# Imaging and Applications of MSCs in Pre-Clinical Animal Models

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## Disclosures

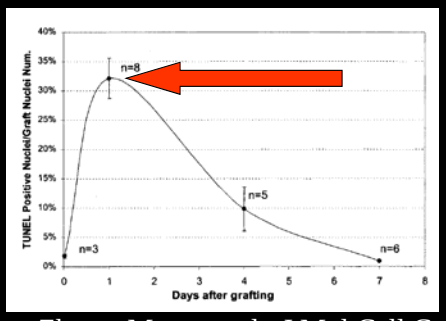
I will discuss off label use and/or investigational use of contrast agents in my presentation.

Financial Relationships to disclose:

- Boston Scientific Corporation
- MRI Interventions, Inc.
- Surefire Medical, Inc.
- Siemens AG

# MSC Therapy Challenges

1. Low engraftment
   - Immunodestruction
   - Restriction of oxygen/nutrient supply
   - Lack of cell survival signal




Zhang, Murry et al., J Mol Cell Cardiol **33**, 907–921 (2001)

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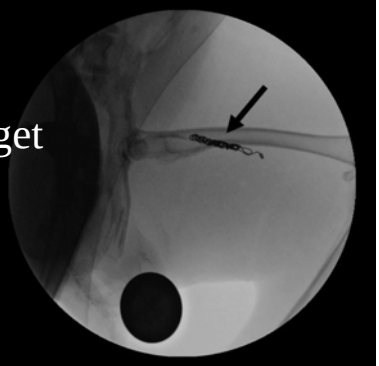
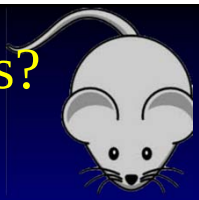
2. Inability to "see" and track where MSCs are

# MSC Therapy Challenges

1. Low engraftment
   - Immunodestruction
   - Restriction of oxygen/nutrient supply
   - Lack of cell survival signal
2. Inability to "see" and track where MSCs are (or non-target organ distribution).
3. Difficulty to assess cell viability and functionality *in vivo*



# Mice, Rats, Dogs, Sheep, Pigs?



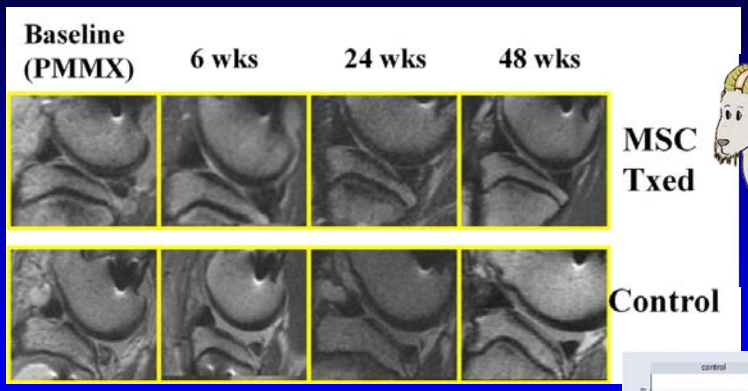
Mice Pros:

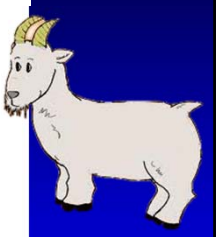
- Low cost
- Small size
  - Limits quantity of drugs
  - Cheaper/easier to house
- Genetic manipulations
- Ethically more acceptable
- Monoclonal abs readily available

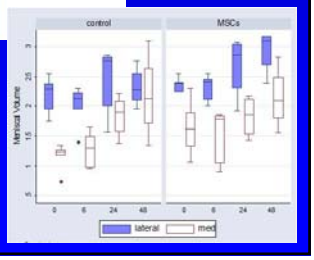
Mice Cons:

- Different lipid metabolism
- Perfusion different than humans
- Not amenable to percutaneous interventions
- Different thromboembolic (4x platelets) /inflammatory system
- MSCs?

# Animal MSC Models - MSK



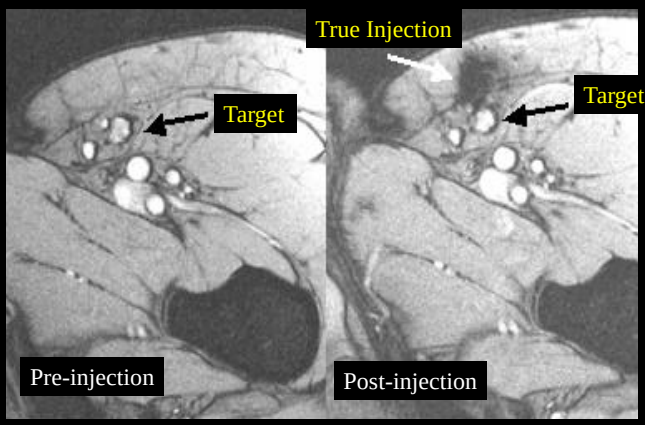





# MSC Therapy Challenges?

For clinical trials, we will need methods to:

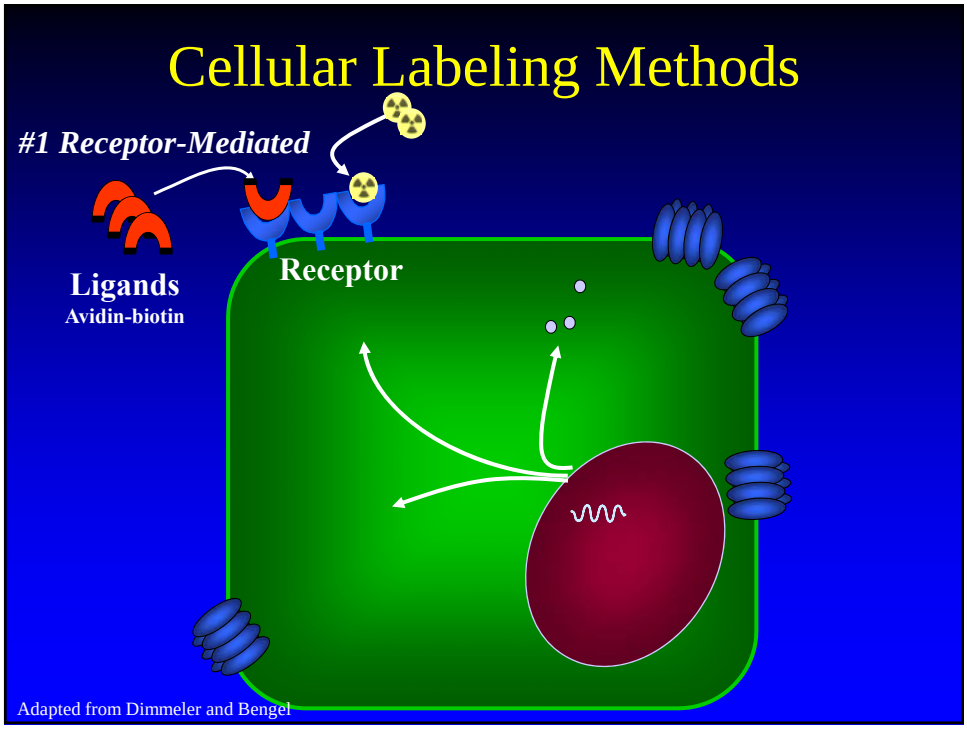
- Determine whether cell reaches target organ

