Midwest Stem Cell Therapy Center

January 14, 2016

KU MIDWEST STEM CELL THERAPY CENTER

Today's Agenda

- ✓Introductions
- ✓Overview of the Center and Activities – Dr. Dawn *(Director, Midwest Stem Cell Therapy Center)*
- ✓Research Advances – Dr. Jim Mitchell *(GMP Facility Manager, Midwest Stem Cell Therapy Center)*
- ✓KU Cancer Center Update and Graft-versus-Host Disease Collaboration – Dr. Joseph McGuirk *(Division Director, Hematologic Malignancies and Cellular Therapeutics, Director, Blood and Bone Marrow Transplant, KU Cancer Center)*
- ✓Marketing & Awareness Efforts – Ms. Pauline Horton *(Communications Specialist, Midwest Stem Cell Therapy Center)*
- ✓Resources – Dr. Dawn
- ✓Q&A
- ✓Tour of Labs
- ✓Adjourn

Senate Bill 199

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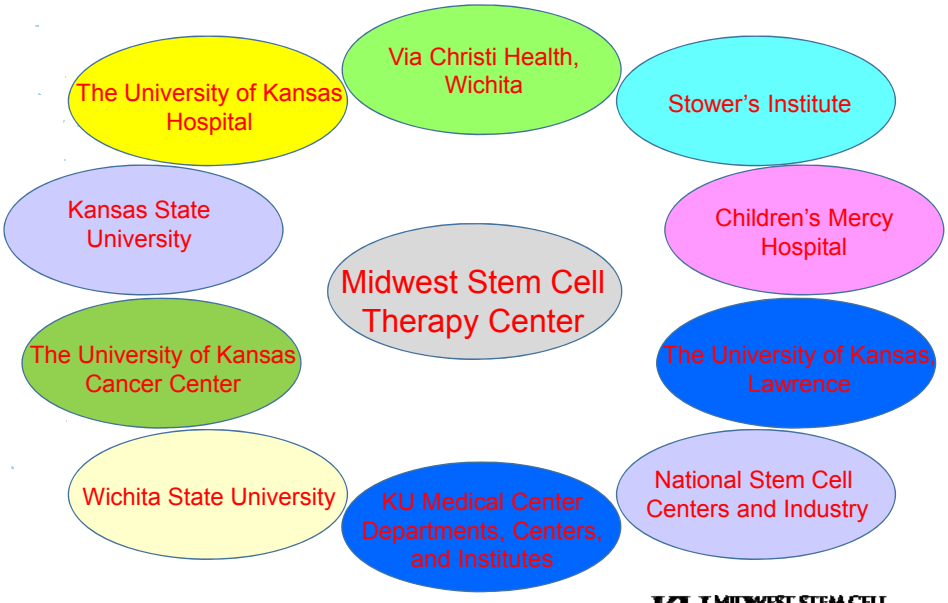
Stem Cell Hub

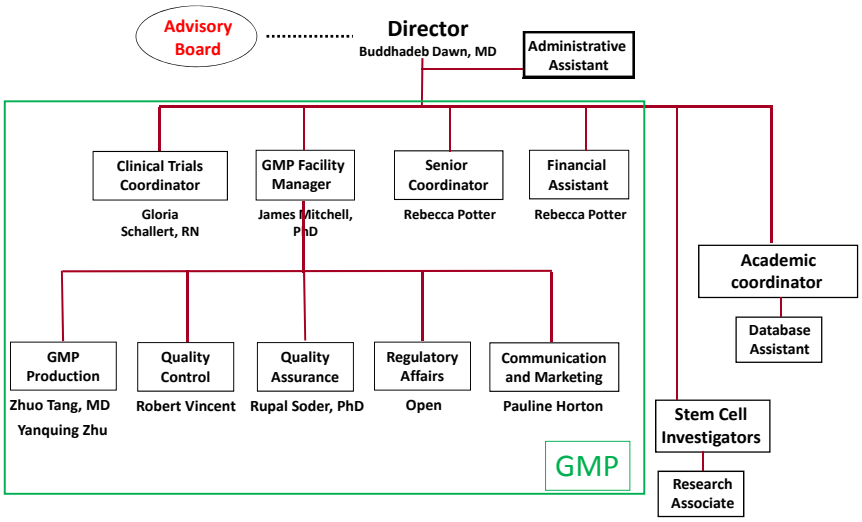


KU MIDWEST STEM CELL THERAPY CENTER

Objectives of the Center - I

- To *advance* adult, cord blood and related stem cell research and therapies for *patient treatment*
- To serve as a *core facility* to produce clinical grade stem cells
- To initiate *clinical trials* with adult, cord blood, and related stem cells

