Stem cell applications-

Cord blood, Cord tissue, Fat tissue

Annual General Meeting of Shareholders

18 May 2011

Arnoud van Tulder

Chief Executive Officer

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Latest news about stem cells (1/3)

- New **heart** with own stem cells (April 2011)
- Storing of stem cells from peripheral blood for Japanese **nuclear workers** (April 2011)
- Senate committee Missouri approves bill about information on UCB (April 2011)
- Surgeons have used a boy's own MSCs to rebuild his **trachea** (March 2011)
- Novel measurements of mammary stem cells in UCB as prospective predictors of **breast cancer** susceptibility in later life (March 2011)
- 5 boys aged 10 to 14 receive tailor-made **urethras** grown in a lab from their own cells (March 2011)

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Latest news about stem cells (2/3)

- Autologous cord blood for pediatric **traumatic brain injury** FDA approved clinical study (Feb 2011)
- New clinical trial to evaluate potential of MSCs in **acute myocardial infarction** (Feb 2011)
- Autologous cord blood to treat children with **Cerebral Palsy** (Jan 2011)
- Autologous HSCs transplantation improves **end-stage liver disease** (Jan 2011)
- Autologous cord blood stem cells successfully transplanted in young patient suffering from **severe brain ischemia** (Jan 2011)

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Latest news about stem cells (3/3)

- Nantes University France team shows **cardiac muscle** recovery significantly improved (Dec 2010)
- Stem cell tests hint at **MS** repair (Dec 2010)
- Human cord tissue MSCs hold high potential for treating **rheumatoid arthritis** (Nov 2010)
- US scientists create first **miniature liver** using stem cells (Oct 2010)
- Stem cells cure 82 one eye **blind** people (June 2010)
- First global study reveals majority (57%) of transplants use person's own stem cells. Family use 81% (May 2010)

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History of Cord Blood transplants

- First “media claimed” cord blood transplant for Fanconi’s Anemia (bone marrow failure) in **1988**. Sibling transplant. Patient alive and well today.
- To date, over **20,000** cord blood transplants (mainly allogeneic from Public cord blood banks)
- **Current proven applications**
- Recovery after **23.5** years comparable to fresh samples (Broxmeyer et al. Blood March 2011)
- NMDP forecast **10,000 cord blood** transplants **per year** by **2015**

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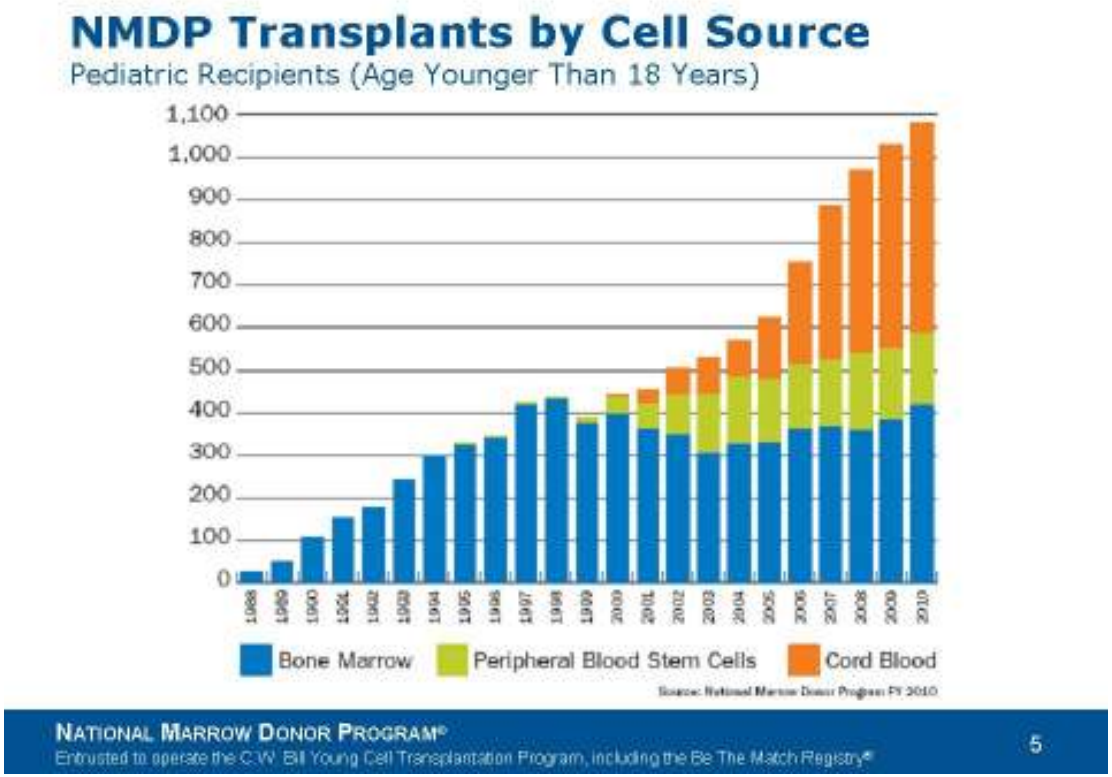
Cord Blood is most frequently used source of stem cells for pediatric patients in the US



