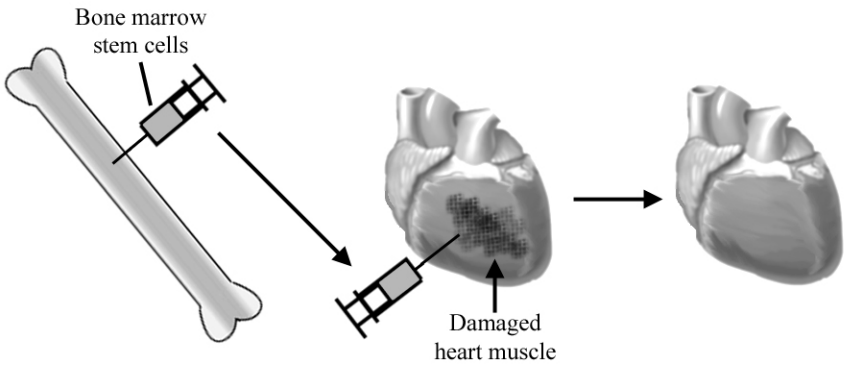
David A. Prentice, Ph.D.
Charlotte Lozier Institute
Washington, D.C.

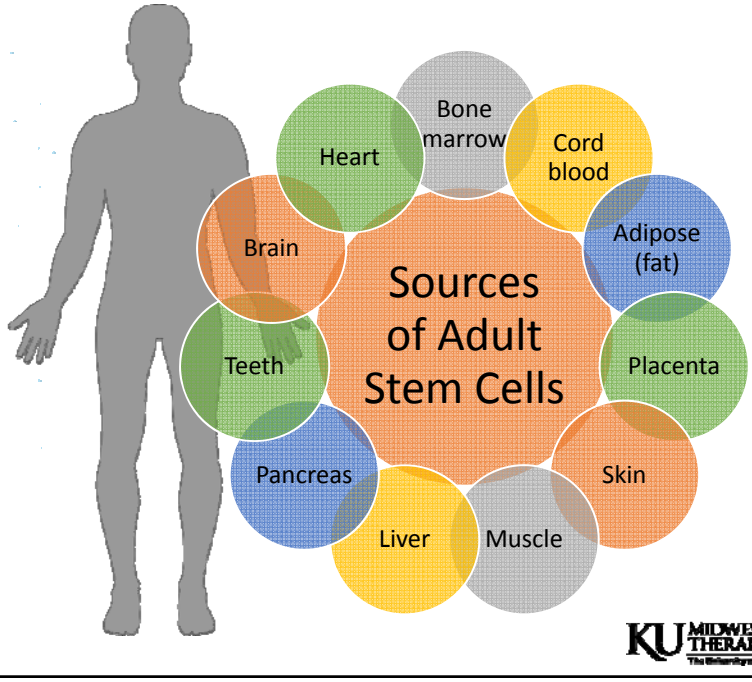
CHARLOTTE LOZIER INSTITUTE

Midwest Stem Cell Therapy Center
Kansas' Unique Stem Cell Center

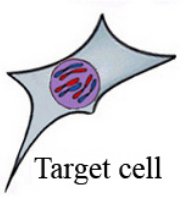
- Focus on therapy
- Exclusively non-embryonic
  No embryonic stem cells. No fetal tissue.
- Focus on dissemination of knowledge
- Comprehensive

Regenerative Medicine with Stem Cells





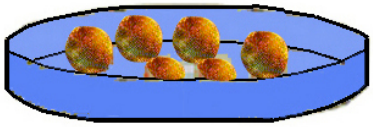
induced Pluripotent Stem Cells (iPS cells)
(Cell Reprogramming)



Target cell

Add 1-4 genes ± chemicals

Oct-4, Sox-2, klf-4, Myc
Oct-4, Sox-2, lin28, nanog



Treated cells behave like pluripotent stem cells
(embryonic-like stem cells)

Shinya Yamanaka receiving his Nobel Prize from His Majesty King Carl XVI Gustaf of Sweden at the Stockholm Concert Hall, 10 December 2012.

One million haemopoietic stem-cell transplants: a retrospective observational study

Alois Gratwohl, Marcelo C Pasquini, Mahmoud Aljurf, Yoshiko Atsuta, Helen Baldomero, Lydia Foeken, Michael Gratwohl, Luis Fernando Bouzas, Dennis Confer, Karl Frauendorfer, Eliane Gluckman, Hildegard Greinix, Mary Horowitz, Minako Iida, Jeff Lipton, Alejandro Madrigal, Mohamad Mohty, Luc Noel, Nicolas Novitzky, José Nunez, Machteld Oudshoorn, Jakob Passweg, Jon van Rood, Jeff Szer, Karl Blumet, Frederic R Appelbaum, Yoshihisa Kodera, Dietger Niederwieser, for the Worldwide Network for Blood and Marrow Transplantation (WBMT)

Summary

Background The transplantation of cells, tissues, and organs has been recognised by WHO as an important medical task for its member states; however, information about how to best organise transplantation is scarce. We aimed to document the activity worldwide from the beginning of transplantation and search for region adapted indications and associations between transplant rates and macroeconomics.