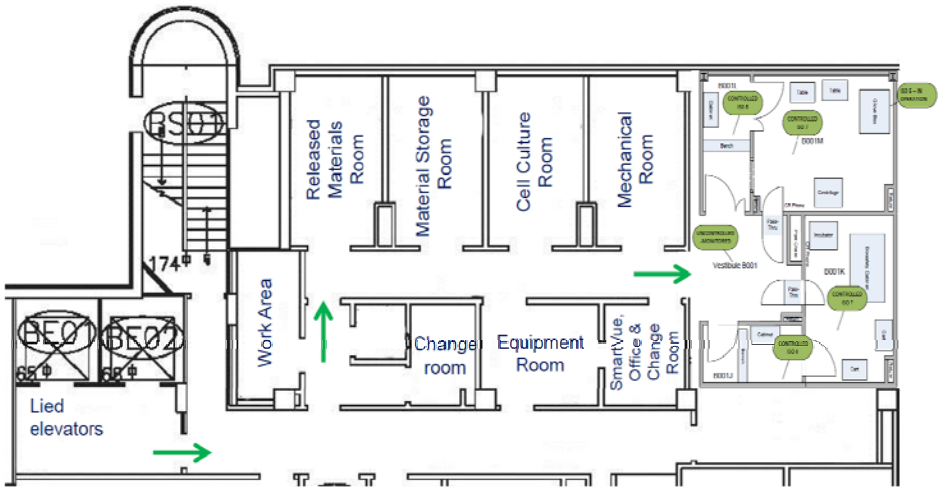
MSCTC Organizational Chart



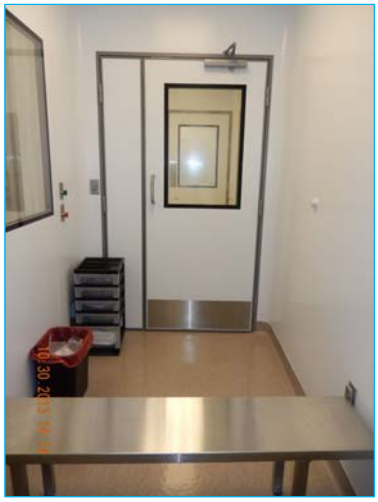
MSCTC Staff

MSCTC Advisory Board

GMP Facility – Lied Building



Good Manufacturing Practice Facility



Focus Areas for Adult Stem Cell Therapy

- Stroke and Neurodegenerative diseases
- Cancer and immunotherapy
- Cardiac and vascular
- Musculoskeletal, trauma, skin, burn, wounds, autoimmune diseases

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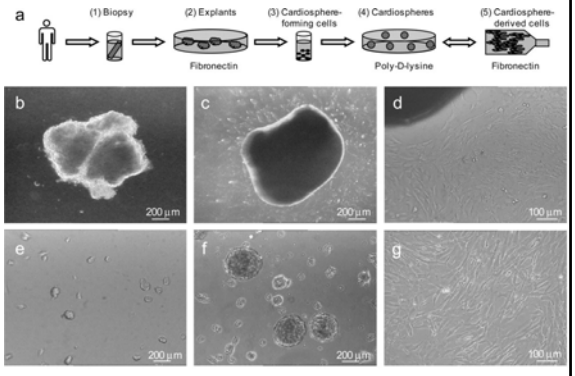
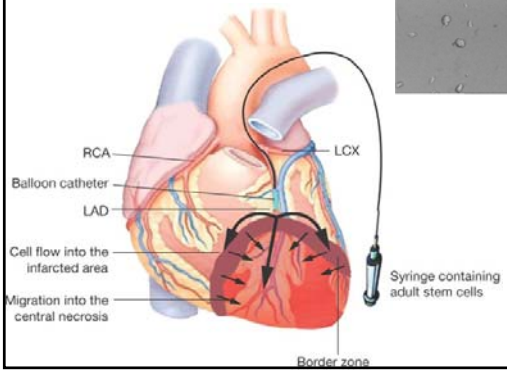
Current Clinical Trials

ALLSTAR: Heart-derived stem cells for patients with heart attack





PreSERVE AMI: Bone marrow-derived CD34+ cells for patients with heart attack

Future Clinical Trials of Heart Repair

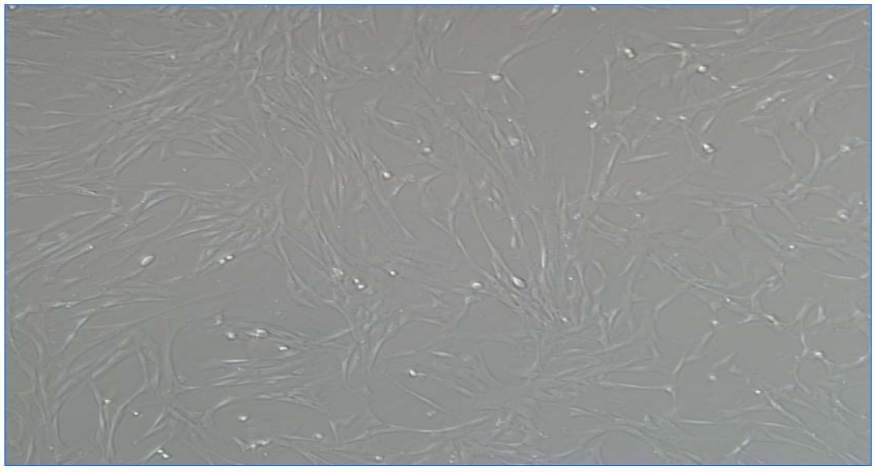
- CardiAMP
  - Selected BM cells delivered intramyocardial to repair of cardiac tissue in patients with heart failure
  - Initial evaluation of clinical study requirements underway by KU
- EXCELLENT
  - CD34+ stem cells for repair of cardiac tissue following an acute heart attack and low EF
  - Collaboration with CellProtehra (European)
  - Possible long-term stem cell manufacturing for supply in US if site approved
  - Site visit to be scheduled

Future Clinical Trials for Stroke

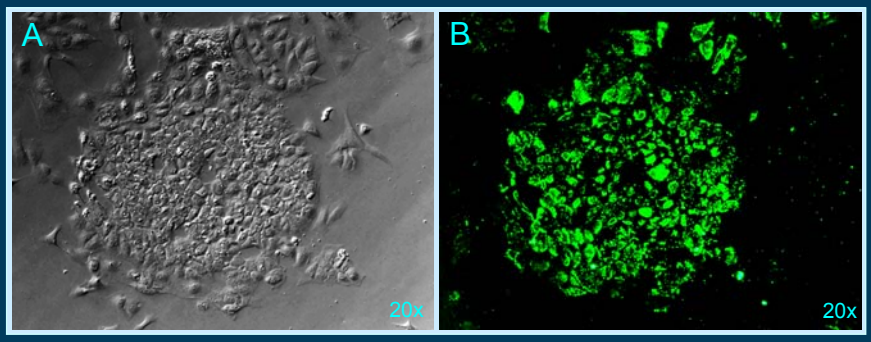
ACTIsSIMA

- Modified adult bone marrow stem cells (SB623) for patients with motor deficiency following an ischemic stroke
- US Biotech company sponsoring trial
- Study to start 1st qtr 2016

Umbilical Cord-derived Mesenchymal Stem Cells (UC-MSCs)



