

Fifteen Cell Therapies/Stem Cell Therapies in Phase III Clinical Trials

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Recently, the Pharmaceutical Research and Manufacturers of America released a report "[Medicines in Development – Biologics, 2013 Report](#)." The report lists 907 biologics currently in development by "America's biopharmaceutical research companies." The list includes biologics targeting more than 100 diseases that are currently in human clinical trials or are under review by the Food and Drug Administration (FDA). In the report, 69 cell therapies were identified as having clinical trials under review with the Food and Drug Administration (FDA), including 15 in Phase III clinical trials. Of the therapies listed, nine therapeutic categories were represented and include: cardiovascular disease, skin diseases, cancer and related conditions, digestive disorders, transplantation, genetic disorders, musculoskeletal disorders, eye conditions, and other.

The purpose of this article is to give an overview of these therapies, the diseases states they are treating, the technologies they employ, and the companies who are working to bring these products to market.

Prochymal – Stem Cell Therapy

Sponsor – [Osiris](#)

Graft vs. Host Disease (GvHD) (Fast Track)

Prochymal for treatment of Graft vs. Host Disease (GvHD) has been approved in Canada and New Zealand and has completed Phase III clinical trials in the United States. It has received Fast Track review from the Food and Drug Administration (FDA). GvHD can occur during stem cell or bone marrow transplants. The immune cells present in the transplant view the cells in the patient receiving the transplant as foreign and begin to attack the patient's tissues and organs. GvHD can cause serious disability and can even be fatal. It is a frequent complication and occurs in about half of the transplants.

Crohn's Disease and Gastrointestinal Injury from Radiation

Prochymal is being evaluated as a therapeutic in Phase III clinical trials for treatment of Crohn's Disease, for which it has received Fast Track status from FDA, and gastrointestinal injury from radiation. Crohn's disease is an inflammatory disease that affects the colon and small intestine. This disease can cause abdominal pain, weight loss, vomiting and diarrhea.

Osiris's Prochymal is an allogenic therapy made up of mesenchymal stem cells derived from donor bone marrow. The cells are isolated and expanded and Osiris states that one donation can yield 10,000 doses. Doses are preserved for storage, after which, they have a two-year shelf life and are delivered to the patient when needed. Cells are infused into the patient and treatment takes thirty minutes to infuse one dose.

Mesenchymal Precursor Cell (MPC) Product – Stem Cell Therapy (Orphan Drug)

Sponsor - [Mesoblast](#)

Bone Marrow Transplant

Mesoblast's MPC product for Bone Marrow Transplant is currently in Phase III clinical studies and has received Orphan Drug Designation. In this therapy, Mesoblast's bone marrow-derived allogeneic MPCs are used as a feeder layer in combination with hematopoietic growth factors to expand and differentiate hematopoietic precursors from cord blood. According to the Mesoblast website, there are approximately 55,000 bone marrow transplant procedures performed worldwide and today more than 70% of people who could use an unrelated donor transplant do not receive one as a fully matched donor cannot be found. In addition, this therapy has the potential to greatly reduce Graft vs. Host Disease, which is a common side effect of bone marrow transplant. Mesoblast allogeneic stem cell treatment consists of adult mesenchymal precursor cells derived from bone marrow or other tissue sources.

MyoCell – Stem Cell Therapy

Sponsor - [Bioheart](#)

Congestive Heart Failure

Bioheart's Myocell, is currently in Phase II/III clinical trials as a treatment for congestive heart failure. The treatment is injected after heart attack to improve cardiac function. Bioheart uses muscle stem cells (myoblasts) and have announced a next generation version of this product called Myocell SDF-1. Myocell SDF-1 is similar to Myocell, but the cells have been modified to express angiogenic proteins to enhance blood vessel formation. Myocell SDF-1 is currently in Phase I clinical trials.