Methods Between Jan 1, 2006, and Dec 31, 2014, the Worldwide Network for Blood and Marrow Transplantation collected data for the evolution of haemopoietic stem-cell transplantation (HSCT) activity and volunteer donors in the 194 WHO member states.

Findings 953 651 HSCTs (553 350 [58%] autologous and 400 301 [42%] allogeneic) were reported by 1516 transplant centres from 75 countries. No transplants were done in countries with fewer than 300 000 inhabitants, a surface area less than 700 km², and a gross national income per person of US$1260 or lower. Use of HSCT increased from the first transplant in 1957 to almost 10 000 by 1985. We recorded a cumulative total of about 100 000 transplants by 1995, and an estimated 1 million by December, 2012. Unrelated donor registries contributed 22·3 million typed volunteer donors and 645 646 cord blood products by 2012. Numbers of allogeneic HSCTs increased in the past 35 years with no signs of saturation (R^2=0·989). Transplant rates were higher in countries with more resources, more transplant teams, and an unrelated donor infrastructure.

Interpretation Our findings show achievements and high unmet needs and give guidance for decisions; to grant access for patients, to provide a donor infrastructure, and to limit overuse by defining risk and region adapted indications for HSCT as an efficient and cost-effective approach for life-threatening, potentially curable diseases.

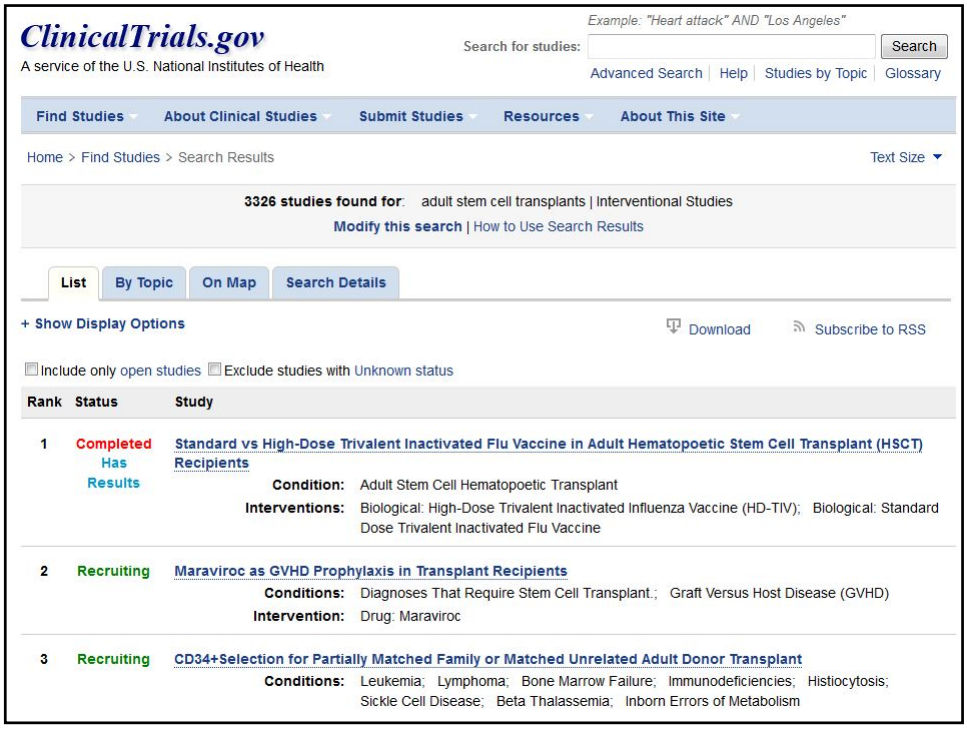
Lancet Haematol 2015; 2: e91–100

Published Online February 27, 2015 http://dx.doi.org/10.1016/S2352-3026(15)00028-9

See Comment page e83

See Online for podcast interview with Dietger Niederwieser

Worldwide Network for Blood and Marrow Transplantation (WBMT) Transplant Activity Survey Office, University Hospital, Basel, Switzerland (Prof A Gratwohl MD, H Baldomero BMS, Prof J Passweg MD); **The Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, USA** (M C Pasquini MD, Prof M Horowitz MD); **The Eastern Mediterranean Blood and Marrow Transplantation**



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Rank	Status	Study
1	Completed Has Results	Standard vs High-Dose Trivalent Inactivated Flu Vaccine in Adult Hematopoetic Stem Cell Transplant (HSCT) Recipients **Condition:** Adult Stem Cell Hematopoetic Transplant **Interventions:** Biological: High-Dose Trivalent Inactivated Influenza Vaccine (HD-TIV); Biological: Standard Dose Trivalent Inactivated Flu Vaccine
2	Recruiting	Maraviroc as GVHD Prophylaxis in Transplant Recipients **Conditions:** Diagnoses That Require Stem Cell Transplant.; Graft Versus Host Disease (GVHD) **Intervention:** Drug: Maraviroc
3	Recruiting	CD34+Selection for Partially Matched Family or Matched Unrelated Adult Donor Transplant **Conditions:** Leukemia; Lymphoma; Bone Marrow Failure; Immunodeficiencies; Histiocytosis; Sickle Cell Disease; Beta Thalassemia; Inborn Errors of Metabolism