Identification of Human iPS Cells by Live Staining with Tra-1-81 Antibody



bright-field

Tra-1-81 (green)

Objectives of the Center - II

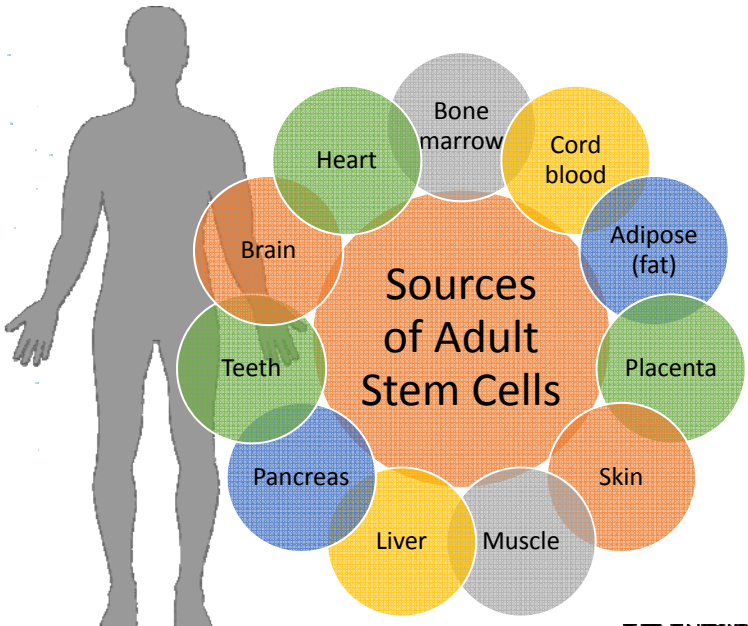
- Informing the public on available adult, cord blood, and related stem cell therapeutic options
- Creating and maintaining a database of available stem cell clinical trials and therapies
- Foster a regional network of physicians trained in adult stem cell therapy

Dissemination of Information

- Website (www.kumc.edu/msctc)
- Compilation of an extensive resource for adult stem cell information
- Providing answers via emails/meetings
- Conferences

Areas of Research Focus

- Cancer and Immunotherapy
- Stroke and Neurodegenerative Disease
- Cardiac and Vascular Disease
- Musculoskeletal Disease and Trauma



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Current Pre-Clinical Projects

- Graft vs. Host Disease (GvHD)
  - Collaboration with University of Kansas Cancer Center
  - Animal efficacy under evaluation in-house
  - FDA teleconference to be held 2/5 to discuss Pre-IND package submitted Nov, 2015
  - Based on response from FDA, pre-clinical efforts will be undertaken and an IND written and submitted for FDA approval to conduct a Phase I human clinical study

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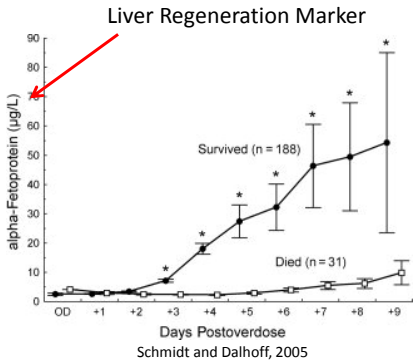
Liver Regeneration Predicts Survival in Patients with Acetaminophen Overdose

- Liver has native potential for regeneration
- After acute liver injury, patients will commonly undergo complete liver regeneration over 10-14 days
- Patients who do not undergo liver regeneration have poor outcomes and commonly enter into an advanced state called Acute Liver Failure
- Mesenchymal stem cells may be able to stimulate regeneration in these patients, providing an entirely novel therapeutic



Schmidt and Dalhoff, 2005

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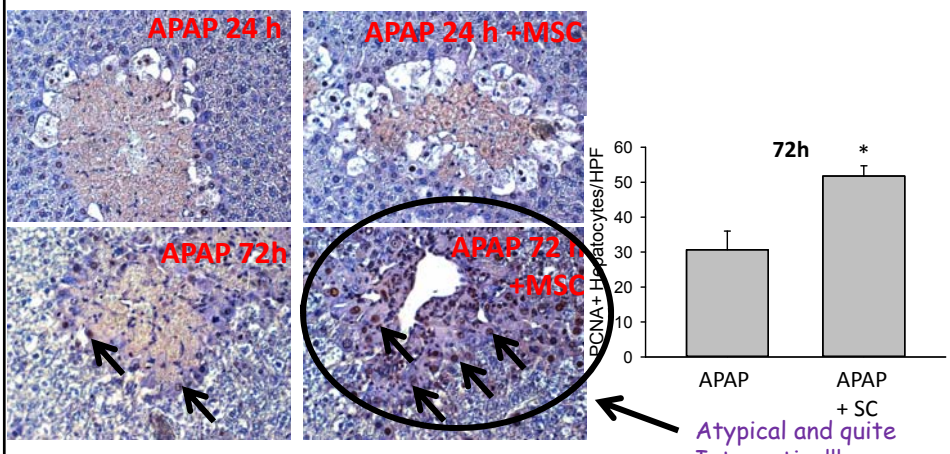
Enhanced Regeneration 72h Post APAP in Late-Stage MSC Post-Treated Mice



Atypical and quite Interesting!!!