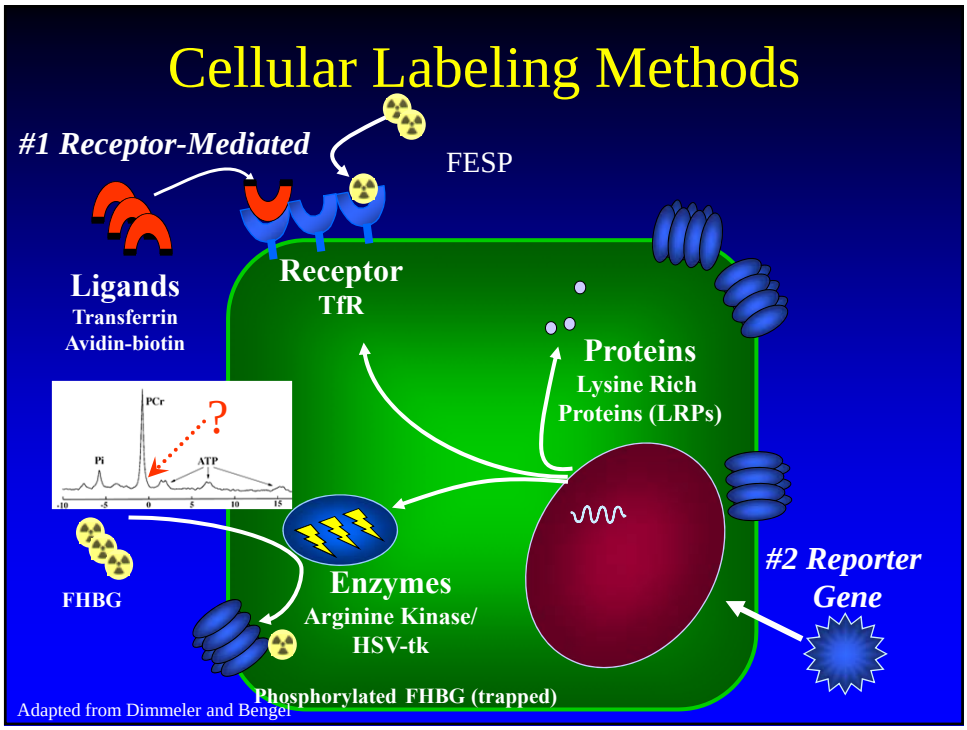



Ultrasound-guided injection of dendritic vaccine into a lymph node

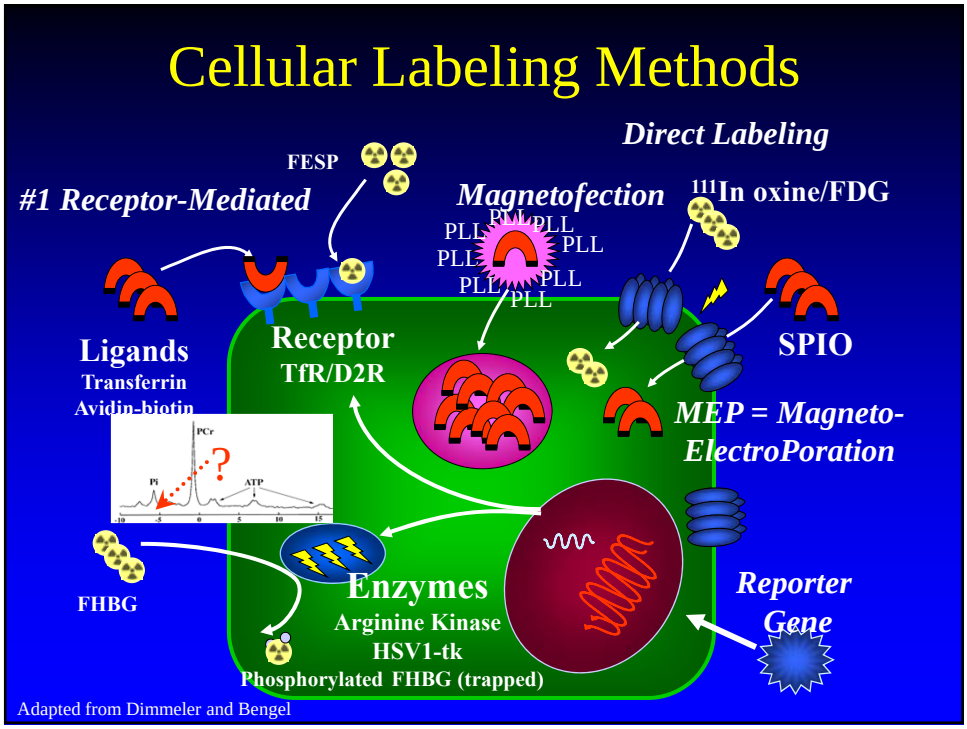
Iron oxide cell labeling demonstrates that the injection did not make "target"

de Vries *et al*., Nature Biotech, 2005; 23(11)


Cellular Labeling Methods
#1 Receptor-Mediated
Ligands
Avidin-biotin
Receptor
Adapted from Dimmeler and Bengel

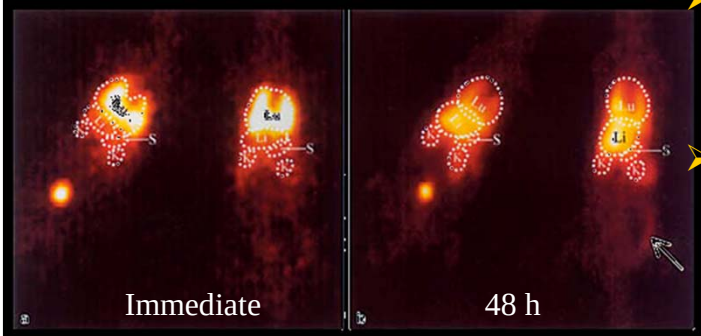

Cellular Labeling Methods
#1 Receptor-Mediated
FESP
Ligands
Transferrin
Avidin-biotin
Receptor
TfR
Proteins
Lysine Rich
Proteins (LRPs)
PCr
Pi
ATP
FHBG
Enzymes
Arginine Kinase/
HSV-tk
#2 Reporter
Gene
Phosphorylated FHBG (trapped)
Adapted from Dimmeler and Bengel

# Cellular Labeling Methods




Adapted from Dimmeler and Bengel

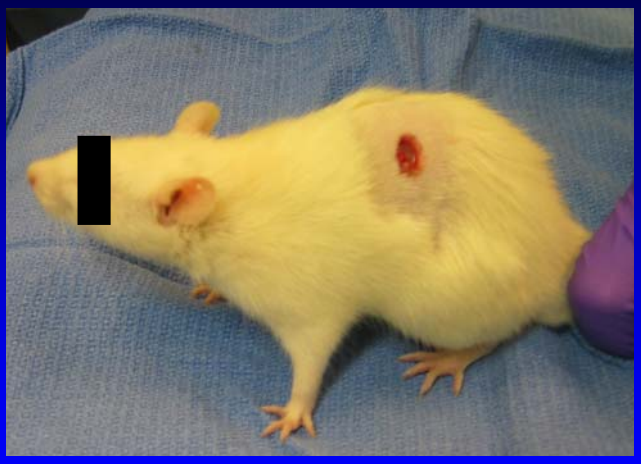
# Distribution After Peripheral Injection




- Rat MSCs labeled with $^{111}$Indium oxine
- Intravenous, intra-arterial, and intra-peritoneal injection

Gao, J., J.E. Dennis, R.F. Muzic, et al., Cell Tissues Organs, 2001. **169**: 12-20.

# Dermal Skin Wounding



- 6 mm punch biopsy full-thickness dermal wound
- Rats received 2-10 million MSCs iv at 3-4 hrs post-wounding

# Redistribution & "Homing" to Wounds

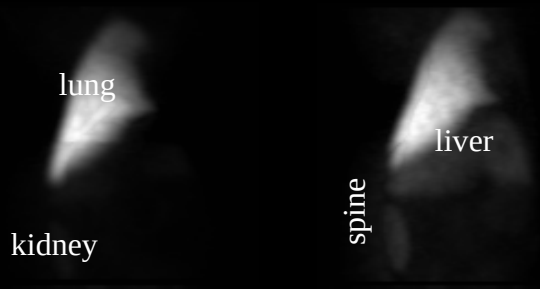
Day 1

Day 4

Fritzges, Tsui, Koprowski, MacKay, Pittenger, Kraitchman at al.