- Childhood cancers are highly curable today – therapy includes stem cell transplant
- First line treatment is chemotherapy, followed by stem cell transplant, if necessary

Ref: NMDP (www.marrow.org)

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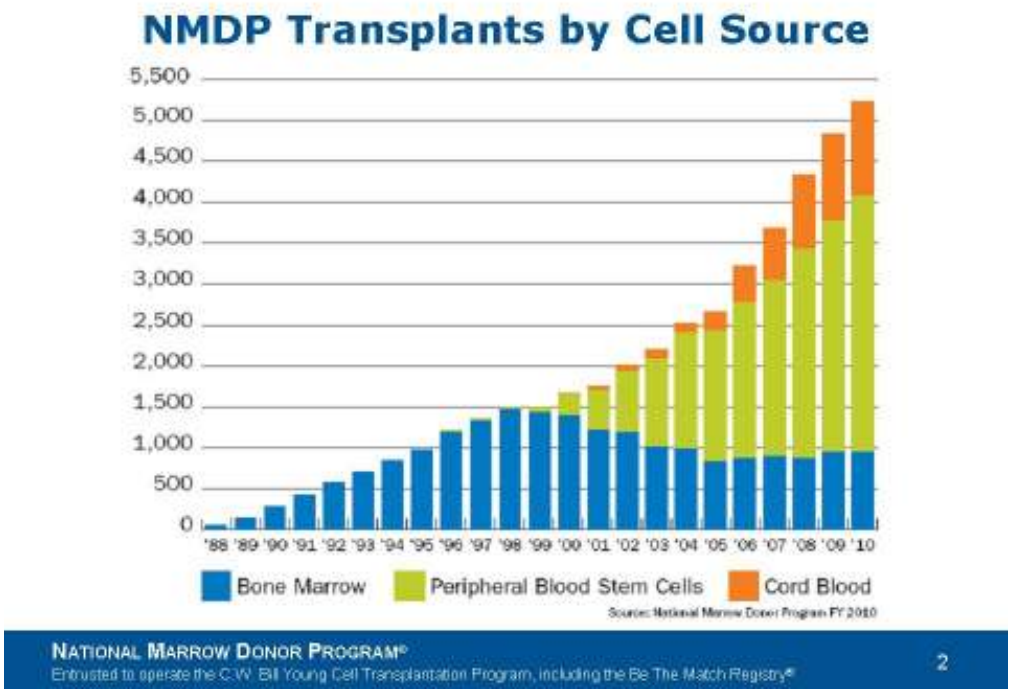
Adult transplants using UCB stem cells on the rise



- First adult UCB stem cell transplant was in 1996
- Increasing adult transplants using UC blood stem cells
- Double cord transplants
- Amplification of stem cells(clinical trials)
- Intra-osseous transplantation(clinical trials)
- Co-transplantation with MSC's and other cells (research)

Ref: NMDPwww.marrow.org

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Private cord blood bank releases

- Cord Blood Europe (7 European Private Cord Blood Banks)
  - 32 releases
    - 22 autologous
    - 10 family
- Two largest USA banks (Cord Blood Registry and Viacord)
  - 332 units released
    - 179 autologous
    - 177 family

❖ Autologous- emerging applications, clinical trials (and current applications)
❖ Family- siblings for current applications.