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Additional Internal Collaborations

- Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)
  - KUMC, Dept. of Neurology, Dept. of Anatomy and Cell Biology
  - WJMSCs shown to produce cytokines believed to be important in nerve repair
- MI Scar Repair
  - KUMC, Cardiovascular Research Institute
  - Animal studies to begin 1st Qtr 2016
- Cartilage Repair
  - KUMC, Dept. of Orthopedic Surgery
  - WJMSCs being evaluated to determine their ability to differentiate into chondrocytes, the cells that generate and maintain cartilage matrices

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Additional Internal Collaborations

- Spinal Cord Repair
  - KUMC, Dept. of Molecular and Integrative Physiology/Dept. of Pathology and Laboratory Medicine
  - WJMSCs being evaluated for the capacity to differentiate into neurons
- Stroke and Traumatic Brain Injury Repair
  - KUMC, Dept. of Rehabilitation Medicine
  - WJMSCs being evaluated for the capacity to differentiate into neurons

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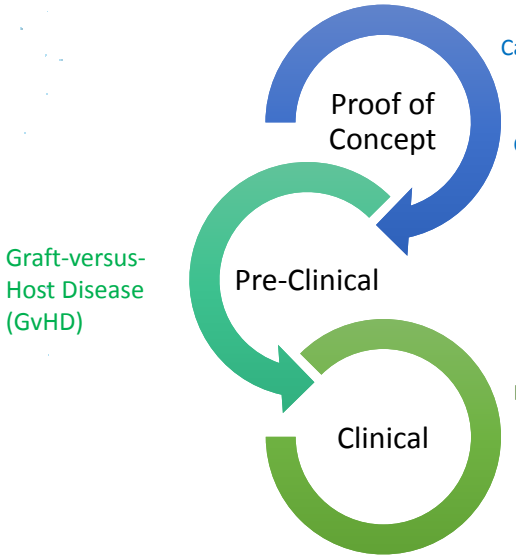
Project Pipeline



Cardiac Scar Repair
Traumatic Brain Injury Repair
ALS
Spinal Cord Repair
Cartilage Repair
Stroke Repair
Liver Repair

Graft-versus-Host Disease (GvHD)

EXELLENT
ACCTISIM
ALLSTAR
Preserve AMI
CardiAMP

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FDA Clinical Trial Process

Investigational New Drug Application (IND)
Researcher files an IND with the FDA to begin testing the treatment in people.

New Drug Application (NDA) Submitted to the FDA and contains all data gathered to date about the drug. An NDA may exceed 100,000 pages.

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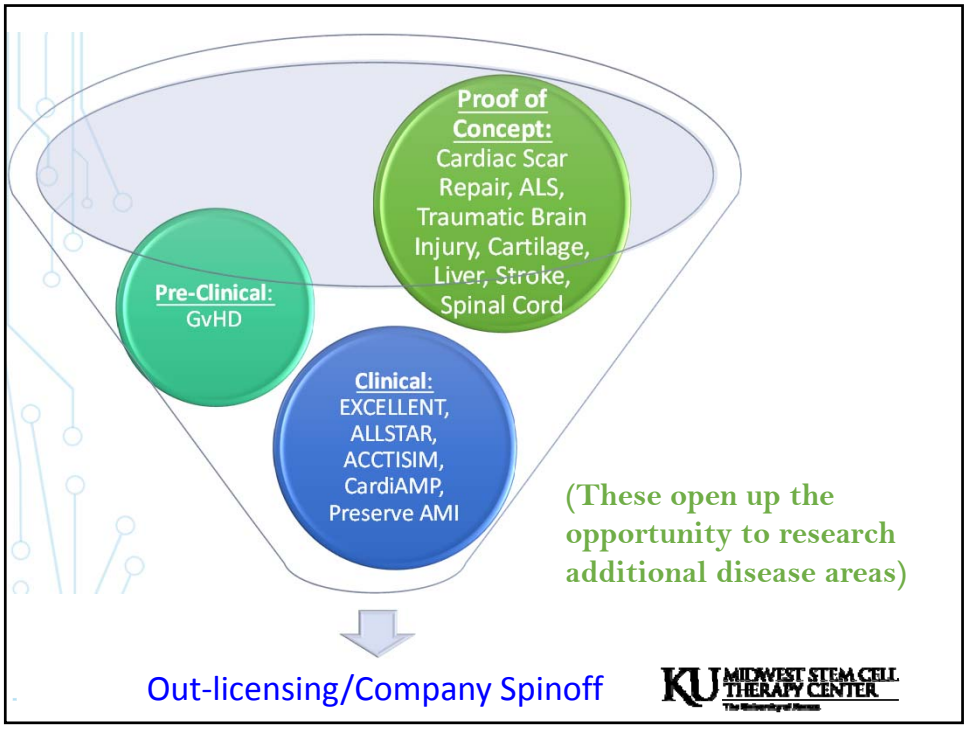
Proof of Concept:
Cardiac Scar Repair, ALS, Traumatic Brain Injury, Cartilage, Liver, Stroke, Spinal Cord
Pre-Clinical:
GvHD
Clinical:
EXCELLENT, ALLSTAR, ACCTISIM, CardiAMP, Preserve AMI
(These open up the opportunity to research additional disease areas)
Out-licensing/Company Spinoff
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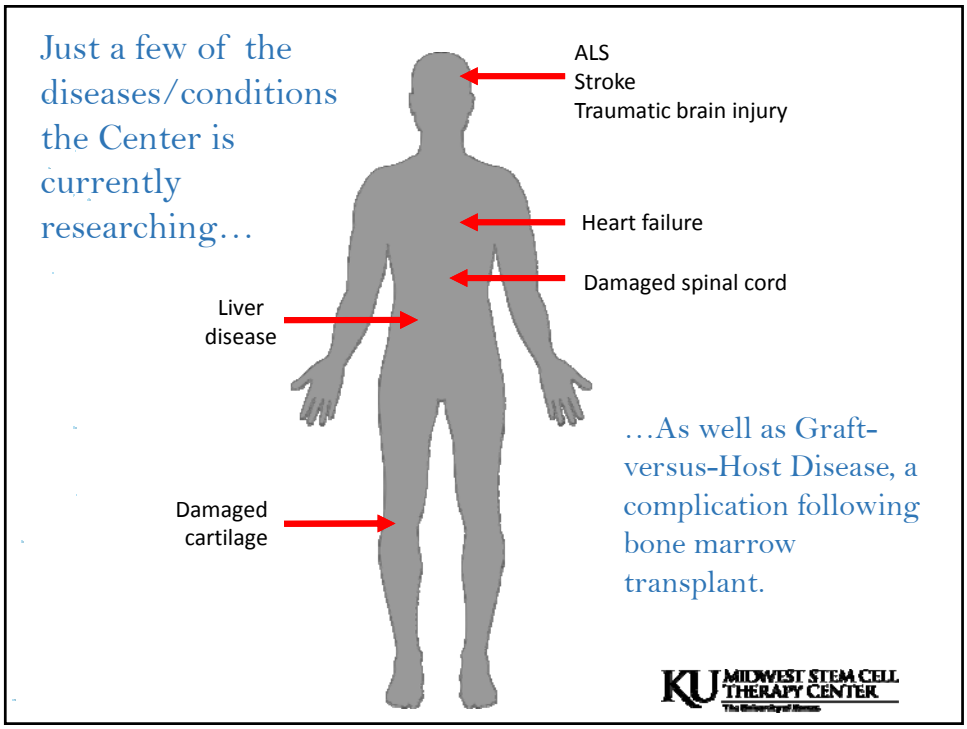
Just a few of the diseases/conditions the Center is currently researching…
ALS
Stroke
Traumatic brain injury
Heart failure
Damaged spinal cord
Liver disease
Damaged cartilage
…As well as Graft-versus-Host Disease, a complication following bone marrow transplant.
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Advances in Stem Cell Transplantation and Cellular Therapeutics