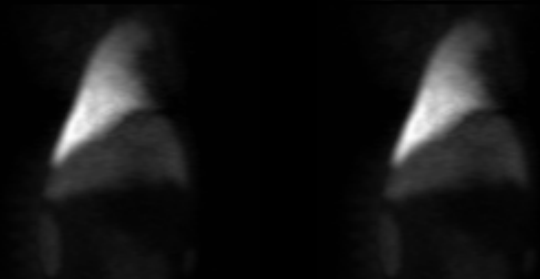
# Biodistribution of MSCs

1 h post $^{111}$Indium-oxine Injection




24 h post $^{111}$Indium-oxine Injection

48 h post $^{111}$Indium-oxine Injection

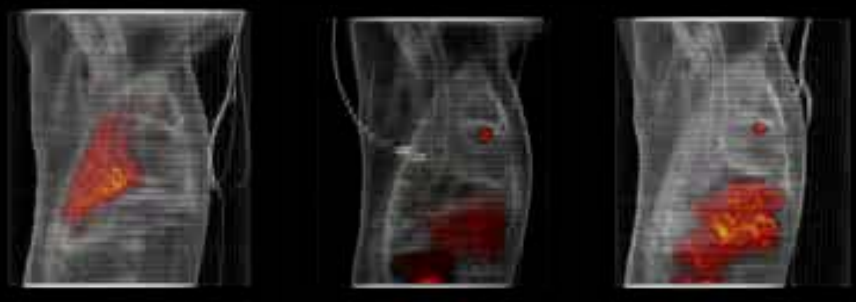


1 week post $^{111}$Indium-oxine Injection

Chin et al., *Nucl Med Commun.* 2003 Nov;24(11):1149-1154

# Canine $^{111}$In MSC Redistribution

**Day 1** **Day 2** **Day 5**

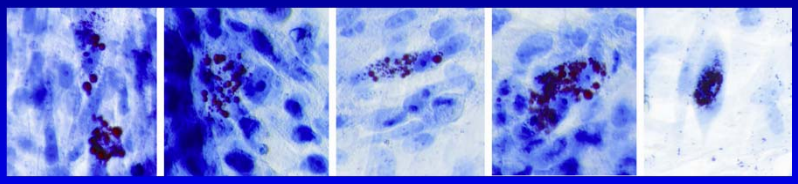


**45 s/stop on Days 0 & 1 and 60 s/stop on Day 4**
**966.5 µCi injection of 195 million MSCs, 71.2 % viability**

Kraitchman et al., Circulation 2005, 112:1454-1464.