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Appendices

Diseases treated with stem cells

Leukemias and lymphomas, including:

- Acute myelogenous leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Chronic myelogenous leukemia
- Juvenile myelomonocytic leukemia
- Hodgkin lymphoma
- Non-Hodgkin lymphoma

Multiple myeloma and other plasma cell disorders

Severe aplastic anemia and other marrow failure states, including:

- Severe aplastic anemia
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Pure red cell aplasia
- Amegakaryocytosis / congenital thrombocytopenia

SCID and other inherited immune system disorders, including:

- Severe combined immunodeficiency (SCID, all sub-types)
- Wiskott-Aldrich syndrome

Hemoglobinopathies, including:

- Beta thalassemia major
- Sickle cell disease

Hurler's syndrome and other inherited metabolic disorders, including:

- Hurler's syndrome (MPS-IH)
- Adrenoleukodystrophy
- Metachromatic leukodystrophy
- Krabbe's disease

Myelodysplastic and myeloproliferative disorders, including:

- Refractory anemia (all types)
- Chronic myelomonocytic leukemia
- Agnogenic myeloid metaplasia (myelofibrosis)

Histiocytic disorders

Other malignancies, including:

- Neuroblastoma
- Retinoblastoma

National Marrow Donor Program

- Mainly blood and blood related disorders
- Genetic diseases- not for autologous use but family/sibling transplants.

www.parentsguidecordblood.org
standard treatments, clinical trials and experimental treatments.

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Beyond current applications

- Regenerative medicine and cellular therapy: research, studies, trials
- Different types of stem cells
- Different sources of stem cells
  - Bone Marrow
  - **Cord blood**
  - **Cord tissue**
  - **Adipose stem cells**
  - Peripheral blood
  - Others

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Promising diseases/fields.

- Cerebral palsy
- Traumatic brain injury
- Stroke
- Spinal cord injuries
- Heart disease
- Type 1 Diabetes
- Orthopedic applications
- Auto-immune disorders
- Ophthalmological applications
- Solid tumors
- Liver disease
- Musculo-skeletal and burns

- Various stages of research
- Stem cell sources-
  BM, adipose, PB, **UCB**, **UCT**
- Stem cell types-**HSC's**, **MSC's,**
  others
- Mainly autologous
- Some allogeneic

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Regenerative medicine and Cellular therapy

Cord Blood as stem cell source

Autologous umbilical cord stem cells clinical trials

- Cerebral Palsy
- Traumatic brain disorders
- Hypoxic ischemic encephalopathy
- Diabetes mellitus

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Pilot study: Autologous cord blood infusion for acquired neurological disorders

- Duke University USA-Dr Joanne Kurtzberg
- Over 184 children treated.
- Diagnosis of treated children:
  - Cerebral Palsy 140 patients (76%)
  - Congenital Hydrocephalus 23 patients (12%)
  - Other injuries 23 patients (12%)
- Age at infusion:
  - Less than 6months =30 patients(15%)
  - 7 months – 3 years =120 patients(61%)
  - Older than 4 years = 48 patients (24%)

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Cerebral Palsy-Definition

- Cerebral palsy (CP) results from damage to certain parts of the developing brain, chiefly in the various areas of body movement.
- CP is a brain injury, not a disease
- CP is non-progressive, non- contagious.
- CP causes physical disability in human development

- NOTE: problem with accessing improvement in children with CP is that each patient is unique. Children improve and develop physically but at different rates and thus is difficult to define the natural progress of a child with CP.

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Cause

- Exact cause not always known
- Result of combination of prenatal, perinatal and postnatal factors
- Thought that majority of CP is caused by lack of oxygen at birth, BUT
  - 70-80% occurs **during** pregnancy (prenatal)
  - 10% at delivery
  - 10% after delivery (postnatal)

REF: http://www.emedicinehealth.com/cerebral_palsy/page2_em.htm

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Statistics

"One out of every 500 children suffer from Cerebral Palsy"

REF: How common are the "common" neurologic disorders?