Dr. Joseph McGuirk
Medical Director, Blood and Marrow Transplantation
Division Director, Hematologic Malignancies & Cellular Therapeutics

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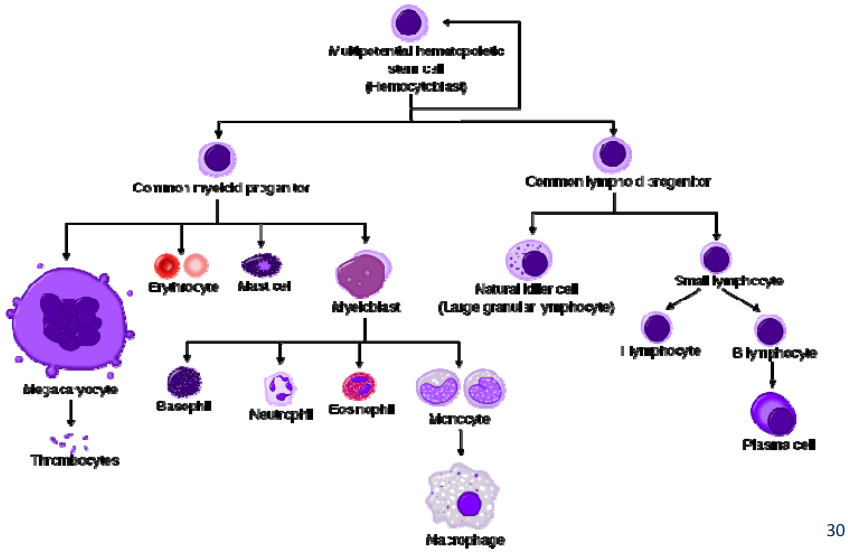
Hematopoiesis



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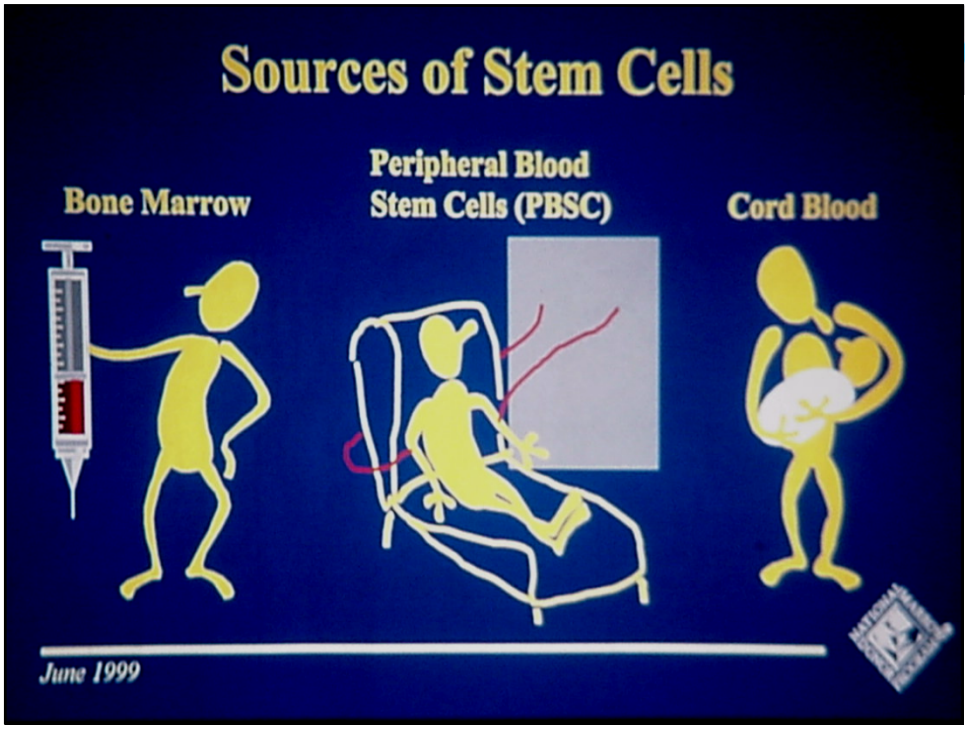
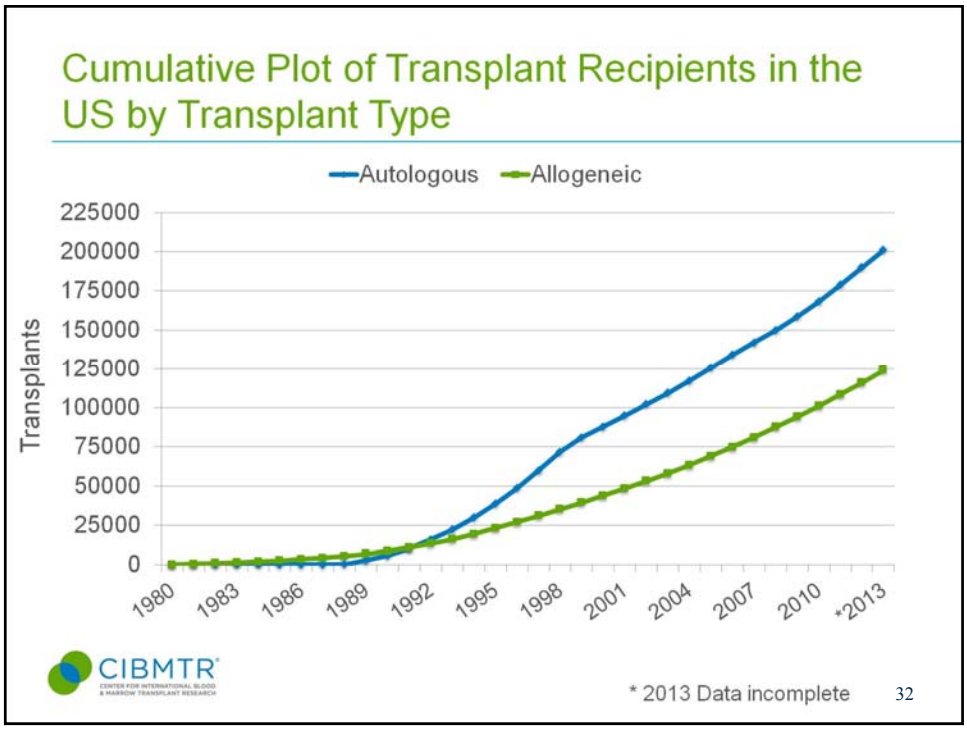