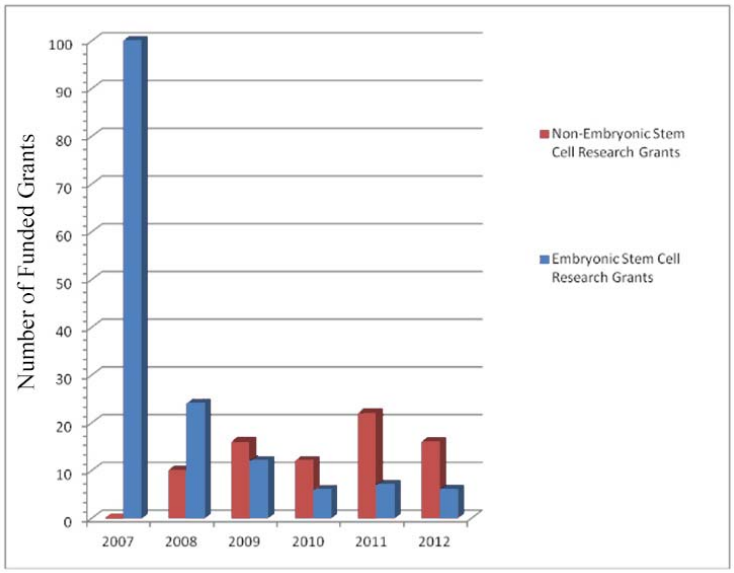
Approximately 53 programs nationwide doing research in the stem cell field.

Most "stem cell centers" focus on basic research with little or no clinical component.

Most "stem cell treatment centers" emphasize certain clinical treatments but do not educate the public or physicians.

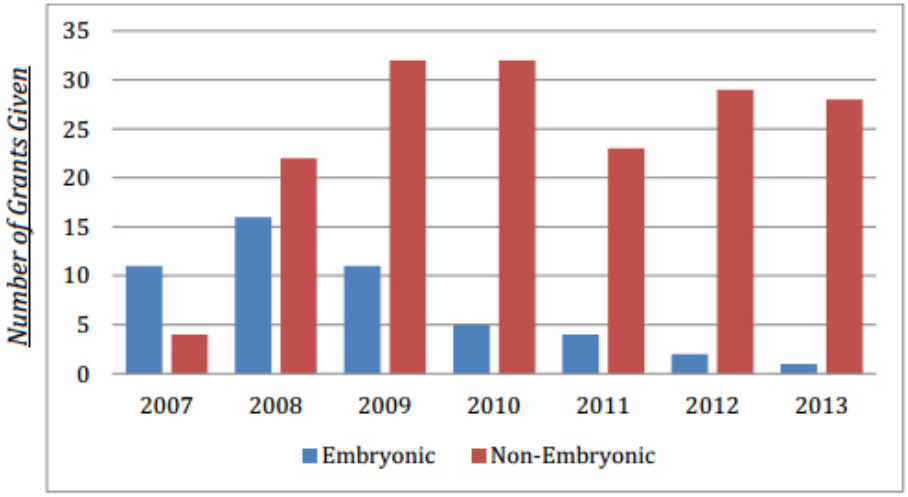
None of the identified stem cell centers provide a comprehensive program of treatment, research, training and education as does the MSCTC

California Funding More Adult Stem Cell Research



From: Gene Tarne, "The Ethical Stems of Good Science", Charlotte Lozier Institute, 2012

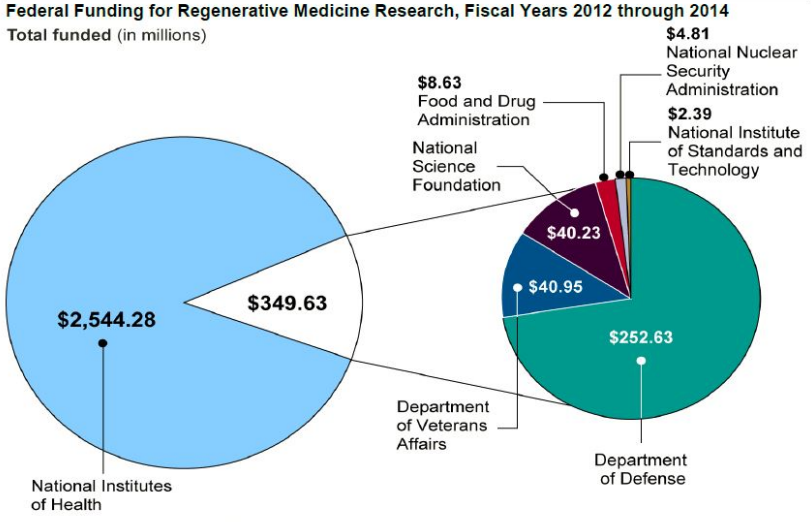
Maryland Funding More Adult Stem Cell Research



From: Gene Tarne and Andrew Mullins, "Maryland Joins the Trend for Ethical Stem Cell Research", Charlotte Lozier Institute, October 2013

Seven federal agencies invested—that is, conducted or funded—approximately $2.89 billion in regenerative medicine research in fiscal years 2012 through 2014. Most (88 percent) was invested by the National Institutes of Health. Agencies funded research related to their missions, including basic research to enhance general scientific knowledge, clinical research to move scientific discoveries into practical applications, and research to develop regulatory science.