Bioheart manufactures its autologous Myocell by harvesting a small piece of thigh muscle from the patient, then isolating and expanding the myoblasts. The cells are then injected into the patient's scar tissue in the heart. The procedure uses an endoventricular needle-injection catheter and is minimally invasive.

ixmyelocel-T – Stem Cell Therapy (Fast Track)

Sponsor - [Aastrom](#)

Critical Limb Ischemia

Shortly after the PhRMA report was released, Aastrom announced that they would end the Phase III clinical study of ixmyelocel-T as a treatment for Critical Limb Ischemia, which had been granted a Fast Track Designation from FDA. Instead they are choosing to focus on ixmyelocel-T as a treatment for Dilated Cardiomyopathy (DCM) that has completed a Phase II clinical trial and has received Orphan Drug Status from FDA. In a Reuter's article titled "[Aastrom Biosciences ends drug trial, to cut half its workforce](#)," CEO Nick Colangelo said in a statement, "... The optimal use of our resources at this time is to focus ...where clinical development may require smaller studies with lower costs and a shorter path to regulatory approval."

Aastrom manufactures its autologous stem cell product under cGMP conditions. Manufacturing capacity is currently at 3,000 patients per year. Aastrom manufactures the product by taking a bone marrow sample from the patient, then isolating and expanding primarily CD90+ mesenchymal cells, CD14+ monocytes and alternatively activated macrophages. The cells are then delivered back to the patient either intramuscularly (CLI) or through endocardial catheter injections (DCM). Culture and expansion of the cells takes 12 days and administration to patient happens within 3 days of manufacture.

ELAD –Cell Therapy (Orphan Drug)

Sponsor – [Vital Therapies](#)

Liver Failure

Vital therapies has created ELAD, a cell based bioartificial liver that has been granted Orphan Drug Designation. The product has completed a Phase II/III clinical study and according to the Vital Therapies website is “in the process of finalizing a pivotal clinical trial program designed to support ELAD's potential approval in the United States, Europe, Australia and New Zealand. This program incorporates two randomized, controlled trials in severe acute alcoholic hepatitis and one randomized, controlled trial in fulminant hepatic failure. We expect to initiate this clinical program in Q1 2013.”

ELAD is made up of a cartridge, which contains proprietary C3A human hepatocyte cells licensed from Wistar Institute and further developed by Baylor College. The cells are grown in specialized cartridges that serve as an artificial liver at the patient’s bedside. Blood is pumped from the patient through the system and the cells are able to perform most of the metabolic functions of a normal liver.

According to the Vital Therapies website, in the United States there were about 6,000 liver transplants performed in 2006, but 16,000 patients were on the waiting list. Each year only about one-third of people who need a liver transplant will receive one. The goal of ELAD is to provide liver support for up to 30 days hopefully allowing patients time to find a suitable liver transplant or give their own liver time to recover to a healthy state.

HP802 (allogenic human skin replacement)–Cell Therapy

Sponsor – [Healthpoint Biotherapeutics](#) (recently acquired by Smith & Nephew)

Leg Ulcers

Healthpoint Biotherapeutics’ HP802 is currently enrolling a Phase III study for treatment of venous leg ulcers. According to Healthpoint Biotherapeutics’ website, “the product is an allogeneic living human cell suspension that consists of two components that are sprayed sequentially on the wound bed at the time of treatment: a fibrinogen solution and a cell preparation containing a mixture of growth arrested, living, allogeneic epidermal keratinocytes and dermal fibroblasts”. The product is believed to release growth factors and cytokines into the wound, which promote wound healing in the patient’s cells.

Venous leg ulcers are caused by poor circulation in the legs caused by damaged veins. Typical risk factors for venous leg ulcers are peripheral arterial disease, obesity, diabetes, immobility, deep vein thrombosis, and serious leg injury.

StemEx (carlecortemcel-L) – Stem Cell Therapy (Orphan Drug) (Fast Track)

Sponsor – [Gamida Cell](#) and [Teva Pharmaceutical](#)

Hematological Malignancies

StemEx is a joint venture between Gamida Cell and Teva Pharmaceutical. StemEx is currently in a Phase III clinical trial for treatment of hematological malignancies. The product would serve as a replacement for a bone marrow transplant and has been granted both Orphan Drug Designation and Fast Track Status with FDA. Patients that suffer from hematological malignancies, such as leukemia and lymphoma, almost always require bone marrow transplants and many patients will not be able to receive one because they will be unable to find a donor that is a suitable match. According to Gamida Cell's website "StemEx is a graft of stem/progenitor derived from part of a single unit of umbilical cord blood and transplanted by IV administration along with the remaining, non-manipulated cells from the same unit." If approved, this product would be able to provide a suitable replacement for bone marrow transplant using donor bone marrow and would greatly increase the number of hematological malignancies patients that could receive treatment.