Sources of Stem Cells
Bone Marrow
Peripheral Blood
Stem Cells (PBSC)
Cord Blood
June 1999


Cumulative Plot of Transplant Recipients in the US by Transplant Type
Autologous
Allogeneic
Transplants
225000
200000
175000
150000
125000
100000
75000
50000
25000
0
1980
1983
1986
1989
1992
1995
1998
2001
2004
2007
2010
*2013
CIBMTR
* 2013 Data incomplete
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THE LANCET Haematology

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

Volume 2, No. 3, e91-e100, March 2015

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

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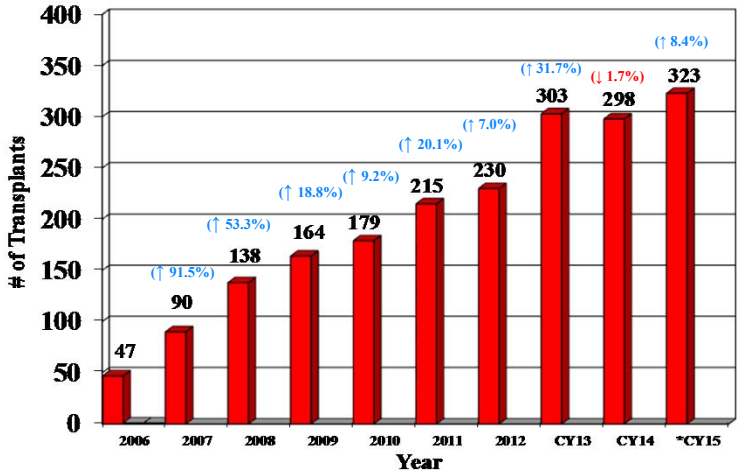
Blood & Marrow Transplant – Annual Volume (CY)



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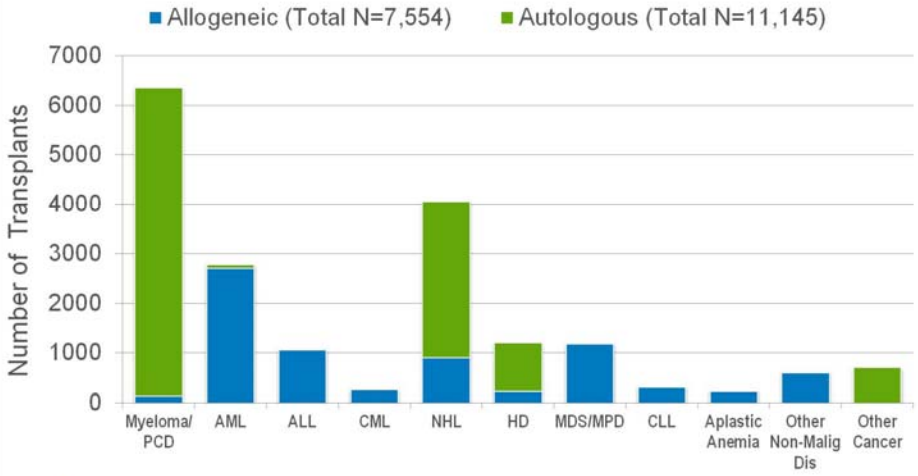
Indications for Hematopoietic Stem Cell Transplants in the US, 2012



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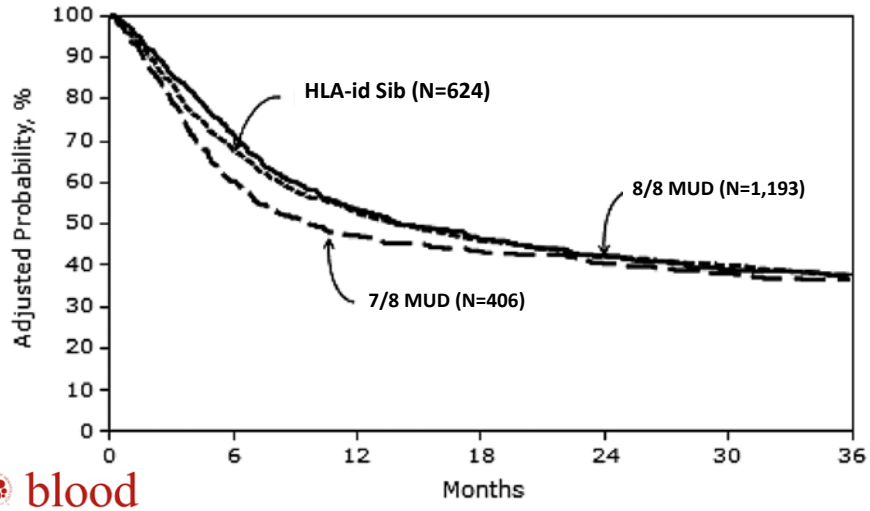
Adjusted probability of overall survival in 2223 adult AML patients by donor type