Federal Funding for Regenerative Medicine Research, Fiscal Years 2012 through 2014



Source: GAO analysis of agency funding on regenerative medicine research. | GAO-15-553

Table 1: Federal Agencies That Conducted or Funded Regenerative Medicine Research, Fiscal Years 2012 through 2014

Federal agency	Agency mission	Regenerative medicine research conducted includes
Department of Defense	Provide the military forces needed to deter war and to protect the security of the country	Research and applications for active-duty personnel including limb repair, traumatic brain injury, and battlefield injuries
Department of Veterans Affairs	Provide veterans and eligible beneficiaries with benefits and services	Research and applications for the veteran population, including limb repair, traumatic brain injury, and care for wounded warriors, as well as for stroke, glaucoma, and other conditions for an aging veteran population
Food and Drug Administration within the Department of Health and Human Services	Protect the public health by ensuring the safety, efficacy, and security of human drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation	Safety and effectiveness research related to regulation of regenerative medicine products and standards development
National Institute of Standards and Technology within the Department of Commerce	Promote innovation and industrial competitiveness by advancing measurement science, standards, and technology	Measurement science and development of consensus documentary standards and standard reference materials to facilitate commercialization of regenerative medicine products[a]
National Institutes of Health within the Department of Health and Human Services	Seek knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability	Biomedical applications and basic, clinical, and translational research, including stem cells and tissue engineering
National Nuclear Security Administration within the Department of Energy	Enhance national security through the military application of nuclear science; responsible for issues of nuclear defense, nonproliferation, and naval research	Research and development, including basic research and experiments designed to determine the utility of new scientific ideas, technical concepts, or devices
National Science Foundation	Promote and advance fundamental scientific progress	Basic research with a focus on expanding current scientific knowledge

Other US State and Collaborative Initiatives

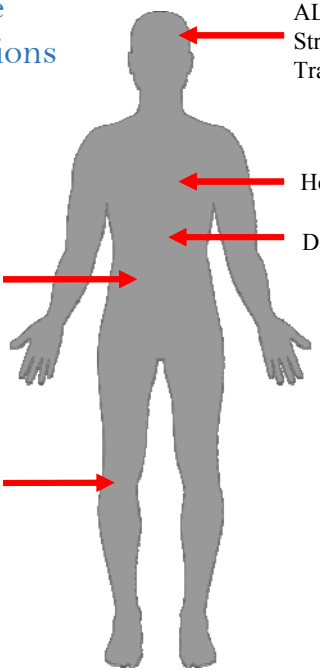
State	Funding Started	Funding Amount	Annual Funding (Average)	Funding to date	Outcomes to date
California	2004	$3B	$172.7M	$1.9B	>>100 grants, 10 clinical studies (FY'15)
Connecticut	2005	Annual Appropriation	$9.8M	$78.6M (2013)	≈ 100 funded research grants
Maryland	2006	Annual Appropriation	$14.4M	$120M (2005-2015) $9.4M in FY'16	349 research grants
New Jersey	2006	$250M	$27.8M	$250M	All for buildings
New York	2007	Annual Appropriation	$37.5M	$300M	> 50 research grants
Minnesota	2013	$50M	$4.3M	≈ $8.7M	None reported
GE Healthcare FedDev Ontario	2016	$28.1M	TBD	$0M	None
Kansas	**2013**	**10.7M**	**$0.9M**	**$2.7M**	**15 research collaborations**

MSCTC Areas of Focus

Adult Stem Cell Therapy

- Stroke and Neurodegenerative Diseases
- Cancer and Immunotherapy
- Cardiovascular Disease
- Musculoskeletal, Trauma, Skin, Burns, Wounds, Autoimmune

Just a few of the diseases/conditions the Center is currently researching…



…As well as Graft-versus-Host Disease, a complication following bone marrow transplant.

KU MIDWEST STEM CELL THERAPY CENTER

Pharmaceuticals **2015**, *8*, 196-220;

Wharton's Jelly-Derived Mesenchymal Stromal Cells as a Promising Cellular Therapeutic Strategy for the Management of Graft-versus-Host Disease

Joseph P. McGuirk [1,†,*], J. Robert Smith [2], Clint L. Divine [1], Micheal Zuniga [2] and Mark L. Weiss [2,†]