# Differentiation Capacity Unaffected

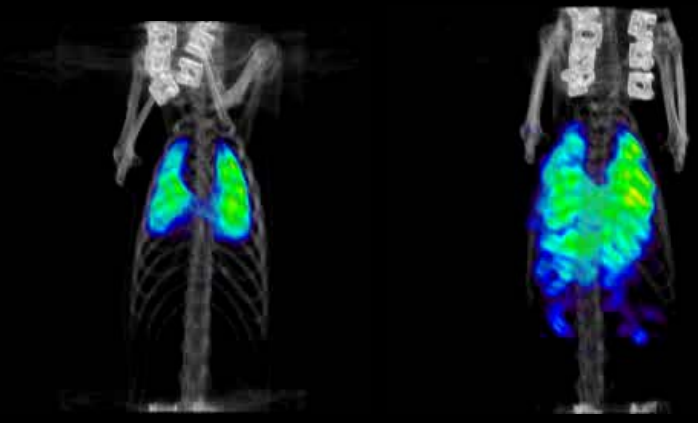
Adipogeneic Capacity *in vitro*



Control 5 µCi 10 µCi 20 µCi 30 µCi

111 Indium oxine / million MSCs

# Pulmonary Uptake of MSCs after IV Injection in the Doxyrubicin-treated Rat

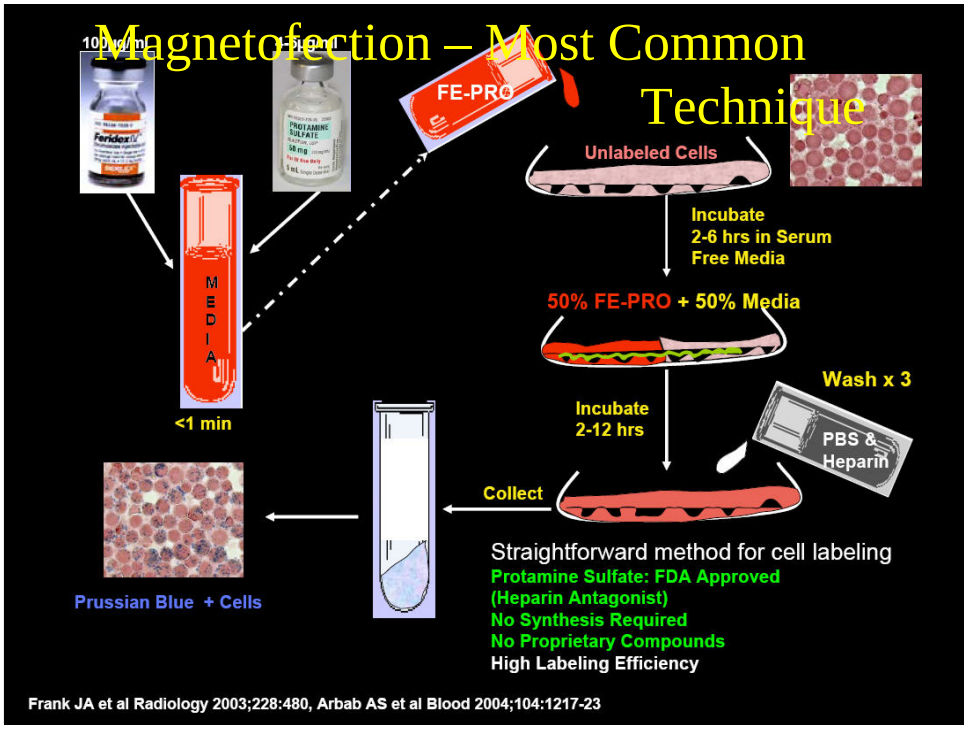


Day 0 Day 1

SPECT/CT

Fritzges, Tsui, Gabrielson, MacKay, Pittenger, Kraitchman at al.

# Magnetofection – Most Common Technique




Frank JA et al Radiology 2003;228:480, Arbab AS et al Blood 2004;104:1217-23

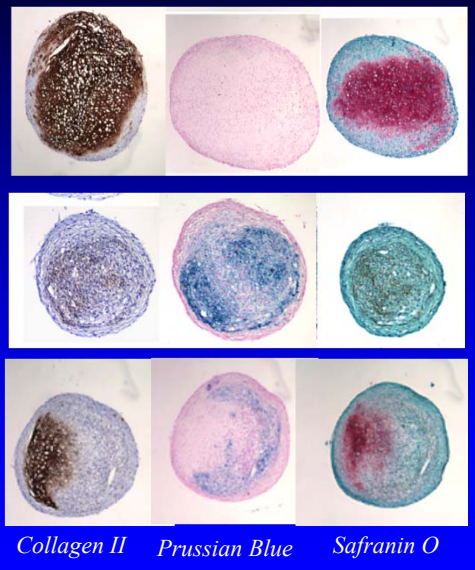
# Iron Oxide Direct Cell Labeling

# Problems with Direct Cellular Labeling?

Unlabeled control MSCs

100% PLL-SPIO

50% PLL-SPIO/ 50% unlabeled

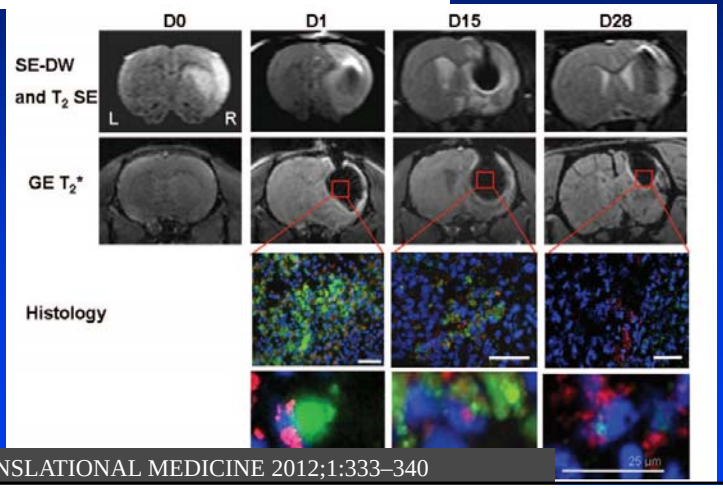


*Collagen II* *Prussian Blue* *Safranin O*

Bulte JW, Kraitchman DL, Mackay AM, Pittenger, Blood, 2004;104(10):3410-3.

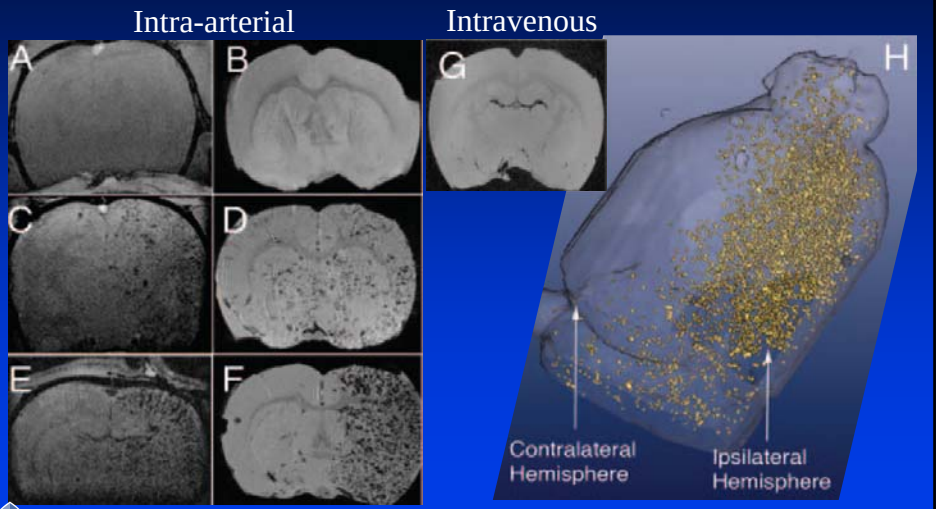
## Magnetic Resonance Imaging and Fluorescence Labeling of Clinical-Grade Mesenchymal Stem Cells Without Impacting Their Phenotype: Study in a Rat Model of Stroke