blood

Wael Saber et al. *Blood.* 2012;119:3908-3916

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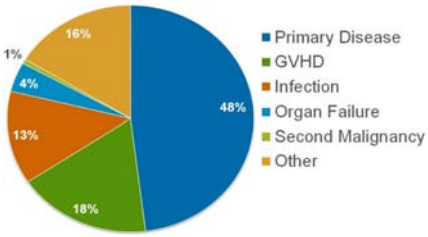
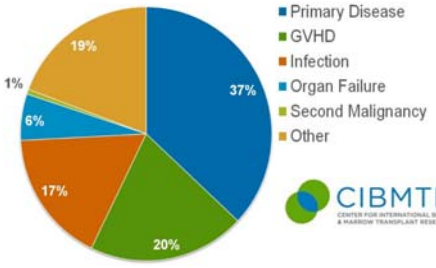
Causes of Mortality related to Allogeneic BMT

(2011-2012)

HLA-identical Sibling



Unrelated Donor



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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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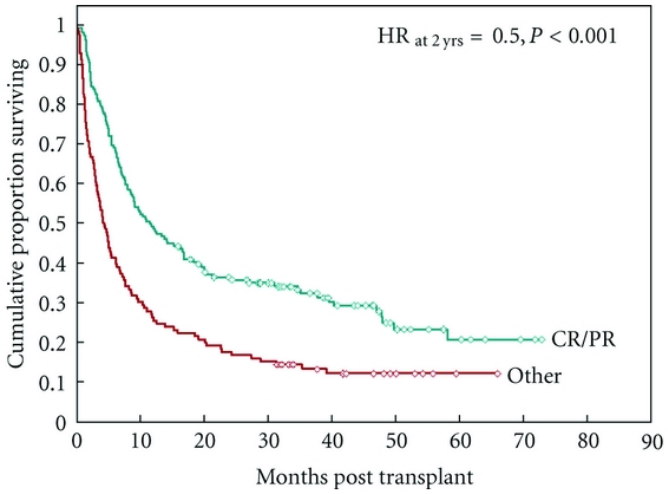
Overall Survival in Steroid-responsive and refractory aGVHD



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J Westin et al. *Adv Hematol*. 2011; 2011: 601953.

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Mechanisms of MSC suppression

Inhibition:
Direct contact dependent
- B7-H1

Indirect Cytokine-mediated
- PGE2
- Cox 1 & 2
- HGF
- TGF-B
- IL-10
- HLA G & E
- LIF
- IDO

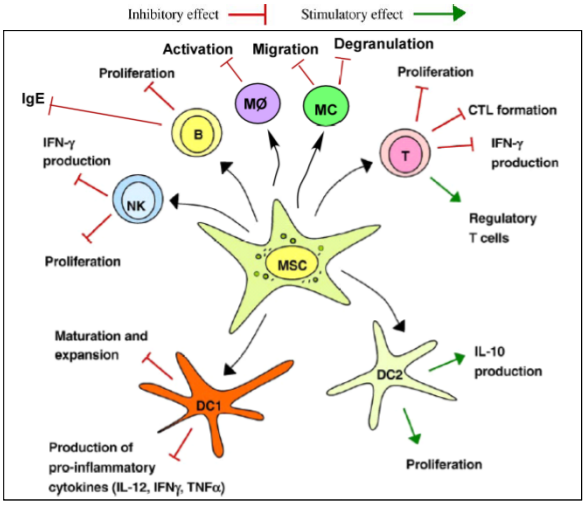

Fig. 1 – Schematic illustration of the effects of MSCs on the immune system. NK, B, and T refer to NK, B, and T cells, respectively. DC1: mature monocytic dendritic cells; DC2: mature plasmacytoid dendritic cells.

Rasmusson I, *Exp Cell Ther.* 2006 – Modified by Weiss M.

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MSCs for GVHD – Summary

- 20 studies used MSCs for GVHD grade 2-4
- MSCs have a positive effect (varies between studies)
- Conditioning varied from myeloablative, nonmyeloablative, RIC, DLI, etc.
  - No apparent difference in response
- MSCs from HLA identical, haploidentical and unrelated, unmatched have been used
  - No apparent differences in response
- MSCs from fresh or frozen/thawed

Source: Mark Weiss

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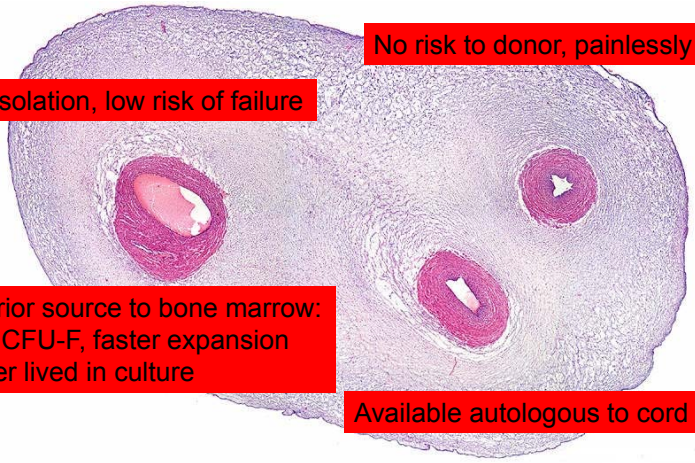
Wharton's Jelly Cells – the MSCs of the Umbilical Cord



No risk to donor, painlessly collected

Easy isolation, low risk of failure

Superior source to bone marrow:
More CFU-F, faster expansion
Longer lived in culture

Available autologous to cord blood

Umbilical cord is not biohazardous waste.
It is a gold mine!

