flame burns	Left leg: 98% healed after 12 applications Right Leg: 78% healed after 12 application
4	64	Burns injuries to left foot and ankle led to contractures and ankle deformity which resulted in 3 year non healing chronic ulcers. Ulcers recurred despite 3 separate episodes of skin grafting.	Anterior ulcer completely healed after 22 applications while posterior ulcer is healed after 42 applications
5	83	Chronic ulcers to right leg of more than 60 years duration which developed while the patient was a prisoner of war in World War II. Six episodes of skin grafting failed to achieve permanent wound closure.	Partial healing of both ulcers with general improvement of the wound and the patient's quality of life
6	44	12 year history of non-healing scalp wounds following initial excision and SSG of full thickness flame burns (15% BSA)	2 Ulcers healed after 2 applications; 2 partially healed after 18 application
7	82	Non healing pretibial wound (6 week duration) secondary to wound dehiscence following debridement and direct closure of a pretibial laceration. The patient was not considered suitable for further surgical intervention because of a postoperative cardiac event.	Complete wound closure following 7 applications; wound remains healed with 6 month follow up.

Summary

For 2 burns patients, Myskin™ facilitated healing of grafted burns wounds. For 5 patients with intractable chronic wounds (with 9 ulcers in total) repeated applications of Myskin™ resulted in complete healing in 5/9 ulcers with a major reduction in ulcer size for all other (4/9) ulcers. This reduction in ulcer size improved the wound conditions for 2 of these patients such that they were then considered suitable for conventional grafting and orthopaedic surgery respectively. Details of these individual treatments can be found here:

http://www.Myskin™-info.com/medicalprofessionals-casestudies.php

Key Q: Approval status

The Myskin™ product is currently regulated by the HTA under the EU Tissues and Cells Directive (2004/23/EC) as it was not defined as a medicinal product by the MHRA at the time of classification in 2003. This is likely to due to the product being autologous and not being sufficiently covered by the EU medicinal products for human use Directive (2001/83/EC). Therefore, it has been used in clinical trials (name trials) without the need for authorisation from the MHRA. The product was launched on the 28th of April 2004

Reimbursement Strategy/Reimbursement Status:

Key Q: What are the requirements for reimbursement? i.e. clinical data, economic data

Myskin™ can be applied under standard dressing change and wound management protocols either in a clinical in-patient or out-patient setting. Myskin™ is only available in the UK and is sold privately per application on a patient-by-patient basis - it is not routinely used within the NHS. The decision on treatment of a patient in community based care rests with the local healthcare authority.

Manufacturing and Supply Strategy:

Key Q: Living cell product?

As a living cell product, Myskin™ is been processed under aseptic conditions and should be handled observing sterile technique. It must be kept in its container on the shipping medium in the sealed bag under controlled temperature (20°C-31°C) until ready for use and should not be refrigerated.

Altrika are using Cranage Healthcare as a UK distributor for their Myskin™ product. Cranage is a healthcare company based in Cheshire, specialising in cosmetic and wound healing products that utilise silicone and collagen – they do not develop cellular products. In December 2010 Cranage Healthcare was sold to Sinclair Pharma, a US healthcare company that specialises in topical treatments for wound care and dermatological conditions. It is not known how this arrangement affects the distribution deal with Altrika.

Key Q: Make or Buy?

Myskin™ is been processed under aseptic conditions within HTA licensed facilities (Sheffield, UK) that were purchased by Celltran for the production of Myskin™. However, these facilities also include an MHRA licensed laboratory for the manufacture of Cryoskin™. These facilities were acquired by Altrika when York Pharma entered administration.

Publications:

M. Moustafa, C. Simpson, M. Glover, R. A. Dawson, S. Tesfaye, F. M. Creagh, D. Haddow, R. Short, S. Heller, S. MacNeil. A new autologous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. Diabetic Medicine 2004, 21(7), 786-789

N. Zhu, R. M. Warner, C. Simpson, M. Glover, C. A. Hernon, J. Kelly, S. Fraser, T. M. Brotherston, D. R. Ralston and S. MacNeil. Treatment of burns and chronic wounds using a new cell transfer dressing for delivery of autologous keratinocytes. European Journal of Plastic Surgery 2005, 28, 319–330

Key Value Steps:

1. POC data
2. Regulatory approval for Myskin™ (UK)
3. Distribution deal to permit UK market penetration
4. Product sales for Myskin™
5. Reimbursement for Myskin™ in the UK (private or public)
6. Phase 3 clinical data for Myskin™
7. Regulatory approval (EU)

Key External Interactions: *Cranage Healthcare – see manufacturing section above.*

Sources:

Altrika website:
http://www.altrika.co.uk/
Ilika websit:
http://www.ilika.com/
Financial information:
http://www.avlar.com/news.147.htm
http://www.fusionip.co.uk/News/CelltranRaisesinFundingRound.htm?p=14
http://www.syif.com/news/news215.asp
http://telegraph.uk-wire.com/cgi-bin/articles/200610030700368359J.html
http://www.londonstockexchange.com/exchange/news/market-news/market-news-detail.html?announcementId=10122962

Non-clinical data:
Haddow, D. B. MacNeil, S. Short, R. D. A cell therapy for chronic wounds based upon a plasma polymer delivery surface. *Plasma Processes and Polymers* 2006, **3**(6-7), 419-430.

Clinical data:
M. Moustafa, C. Simpson, M. Glover, R. A. Dawson, S. Tesfaye, F. M. Creagh, D. Haddow, R. Short, S. Heller, S. MacNeil. A new autologous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. *Diabetic Medicine* 2004, **21**(7), 786-789

N. Zhu, R. M. Warner, C. Simpson, M. Glover, C. A. Hernon, J. Kelly, S. Fraser, T. M. Brotherston, D. R. Ralston and S. MacNeil. Treatment of burns and chronic wounds using a new cell transfer dressing for delivery of autologous keratinocytes. *European Journal of Plastic Surgery* 2005, **28**, 319–330

Investor websites:
Biofusion (now *Fusion IP*): http://www.fusionip.co.uk/
YFM group: http://www.yfmep.com/home-interstitial/
White RoseTechnology Seedcorn Fund: http://www.whiteroseseedcorn.com/
Sheffield University Enterprises Ltd: http://suel.group.shef.ac.uk/
Catalyst BioMedica: http://www.wellcome.ac.uk/News/2003/News/WTD003992.htm
Partnerships UK and PUK Ventures: http://www.partnershipsuk.org.uk/ and
http://www.pukventures.com/
South Yorkshire Investment Fund: http://www.syif.com/
Innogenetics NV: http://www.innogenetics.com/default.html