Olivier Detante,[a,b,c] Samuel Valable,[a,b] Florence de Fraipont,[b,d,e] Emmanuelle Grillon,[a,b] Emmanuel Luc Barbier,[a,b] Anaïck Moisan,[a,b] Josiane Arnaud,[b,f] Christine Moriscot,[b,d,g] Christoph Segebarth,[a,b] Marc Hommel,[b,h] Chantal Remy,[a,b] Marie-Jeanne Richard[b,d,e,g]




STEM CELLS TRANSLATIONAL MEDICINE 2012;1:333–340

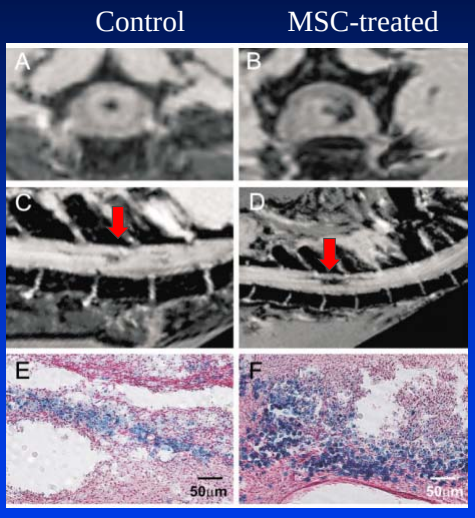
# Delivery Route in Rat Stroke




Walczak et al., Stroke. 2008 May; 39(5): 1569–1574.

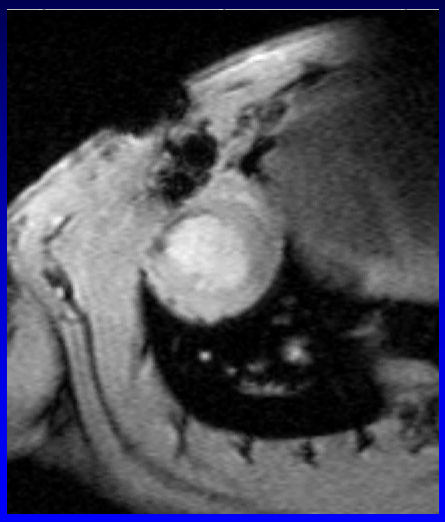
# Spinal Cord

- Balloon compressive spinal cord lesion in the rat treated with intravenous iron-oxide labeled MSCs.



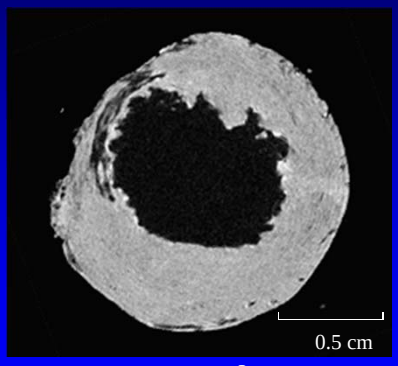

Jendelova et al., Jof Neuroscience Research 76:232–243 (2004)

# Homing of MSCs to Rat MI



In vivo, 240 $mm^2$ resolution

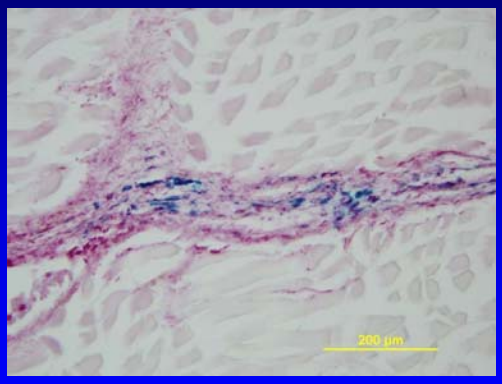
- Reperfused MI
- 8 x $10^6$ iron labeled MSCs iv
- 5 days post surgery




Ex vivo, 60 $mm^2$ resolution

•Sorger, Hill, McVeigh, et al.

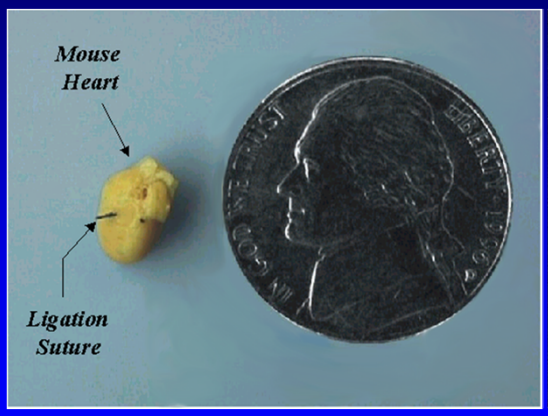
# Unlabeled Stem Cell Injection




Acid Phosphatase + Prussian Blue

- Not all iron is from SPIO labeling!
- Ischemia-reperfusion models and permanent occlusion models may not yield same results
- Immunorejection of xenogeneic cells may be different than allogeneic/autologous grafts.