LaViv – Fibroblast Cell Therapy

Sponsor – [Fibrocell Science](#)

Scars

LAVIV for treatment of scarring has completed a Phase II/III clinical study. LAVIV is already approved by the FDA for treatment of moderate to severe nasolabial fold wrinkles in adults. In this autologous therapy, skin is collected from behind the patient's ear then the sample is expanded to hundreds of millions of fibroblast cells prior to treatment. Fibrocell Science states the expansion time plus quality control takes 90 days. Cells are then injected back into the patient at the site of the scar or wrinkle.

GSK 2696273 – Stem Cell Therapy

Sponsor – [GlaxoSmithKline](#)

Adenosine Deaminase Severe Combined Immune Deficiency

GlaxoSmithKline's 2696273, although listed as a stem cell therapy, uses an ADA gene transfer into hematopoietic stem/progenitor cells for the treatment of Adenosine Deaminase Severe Combined Immune Deficiency. According to the clinical trials.gov listing for their Phase II study, "The drug product studied in this protocol consists of autologous CD34+ hematopoietic stem/progenitor cells engineered ex vivo with a retroviral vector

encoding the therapeutic gene ADA. The engineered CD34+ cells are infused following a nonmyeloablative conditioning with busulfan to make space in the bone marrow.”

Adenosine Deaminase Severe Combined Immune Deficiency (ADSCID) is a genetic disorder that is inherited. Children with (ADSCID) have a damaged immune system that does not provide immune protection from common challenges such as bacteria, fungi and viruses. These infections can be life threatening to children with this disorder and as a result, they typically only live a year or two.

Adult Autologous Stem Cell Therapy (Renew) –Stem Cell Therapy

Sponsor – [Baxter International](#)

Myocardial Ischemia

Baxter International has developed an adult autologous stem cell therapy for treatment of chronic myocardial ischemia. In February 2012, Baxter announced that they were launching a Phase III clinical study for this product to evaluate safety and efficacy and according to ClinicalTrials.gov it is still enrolling. The trial will enroll 450 patients that will receive one of the following treatments: the stem cell therapy, a placebo or unblinded standard of care. The goal of the study is to evaluate the treatment’s ability to improve exercise capacity in patients with chronic myocardial ischemia, which will be evaluated at twelve months following treatment. Secondary objectives include a reduction of angina and safety.

The product, also called Renew, is made up of CD34+ stem cells derived from the patient’s bone marrow. Cells are collected and processed then delivered back into the patient through 10 intramyocardial injections into targeted areas of the heart. In a [February 2012, Baxter press release](#) the company stated that, “Stem cell processing will be conducted in GMP facilities in the United States by Progenitor Cell Therapy (PCT), a subsidiary of NeoStem, Inc.”

Myocardial ischemia happens when blood flow to heart muscle is reduced because of coronary artery blockage, either partial or complete. The blockage reduces the heart’s supply of oxygen.

NT-501 (ciliary neurotrophic factor) (Renexus) – Cell Therapy (Orphan Drug) (Fast Track)

Sponsor – [Neurotech Pharmaceuticals](#)

Retinitis Pigmentosa

Neurotech Pharmaceuticals has developed NT-501 (Renexus) for treatment of Retinitis Pigmentosa (RP) and a number of other eye diseases. According to ClinicalTrials.gov, Neurotech has completed a Phase II/III for early stage RP and a Phase II/III for late stage RP and has another trial currently recruiting.