Received: 10 December 2014 / Accepted: 8 April 2015 / Published: 16 April 2015

Abstract: Allogeneic hematopoietic cell transplantation (allo-HCT), a treatment option in hematologic malignancies and bone marrow failure syndromes, is frequently complicated by Graft-versus-host disease (GVHD). The primary treatment for GVHD involves immune suppression by glucocorticoids. However, patients are often refractory to the steroid therapy, and this results in a poor prognosis. Therefore alternative therapies are needed to treat GVHD. Here, we review data supporting the clinical investigation of a novel cellular therapy using Wharton's jelly (WJ)-derived mesenchymal stromal cells (MSCs) as a potentially safe and effective therapeutic strategy in the management of GVHD. Adult-derived sources of

Clinical Track

Adult Bone Marrow Cell Therapy for Ischemic Heart Disease

Evidence and Insights From Randomized Controlled Trials

Muhammad R. Afzal, Anweshan Samanta, Zubair I. Shah, Vinodh Jeevanantham, Ahmed Abdel-Latif, Ewa K. Zuba-Surma, Buddhadeb Dawn

Rationale: **Notwithstanding the uncertainties about the outcomes of bone marrow cell (BMC) therapy for heart repair, further insights are critically needed to improve this promising approach.**

Objective: **To delineate the true effect of BMC therapy for cardiac repair and gain insights for future trials through systematic review and meta-analysis of data from eligible randomized controlled trials.**

Circulation Research **August 28, 2015**

RESEARCH ARTICLE

Generation of Functional Cardiomyocytes from Efficiently Generated Human iPSCs and a Novel Method of Measuring Contractility

Sheeja Rajasingh[1], Jayakumar Thangavel[1], Andras Czirok[2], Saheli Samanta[1], Katherine F. Roby[2], Buddhadeb Dawn[1], Johnson Rajasingh[1,3]*

PLOS ONE | DOI:10.1371/journal.pone.0134093 August 3, 2015

Abstract

Human induced pluripotent stem cells (iPSCs) derived cardiomyocytes (iCMCs) would provide an unlimited cell source for regenerative medicine and drug discoveries. The objective of our study is to generate functional cardiomyocytes from human iPSCs and to develop a novel method of measuring contractility of CMCs. In a series of experiments, adult human skin fibroblasts (HSF) and human umbilical vein endothelial cells (HUVECs) were treated with a combination of pluripotent gene DNA and mRNA under specific conditions. The iPSC

Concise Review: Review and Perspective of Cell Dosage and Routes of Administration From Preclinical and Clinical Studies of Stem Cell Therapy for Heart Disease

Samuel Golpanian,[a,b] Ivonne H. Schulman,[a,c] Ray F. Ebert,[d] Alan W. Heldman,[a,c] Darcy L. DiFede,[a] Phillip C. Yang,[e] Joseph C. Wu,[e] Roberto Bolli,[f] Emerson C. Perin,[g] Lem Moyé,[h] Robert D. Simari,[i] Ariel Wolf,[a] Joshua M. Hare,[a,c] for the Cardiovascular Cell Therapy Research Network

Key Words. Stem cell • Cardiovascular disease • Cell dosage • Route of administration

Abstract

An important stage in the development of any new therapeutic agent is establishment of the optimal dosage and route of administration. This can be particularly challenging when the treatment is a biologic agent that might exert its therapeutic effects via complex or poorly understood mechanisms. Multiple preclinical and clinical studies have shown paradoxical results, with inconsistent findings regarding the relationship between the cell dose and clinical benefit. Such phenomena can, at least in part, be attributed to variations in cell dosing or concentration and the route of administration (ROA). Although clinical trials of cell-based therapy for cardiovascular disease began more than a decade ago, specification of the optimal dosage and ROA has not been established. The present review summarizes what has been learned regarding the optimal cell dosage and ROA from preclinical and clinical studies of stem cell therapy for heart disease and offers a perspective on future directions. Stem Cells Translational Medicine *2016;5:186–191*

Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With Relapsing-Remitting Multiple Sclerosis

Richard K. Burt, MD; Roumen Balabanov, MD; Xiaoqiang Han, MD; Basil Sharrack, MD; Amy Morgan, NP; Kathleeen Quigley, RN; Kim Yaung, RN; Irene B. Helenowski, PhD; Borko Jovanovic, PhD; Dzemila Spahovic, MD; Indira Arnautovic, MD; Daniel C. Lee, MD; Brandon C. Benefield, MS; Stephen Futterer, MD; Maria Carolina Oliveira, MD; Joachim Burman, MD

IMPORTANCE No current therapy for relapsing-remitting multiple sclerosis (MS) results in significant reversal of disability.

OBJECTIVE To determine the association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability and other clinical outcomes in patients with MS.

Editorial page 251

Author Audio Interview at jama.com

Supplemental content at jama.com

JAMA. 2015;313(3):275-284. doi:10.1001/jama.2014.17986

Umbilical Cord Mesenchymal Stromal Cell With Autologous Bone Marrow Cell Transplantation in Established Type 1 Diabetes: A Pilot Randomized Controlled Open-Label Clinical Study to Assess Safety and Impact on Insulin Secretion

Diabetes Care 2016;39:149–157 | DOI: 10.2337/dc15-0171

Jinquan Cai,[1] Zhixian Wu,[1] Xiumin Xu,[2,3,4,5] Lianming Liao,[1] Jin Chen,[1] Lianghu Huang,[1] Weizhen Wu,[1] Fang Luo,[1] Chenguang Wu,[1] Alberto Pugliese,[2,6] Antonello Pileggi,[2,3,4,5] Camillo Ricordi,[2,3,4,5,6] and Jianming Tan[1,3,4]

OBJECTIVE

To determine the safety and effects on insulin secretion of umbilical cord (UC) mesenchymal stromal cells (MSCs) plus autologous bone marrow mononuclear cell (aBM-MNC) stem cell transplantation (SCT) without immunotherapy in established type 1 diabetes (T1D).