D. Hirtz, MD, D. J. Thurman, MD, MPH, K. Gwinn-Hardy,

MD, M. Mohamed, MPH, A. R. Chaudhuri, PhD and R. Zalutsky, PhD

Neurology 2007;68:326-337

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Current medical treatment

- no curative treatment, only supportive.
- no standard therapy that works for all patients.
- prevention and prediction is often difficult

Thus- researchers looking at regenerative stem cell therapies - offer a treatment option to regenerate nerve tissue and repair damage to the brain.

Proposed mechanism of working of stem cells for Cerebral Palsy

- Brain imaging scans of cerebral palsy children show hypo perfusion in various regions of the brain
- Main hypothesis: Umbilical cord derived stem cells have the ability to help repair the entire system by:
  - stimulating angiogenesis (blood vessel growth)
  - Direct- dividing into new neurons once the oxygen and nutrient supply can support them
  - Indirect- stimulation of neurogenesis and neuroprotection via growth factors, neurotrophic factors and others.

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FDA approved clinical trial for Cerebral Palsy- Duke's University

- Randomized, Blinded, Placebo-Controlled, Crossover
  - Phase 11
  - 120 patients
  - June 2010-July 2013, follow up for 2 years
- Child
  - Age 12months to 6 years
- CB sample
  - 10 million stem cells per kg body weight
  - Free from infectious diseases
  - Free from contamination
  - HLA match confirmed

REF: www.clinicaltrials.gov NCT 01147656

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FDA approved clinical trial for Cerebral Palsy- Medical College of Georgia

- Randomized, Blinded, Placebo-Controlled, Crossover (at 3 months)
  - phase I/II
  - 40 patients
  - Jan 2010- Feb 2013 , follow up for one year
- Child
  - Age 2-12 years old
  - CP diagnosis-and unable to sit independently by 12 months of age or unable to walk independently by 18 months of age
- CB sample
  - 20 million stem cells/kg body weight.
  - Free from infectious diseases
  - Free from contamination
  - HLA match confirmed

REF: www.clinicaltrials.gov NCT 01072370

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Traumatic brain injury - FDA approved autologous UCB

- University Texas Health & Science Centre
- PI- Professor Charles S. Cox
  - Phase 1 safety study
  - 10 patients
  - Age 18 months - 17 years
  - Within 6-18 months of their injury
  - Moderate to severe TBI
- Intravenous autologous cord blood infusion
- CB must be stored at CBR
- Follow up at 6months, 1 year , 2 years

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Hypoxic Ischemic Encephalopathy- Pilot study (Duke's University)

- Joanna Kurtzberg-Duke's University
- Autologous cord blood given within 14 days postnatal after diagnosis of HIE made
- Pilot study with selected obstetrical hospitals
- Labor suites and obstetricians informed of trial and emergency kits available in labor suite
- Suspected problem at birth triggers obstetrician to collect cord blood

REF: www.clinicaltrials.gov NCT 00593242

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Allogeneic UCB stem cells clinical trials

- Spinal cord injuries
- Stroke
- Critical Limb Ischemia

- As current children who have their umbilical cord blood stored, age in years and enter a higher risk group for certain diseases – we should see further utilization of autologous cord blood.

Regenerative Medicine & Cellular Therapy

MSC's as stem cell type

Regenerative Medicine & Cellular Therapy- MSC's as stem cell type

- Over 130 clinical trials using MSC's (www.clinicaltrials.gov)
- Source of MSC's traditionally BM , but now CORD tissue and adipose tissue emerging (most advanced)
- Not all MSC's are the same- pre-clinical work and clinical trials evaluating
- CORD- easy to harvest, young, more primitive

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BM MSC's

- BM has been considered as one of the main sources of MSCs for both experimental and clinical applications
- Most of the knowledge concerning MSCs came from BM studies
- However, problems/limitation due to aging:
  - Decrease in ability to divide/self replicate
  - Decrease in ability to differentiate
  - Decrease in cell numbers

Why obtain MSC's from umbilical cord

- Easy to obtain and present in all cords
- More primitive and younger
- Greater proliferative capacity
- Other sources of MSC's involves invasive procedures to collect
- Optimal bone marrow donors are age 18-19 years old

Cytotherapy, 2010; 12: 17–30

informa
healthcare

Age-dependent neuroectodermal differentiation capacity of human mesenchymal stromal cells: limitations for autologous cell replacement strategies

Conclusions. Our data provide evidence that only young donor-derived hMSC can be epigenetically differentiated in vitro into neuroectodermal cells, pointing towards senescence of multipotentiality of old donor-derived hMSC. There is thus an

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CORD storage for the future.