# It's more than just size…

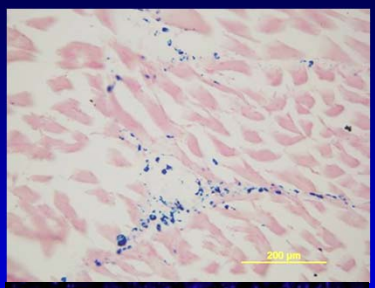


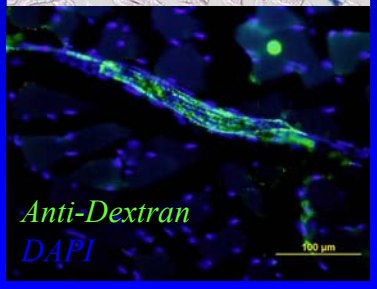

Courtesy of Dr. Fred Epstein, UVA

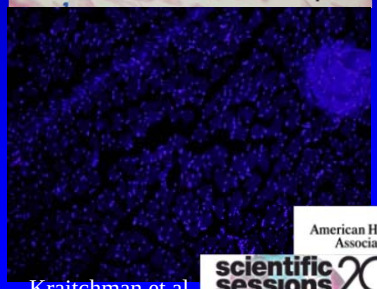
# Ischemic-Reperfusion Injury

SPIO-MSC Treated

SPIO Sham-Treated

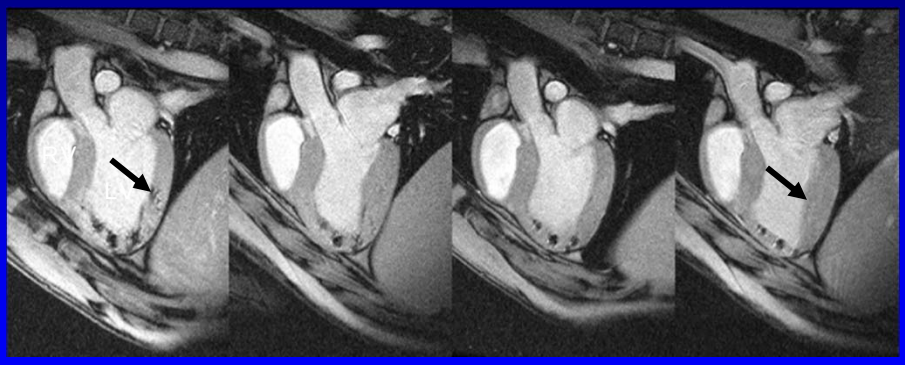


Kraitchman et al.

# Intramyocardial Stem Cell Tracking

bh, ECG-gated FGRE with 500 x 500 $\mu m^2$ in plane resolution



T=0 T=1 wk T=2 wk T=4 wk

Loss of MSCs in normal myocardium!