Intraportal Infusion of Bone Marrow Mononuclear or CD133$^+$ Cells in Patients With Decompensated Cirrhosis: A Double-Blind Randomized Controlled Trial

MEHDI MOHAMADNEJAD,[a,b,*] MASSOUD VOSOUGH,[c,*] SHIRIN MOOSSAVI,[a,b,*] SEPIDEH NIKFAM,[a,b] SOURA MARDPOUR,[c] SHAHRAM AKHLAGHPOOR,[d] MANDANA ASHRAFI,[a,b] VAJIHEH AZIMIAN,[c] NEDA JARUGHI,[c] SEYEDEH-ESMAT HOSSEINI,[c] FATEMEH MOEININIA,[e] MOHAMAD BAGHERI,[a,b] MARYAM SHARAFKHAH,[a,b] NASSER AGHDAMI,[c] REZA MALEKZADEH,[a,b] HOSSEIN BAHARVAND[c]

Key Words. Cirrhosis • Hematopoietic stem cell • Regenerative medicine • Cell-based therapy

ABSTRACT

The present study assessed the effects of intraportal infusions of autologous bone marrow-derived mononuclear cells (MNCs) and/or CD133$^+$ cells on liver function in patients with decompensated cirrhosis. We randomly assigned 27 eligible patients to a placebo, MNCs, and/or CD133$^+$ cells. Cell infusions were performed at baseline and month 3. We considered the absolute changes in the Model for End-Stage Liver Disease (MELD) scores at months 3 and 6 after infusion as the primary outcome. The participants and those who assessed the outcomes were unaware of the treatment intervention assignments. After 6 months, 9 patients were excluded because of liver transplantation (*n* = 3), hepatocellular carcinoma (*n* = 1), loss to follow-up (*n* = 3), and death (*n* = 2). The final analysis included 4 patients from the CD133$^+$ group, 8 from the MNC group, and 6 from the placebo group. No improvement was seen in the MELD score at month 6 using either CD133$^+$ cells or MNC infusions compared

STEM CELLS TRANSLATIONAL MEDICINE 2016;5:87–94 **een toward a higher mean absolute**

Engineering pulmonary vasculature in decellularized rat and human lungs

Xi Ren[1,2], Philipp T Moser[1,2], Sarah E Gilpin[1,2], Tatsuya Okamoto[1,2], Tong Wu[1,2], Luis F Tapias[1–3], Francois E Mercier[1,2], Linjie Xiong[1,2], Raja Ghawi[1,2,4], David T Scadden[1,2,5], Douglas J Mathisen[2,3] & Harald C Ott

Bioengineered lungs produced from patient-derived cells may one day provide an alternative to donor lungs for transplantation therapy. Here we report the regeneration of functional pulmonary vasculature by repopulating the vascular compartment of decellularized rat and human lung scaffolds with human cells, including endothelial and perivascular cells derived from induced pluripotent stem cells. We describe improved methods for delivering cells into the lung scaffold and for maturing

NATURE BIOTECHNOLOGY VOLUME 33 NUMBER 10 OCTOBER 2015

Small airway-on-a-chip enables analysis of human lung inflammation and drug responses *in vitro*

Kambez H Benam[1,8], Remi Villenave[1,8], Carolina Lucchesi[1,7], Antonio Varone[1,7], Cedric Hubeau[2], Hyun-Hee Lee[3], Stephen E Alves[3], Michael Salmon[3], Thomas C Ferrante[1], James C Weaver[1,4], Anthony Bahinski[1], Geraldine A Hamilton[1,7] & Donald E Ingber[1,4–6]

Here we describe the development of a human lung 'small airway-on-a-chip' containing a differentiated, mucociliary bronchiolar epithelium and an underlying microvascular endothelium that experiences fluid flow, which allows for analysis of organ-level lung pathophysiology *in vitro*. Exposure of the epithelium to interleukin-13 (IL-13) reconstituted the goblet cell hyperplasia, cytokine hypersecretion and decreased ciliary function of asthmatics. Small airway chips lined with epithelial cells from individuals with chronic obstructive pulmonary disease recapitulated features of the disease such

NATURE METHODS | VOL.13 NO.2 | FEBRUARY 2016 | 151

The Effect of Platelet-Rich Plasma in Hair Regrowth: A Randomized Placebo-Controlled Trial

PIETRO GENTILE,[a,b] SIMONE GARCOVICH,[c] ALESSANDRA BIELLI,[d] MARIA GIOVANNA SCIOLI,[d] AUGUSTO ORLANDI,[d] VALERIO CERVELLI[a]