Biology of Blood and Marrow Transplantation 13:1477-1486 (2007)

1083-8791/07/1312-0001$32.00/0
doi:10.1016/j.bbmt.2007.08.048

ASBMT
American Society for Blood and Marrow Transplantation

Umbilical Cord Mesenchymal Stem Cells: Adjuvants for Human Cell Transplantation

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Received July 3, 2007; accepted August 30, 2007

The Wharton's jelly of the umbilical cord is rich in mesenchymal stem cells (UC-MSCs) that fulfill the criteria for MSCs. Here we describe a novel, simple method of obtaining and cryopreserving UC-MSCs by extracting the Wharton's jelly from a small piece of cord, followed by mincing the tissue and cryopreserving it in autologous

*Minimal manipulation
*Blood vessels not dissected
*All cells preserved for future technology and discoveries

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MSC's in clinical trials

- Liver disease (14)
- Heart disease (15)
- T1 Diabetes (6)
- T2 Diabetes (2)
- Diabetic foot (2)
- Limb ischemia (5)
- Multiple Sclerosis (5)
- GvHD (13)
- Blood and blood related disorders (3)
- Co transplant for HSCT (3)
- Orthopedic applications (24)

www.clinicaltrials.gov

Over 130 trials

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MSC's in clinical trials -continued

- Sjogrens Syndrome
- Systemic Sclerosis
- SLE
- Kidney diseases- nephritis, acute renal failure
- Multiple system atrophy
- Lung – COPD and Bronchopulmonary dysplasia (2)
- Expansion with MSC's
- Spinal cord (3)
- Parkinson's
- Epidermolysis Bullosa
- Osteogenesis Imperfecta (2)
- Neuroblastoma
- Erectile dysfunction