# Issues with Direct Cell Labeling

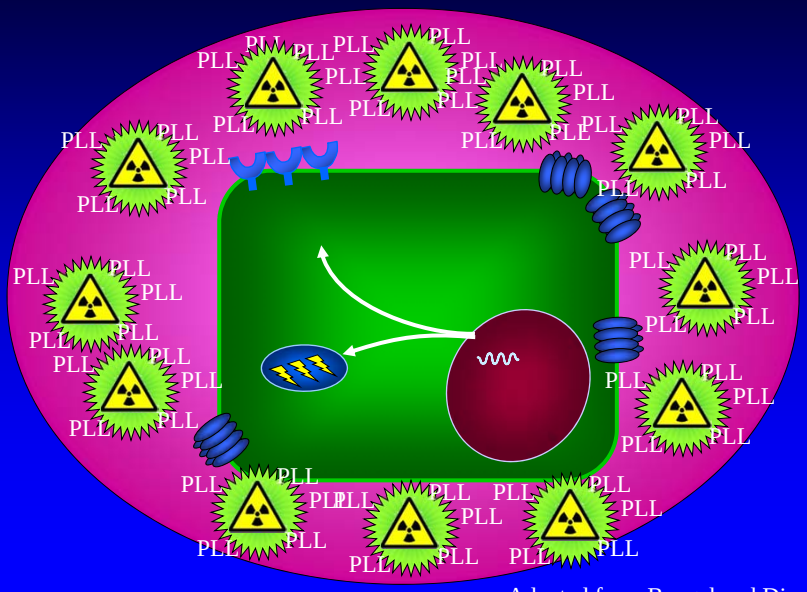
Label detaches from Cell

Dilution of label

Label half-life

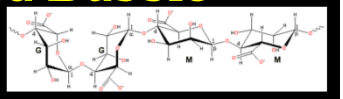
Toxicity of label

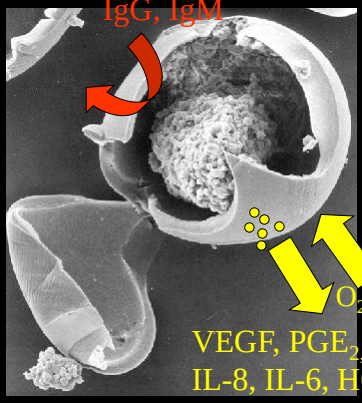
# Cellular Labeling and Encapsulation




# Place Cells in "Seaweed Bubble"

*APA ≡Alginate-poly-L-lysine-alginate*



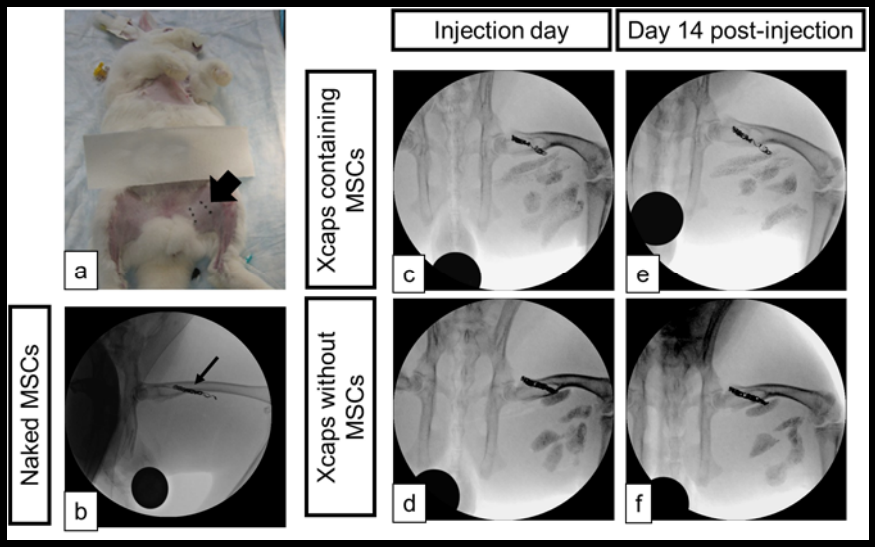



Courtesy: Ming Chen

- Biocompatible
  - Provides surface for cell adhesion
- Selective permeability
  - Blocks antibody and cellular destruction – good for transplanted donor cells
  - Permits diffusion of nutrients and waste products.

Lim and Sun, Science 1980

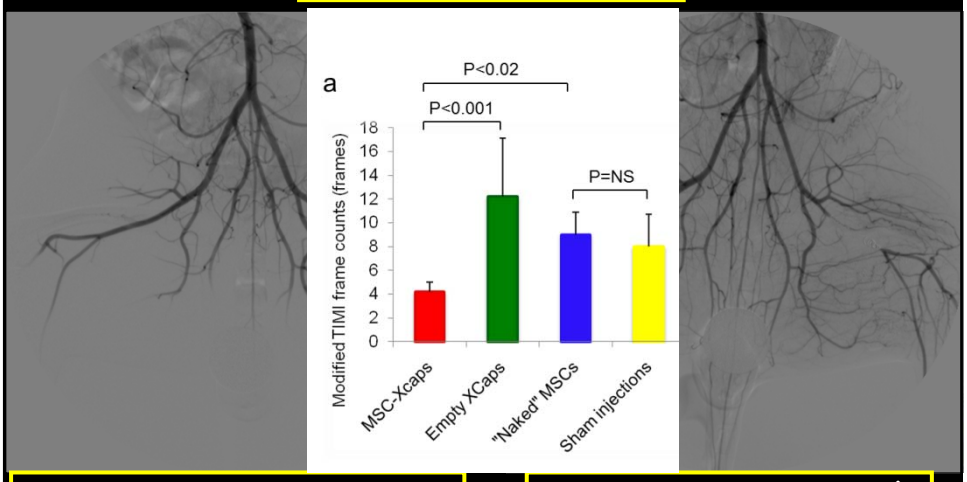
# X-ray Visible Microcapsules




Kedziorek *et al*. Stem Cells, *2012,* 30, 1286

# XCaps with and without MSCs

14 Days Post-occlusion




Capsules without Stem Cells

Capsules with Stem Ce

Kedziorek, Hofmann, Bulte, Kraitchman, et al. Stem Cells, *2012,* 30, 1

# Acknowledgments


- Aravind Arepally
- Nicole Azene
- Brad Barnett
- Cyrus Beh
- Jeff Bulte
- Judy Cook
- Ken Cosby
- Yingli Fu
- Kathleen Gabrielson
- Shashank Hedge
- Rusty Hofmann
- Charles Hu
- Gary Huang
- Takayoshi Ishimori
- Dorota Kedziorek
- Hai-Quan Mao
- Jeremy Mauer
- Peter Johnston
- Brady Sieber
- Matthias Stuber
- Mitsuaki Tatumi
- Ben Tsui
- Frank Wacker
- Guan Wang
- Jeff Tza-Huei Wang
- Rich Wahl
- Piotr Walczak
- Cliff Weiss
- Bob Weiss
- Brad Martin
- Michelle Marcelino
- Mark Pittenger
- Jerry Skwarek
- Randall Young
- Pelin Aksit
- Thomas G. Foo
- Sandeep Gupta
- Dan Rettmann
- Manoj Saranathan
- Elliot McVeigh
- Jonathan Hill
- Robert Lederman
- Michael Guttman
- Joseph Wu
- Christine Lorenz
- Tina Ehtati
- Aaron Flammang
- Wesley Gilson
- Andy Hall
- Steven Shea

Grants: NIH R01-HL63439, R01-HL73223, K02-HL05193, K08 EB004348, R01-HL73223, R21/R33-HL89029, Siemens Healthcare, and Maryland Stem Cell Research Fund (2008-MD-SCRFII-0399-00, and 2011-MSCRFII-0043)