Key Words. Autologous • Aging • Clinical translations • Clinical trials

ABSTRACT

Platelet-rich plasma (PRP) has emerged as a new treatment modality in regenerative plastic surgery, and preliminary evidence suggests that it might have a beneficial role in hair regrowth. Here, we report the results of a randomized, evaluator-blinded, placebo-controlled, half-head group study to compare, with the aid of computerized trichograms, hair regrowth with PRP versus placebo. The safety and clinical efficacy of autologous PRP injections for pattern hair loss were investigated. PRP, prepared from a small volume of blood, was injected on half of the selected patients' scalps with pattern hair loss. The other half was treated with placebo. Three treatments were administered to each patient at 30-day intervals. The endpoints were hair regrowth, hair dystrophy as measured by dermoscopy, burning or itching sensation, and cell proliferation as measured by Ki67 evaluation. Patients were followed for 2 years. Of the 23 patients enrolled, 3 were excluded. At the end of the 3 treatment cycles, the patients presented clinical improvement in the mean number of hairs, with a mean increase of 33.6 hairs in the target area, and a mean increase in total hair density of 45.9 hairs per cm^2 compared with baseline values. No side effects were noted during treatment. Microscopic

STEM CELLS TRANSLATIONAL MEDICINE 2015;4:1317–1323 mber of hair follicles 2 weeks We also observed an increase

PM R 7 (2015) S41-S52

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Regenerative Medicine

Regenerative Treatments to Enhance Orthopedic Surgical Outcome

William D. Murrell, MD, Adam W. Anz, MD, Humeira Badsha, MD, William F. Bennett, MD, Robert E. Boykin, MD, Arnold I. Caplan, PhD

Abstract

In orthopedic surgery there has been a never-ending quest to improve surgical outcome and the patient's experience. Progression has been marked by the refinement of surgical techniques and instruments and later by enhanced diagnostic imaging capability, specifically magnetic resonance. Over time implant optimization was achieved, along with the development of innovative minimally invasive arthroscopic technical skills to leverage new versions of classic procedures and implants to improve short-term patient morbidity and initial, mid-term, and long-term patient outcomes. The use of regenerative and/or biological adjuncts to aid the healing process has followed in the drive for continual improvement, and major breakthroughs in basic science have significantly unraveled the mechanisms of key healing and regenerative pathways. A wide spectrum of primary and complementary regenerative treatments is becoming increasingly available, including blood-derived preparations, growth factors, bone marrow preparations, and stem cells. This is a new era in the application of biologically active material, and it is transforming clinical practice by providing effective supportive treatments either at the time of the index procedure or during the postoperative period. Regenerative treatments are currently in active use to enhance many areas of orthopedic surgery in an attempt to improve success and outcome. In this review we provide a comprehensive overview of the peer-reviewed evidence-based literature, highlighting the clinical outcomes in humans both with preclinical data and human clinical trials involving regenerative preparations within the areas of rotator cuff, meniscus, ligament, and articular cartilage surgical repair.

Bioengineered vocal fold mucosa for voice restoration

Changying Ling,[1] Qiyao Li,[2] Matthew E. Brown,[3] Yo Kishimoto,[1]* Yutaka Toya,[1]†
Erin E. Devine,[1] Kyeong-Ok Choi,[4] Kohei Nishimoto,[1] Ian G. Norman,[3] Tenzin Tsegyal,[1]
Jack J. Jiang,[1] William J. Burlingham,[3] Sundaram Gunasekaran,[4] Lloyd M. Smith,[2]
Brian L. Frey,[2] Nathan V. Welham[1]‡

Patients with voice impairment caused by advanced vocal fold (VF) fibrosis or tissue loss have few treatment options. A transplantable, bioengineered VF mucosa would address the individual and societal costs of voice-related communication loss. Such a tissue must be biomechanically capable of aerodynamic-to-acoustic energy transfer and high-frequency vibration and physiologically capable of maintaining a barrier against the airway lumen. We isolated primary human VF fibroblasts and epithelial cells and cocultured them under organotypic conditions. The resulting engineered mucosae showed morphologic features of native tissue, proteome-level evidence of mucosal morphogenesis and emerging extracellular matrix complexity, and rudimentary barrier function in vitro. When grafted into canine larynges ex vivo, the mucosae generated vibratory behavior and acoustic output that were indistinguishable from those of native VF tissue. When grafted into humanized mice in vivo, the mucosae survived and were well tolerated by the human adaptive immune system. This tissue engineering approach has the potential to restore voice function in patients with otherwise untreatable VF mucosal disease.

www.ScienceTranslationalMedicine.org 18 November 2015 Vol 7 Issue 314 314ra187

Human CD34^{+} CD133^{+} Hematopoietic Stem Cells Cultured with Growth Factors Including Angptl5 Efficiently Engraft Adult NOD-SCID Il2r$\gamma^{-/-}$ (NSG) Mice