www.clinicaltrials.gov

Over 130 trials

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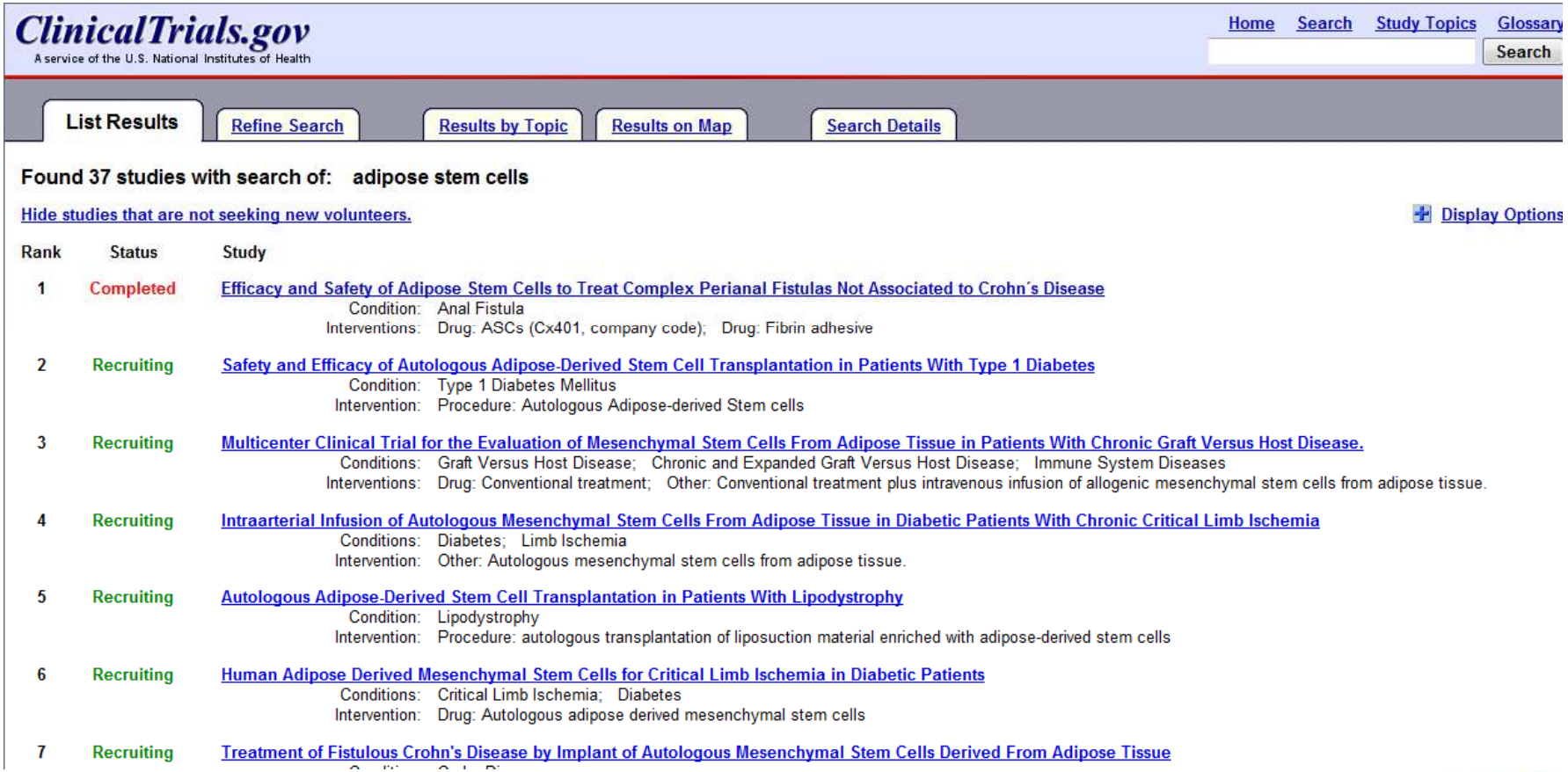
Adipose stem cells in clinical trials

Adipose stem cells in clinical trials-37



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Search

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Found 37 studies with search of: adipose stem cells

Hide studies that are not seeking new volunteers.

Display Options

Rank	Status	Study
1	Completed	Efficacy and Safety of Adipose Stem Cells to Treat Complex Perianal Fistulas Not Associated to Crohn´s Disease Condition: Anal Fistula Interventions: Drug: ASCs (Cx401, company code); Drug: Fibrin adhesive
2	Recruiting	Safety and Efficacy of Autologous Adipose-Derived Stem Cell Transplantation in Patients With Type 1 Diabetes Condition: Type 1 Diabetes Mellitus Intervention: Procedure: Autologous Adipose-derived Stem cells
3	Recruiting	Multicenter Clinical Trial for the Evaluation of Mesenchymal Stem Cells From Adipose Tissue in Patients With Chronic Graft Versus Host Disease. Conditions: Graft Versus Host Disease; Chronic and Expanded Graft Versus Host Disease; Immune System Diseases Interventions: Drug: Conventional treatment; Other: Conventional treatment plus intravenous infusion of allogenic mesenchymal stem cells from adipose tissue.
4	Recruiting	Intraarterial Infusion of Autologous Mesenchymal Stem Cells From Adipose Tissue in Diabetic Patients With Chronic Critical Limb Ischemia Conditions: Diabetes; Limb Ischemia Intervention: Other: Autologous mesenchymal stem cells from adipose tissue.
5	Recruiting	Autologous Adipose-Derived Stem Cell Transplantation in Patients With Lipodystrophy Condition: Lipodystrophy Intervention: Procedure: autologous transplantation of liposuction material enriched with adipose-derived stem cells
6	Recruiting	Human Adipose Derived Mesenchymal Stem Cells for Critical Limb Ischemia in Diabetic Patients Conditions: Critical Limb Ischemia; Diabetes Intervention: Drug: Autologous adipose derived mesenchymal stem cells
7	Recruiting	Treatment of Fistulous Crohn's Disease by Implant of Autologous Mesenchymal Stem Cells Derived From Adipose Tissue

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