Source: Mark Weiss

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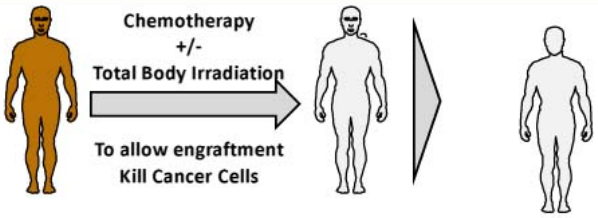
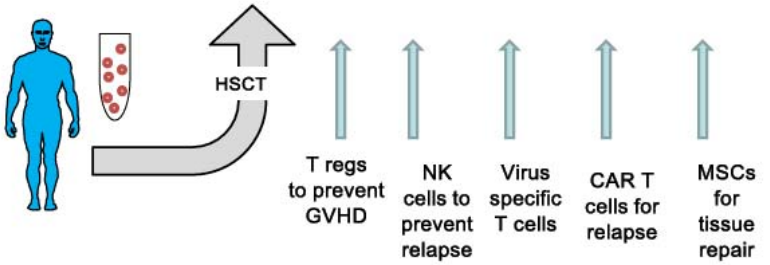
Engineering Transplants





Source: Helen Heslop

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Communications Initiatives

1. Inform/educate patients and medical professionals
2. Create Awareness of Center
3. Grow Donors

www.kumc.edu/msctc/

KU MIDWEST STEM CELL THERAPY CENTER

Annual Conference

September 16-17, 2016
Sheraton Overland Park Hotel

2016 Objectives

- Continue to be a reliable and trustworthy source for practitioners who want up-to-date training on adult stem cell therapy
- Continue to build awareness of Center

KU MIDWEST STEM CELL THERAPY CENTER

Establishing Relationships

External

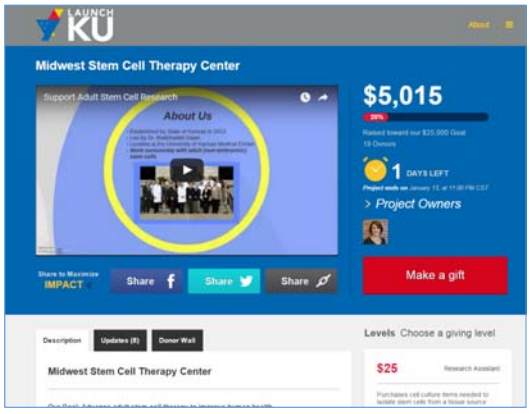
- Archdiocese of Kansas City, Kan.
- Vatican
- BioKansas

KU MIDWEST STEM CELL THERAPY CENTER

Establishing Relationships

Internal

- KU Communications departments
- KU Endowment
  - Pilot for new crowdfunding initiative



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Donors

- Calendar Year 2015 (includes LaunchKU campaign)
  - Approx. 90 donors contributing $9,000
  - Average donor contribution: $113
- Prior to campaign, average donation was approx. $60

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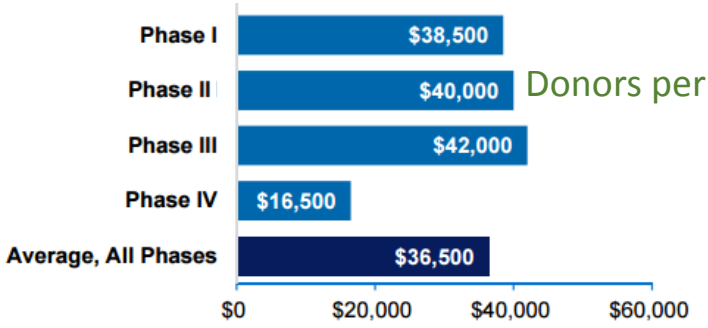
Estimated Average Per-Patient Clinical Trial Costs, by Phase



642 Donors per patient

Source: Battelle, based on survey data from Cutting Edge Information.

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Donor Communications

A Unique Stem Cell Center

- Focus on therapy
- Exclusively non-embryonic
- Focus on dissemination of knowledge
- Comprehensive

Major Support from KU Medical Center and the Kansas Legislature

- Funds toward initial GMP construction, personnel salary and benefits
- Space and other key infrastructure support
- Administrative support, RI
- Brand recognition
- Abundance of collaborators
- Continued funding from the State of Kansas

Business Initiatives

Sponsored R&D

- Nueterra
  - Adipose MSC treatment for Osteoarthritis/Cartilage Repair
  - Project proposal being drafted for review by Nueterra for review
- Stemodontics
  - Isolation, recovery of dental pulp MSCs and long-term banking
  - Site Qualification to be initiated within the next 4-6 weeks
- Applied Stemcell
  - Gene Therapy for Aplastic Anemia
  - Contract in development
- KUCC and Stowers
  - Cord Blood Stem Cell Expansion for transplant
  - Cord Blood IRB approved, work to start in 2016
- Cell Prothera
  - Expanding bone marrow CD34+ cells using proprietary StemXpand Automated system

Business Initiatives

Clinical Trials

- Capricor
  - ALLSTAR – MI Scar repair
- Sanbio
  - ACTIsSIMA – Stroke repair

Sale of Stem Cells

- Developed process
- Documents being developed

Grant Initiatives

- Gene Therapy for Aplastic Anemia
  - Applied StemCell applied for an SBIR grant
    - Included KUCC, Stowers and MSCTC
    - Grant not funded
    - Opportunity to resubmit following company funded proof of concept
- Gene Therapy for Severe Cellular Immunodeficiency
  - Includes KUCC and Stowers
  - Applying for an NIH grant, February 8, 2016

Philanthropic Initiatives

- Crowdfunding
- Working with KU Communications departments to increase awareness
- Midwest Stem Cell Therapy Center Website

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**

Thank you.

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