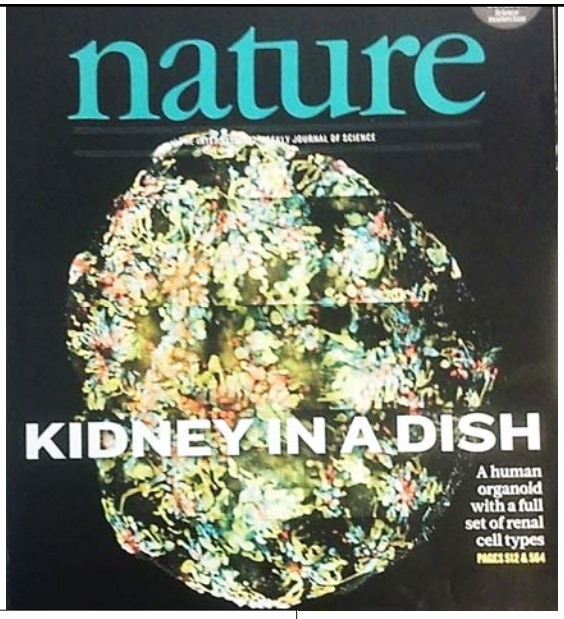
Adam C. Drake[1¶], Maroun Khoury[1,2¶], Ilya Leskov[1], Bettina P. Iliopoulou[1], Maria Fragoso[1], Harvey Lodish[1,3], Jianzhu Chen[1,2*]

1 Koch Institute for Integrative Cancer Research, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, **2** Interdisciplinary Research Group in Infectious Diseases, Singapore-MIT Alliance for Research and Technology (SMART), Singapore, Singapore, **3** Whitehead Institute for Biomedical Research, Cambridge, Massachusetts, United States of America

Abstract

Increasing demand for human hematopoietic stem cells (HSCs) in clinical and research applications necessitates expansion of HSCs *in vitro*. Before these cells can be used they must be carefully evaluated to assess their stem cell activity. Here, we expanded cord blood CD34^{+} CD133^{+} cells in a defined medium containing angiopoietin like 5 and insulin-like growth factor binding protein 2 and evaluated the cells for stem cell activity in NOD-*SCID Il2rg*$^{-/-}$ (NSG) mice by multi-lineage engraftment, long term reconstitution, limiting dilution and serial reconstitution. The phenotype of expanded cells was characterized by flow cytometry during the course of expansion and following engraftment in mice. We show that the SCID repopulating activity resides in the CD34^{+} CD133^{+} fraction of expanded cells and that CD34^{+} CD133^{+} cell number correlates with SCID repopulating activity before and after culture. The expanded cells mediate long-term hematopoiesis and serial reconstitution in NSG mice. Furthermore, they efficiently reconstitute not only neonate but also adult NSG recipients, generating human blood cell populations similar to those reported in mice reconstituted with uncultured human HSCs. These findings suggest an expansion of long term HSCs in our culture and show that expression of CD34 and CD133 serves as a marker for HSC activity in human cord blood cell cultures. The ability to expand human HSCs *in vitro* should facilitate clinical use of HSCs and large-scale construction of humanized mice from the same donor for research applications.

Citation: Drake AC, Khoury M, Leskov I, Iliopoulou BP, Fragoso M, et al. (2011) Human CD34^{+} CD133^{+} Hematopoietic Stem Cells Cultured with Growth Factors Including Angptl5 Efficiently Engraft Adult NOD-SCID Il2r$\gamma^{-/-}$ (NSG) Mice. PLoS ONE 6(4): e18382. doi:10.1371/journal.pone.0018382



Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis

Minoru Takasato[1,2], Pei X. Er[1], Han S. Chiu[2], Barbara Maier[2], Gregory J. Baillie[2], Charles Ferguson[2], Robert G. Parton[2], Ernst J. Wolvetang[3], Matthias S. Roost[4], Susana M. Chuva de Sousa Lopes[4] & Melissa H. Little[1,2,5]

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Adoptive cell transfer as personalized immunotherapy for human cancer

Steven A. Rosenberg* and Nicholas P. Restifo*

Adoptive cell therapy (ACT) is a highly personalized cancer therapy that involves administration to the cancer-bearing host of immune cells with direct anticancer activity. ACT using naturally occurring tumor-reactive lymphocytes has mediated durable, complete regressions in patients with melanoma, probably by targeting somatic mutations exclusive to each cancer. These results have expanded the reach of ACT to the treatment of common epithelial cancers. In addition, the ability to genetically engineer lymphocytes to express conventional T cell receptors or chimeric antigen receptors has further extended the successful application of ACT for cancer treatment.

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CAR-T cells
and
Genetically-modified
stem cell applications

CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy

Gene editing used to create "off-the-shelf" T cells

By Jennifer Couzin-Frankel **SCIENCE** 13 NOVEMBER 2015 • VOL 350 ISSUE 6262 **731**

Adult Stem Cells Save Lives, Improve Health

Midwest Stem Cell Therapy Center

- Unique, comprehensive center
- Focus- patients, education, research, training
- Source of clinical-grade stem cells.
- Global resource for patients and physicians

Kansas a leader in adult stem cell therapies and information for physicians and patients around the world