This product, given both Orphan Drug Designation and Fast Track Status by FDA, acts like a mini-bioreactor in the eye. Renexus utilizes an encapsulated cell technology implant to produce and release neurotrophic cytokine to treat the disease. The implant is a device that is semi-permeable and contains the NTC-200 cell line, which is a naturally immortalized retinal pigmented epithelial cell line. The cell line then secretes a biotherapeutic, in this case recombinant ciliary neurotrophic factor (CNTF). The semi-permeable nature of the device allows for nutrients to flow into the device and reach the cells and allows the recombinant CNTF to flow out. Neurotech states on their website, that implants are capable of continuously producing recombinant biotherapeutics for up to two years in the eye. After filling the implants with cells in their Rhode Island manufacturing facility, Neurotech Pharmaceuticals ships implants to ophthalmic surgeons for implantation into patients.

Retinitis Pigmentosa represents a number of inherited eye diseases that cause retinal degeneration and over time causes a deterioration of vision.

Neocart (autologous chondrocyte implantation) - Cell Therapy

Sponsor – [Histogenics](#)

Cartilage Disorders

Neocart is currently being evaluated in Phase II/III clinical trials. The Phase III clinical trial is for treatment of cartilage defects in the knee and is currently active. The product consists of an implant that is grown using the patient's own cartilage cells and is being compared to the current standard of care, which is microfracture treatment.

To produce the product, a cartilage sample is collected from the patient in a non-weight bearing area of the joint. Chondrocyte cells are then isolated from the sample and according to Neocart's website the cells are "harvested, seeded into a unique 3-dimensional collagen scaffold, and cultured under exacting conditions of high pressure, oxygen concentration and perfusion." The implant takes a few weeks to produce and is then sent to the surgeon to implant into the patient. After a few months the implant integrates with the patient's tissue.

Juvenile Chondrocyte Grafts (DeNovo ET) - Cell Therapy

Sponsor – [ISTO Technologies](#)

Cartilage Disorders

DeNovo ET has an active Phase III clinical trial for treatment of articular cartilage lesions of the knee. The product is being compared to microfracture treatment, which is the current standard of care.

DeNovo ET is an allogeneic, scaffold-free, living cartilage implant. The product is produced using donor juvenile tissue to source the chondrocytes. The harvested cells are then expanded and a thin disk of cartilage tissue about the size of a quarter is produced for the

implant. If approved, this would be an off the shelf product, so there would be minimal wait time for implantation.

According to ISTO Technologies' website, "juvenile cartilage cells have far superior regenerative properties than adult cartilage cells," based on the study "The potential of human allogenic juvenile chondrocytes for restoration of articular cartilage," published in the American Journal of Sports Medicine in 2010.

MACI (matrix induced autologous chondrocyte implantation) – Cell Therapy

Sponsor – [Genzyme](#)

Articular Cartilage Defects

Genzyme's MACI implant is an autologous implant for treatment of articular cartilage defects. MACI has completed one Phase III clinical study for the treatment of articular cartilage defects in the knee compared to current standard of care, microfracture treatment. MACI also has a Phase III clinical study enrolling by invitation to look at the five-year efficacy and safety for patients that previously received MACI treatment in comparison with patients that have received the microfracture treatment.

MACI is created by collecting a sample of cartilage from the patient, then chondrocyte cells are cultured and expanded to over ten million cells. The cells are seeded on the biodegradable ACI-Maix Membrane and after culturing is complete the implant is returned to the surgeon for implantation.

The future certainly looks bright for cell therapies. In just this group of Phase III candidates there are four therapies that have received Orphan Drug Designation and four that have received Fast Track Status from the FDA. The therapies listed here are just a small sample of the 69 cell therapies in front of the FDA for review. I am encouraged by the progress being made in this area, particularly in treatment for diseases for which innovative treatments are lacking. I look forward to seeing which of these, or maybe another, is the first to receive approval.

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Brandy Sargent is Editor and frequent author of the blog, *Cell Culture Dish*. She has worked in the biotechnology industry for over twelve years, first in corporate communications and public relations, then in technical sales and marketing, and most recently as a consultant. She continues to be fascinated by the ever-evolving biotechnology landscape and enjoys sharing her enthusiasm with blog readers. She invites readers to share their expertise and experience about important cell culture applications to further the development of biologics for human health.

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