

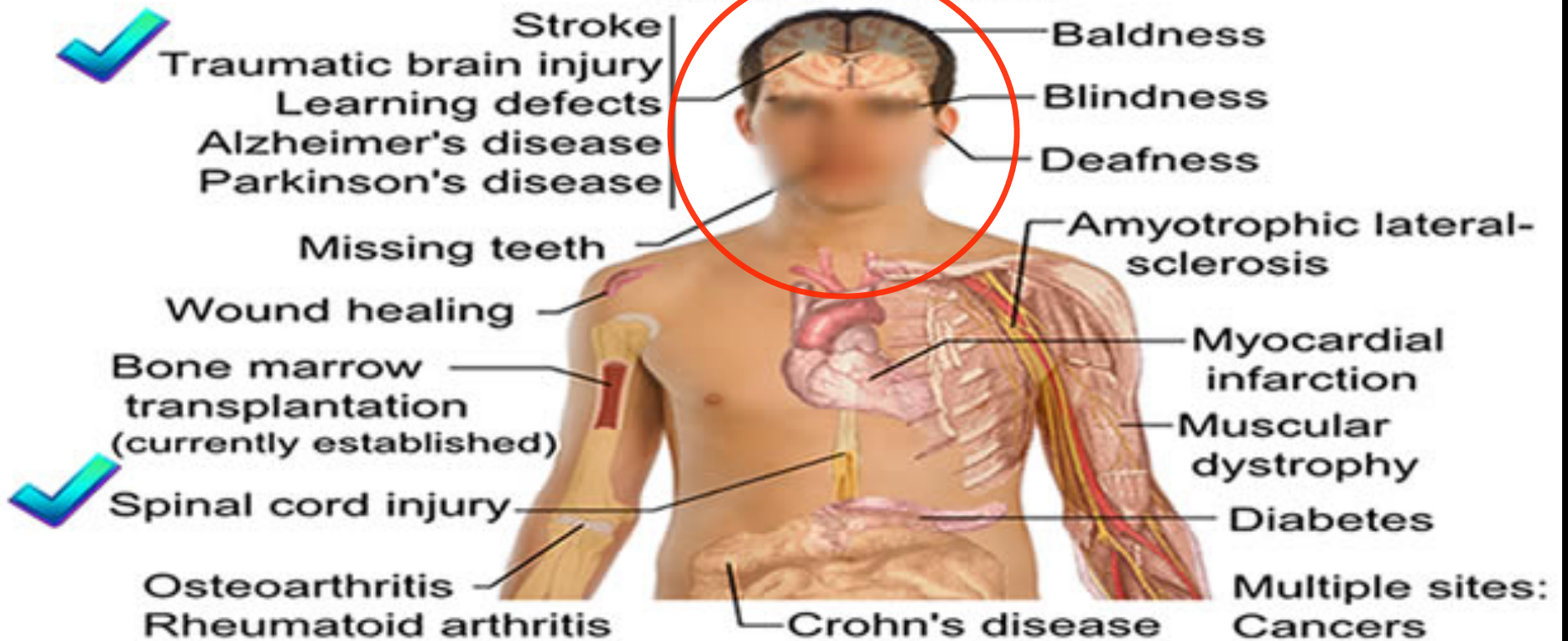
Tracking Transplanted Stem Cells

Jeff W.M. Bulte, Ph.D.

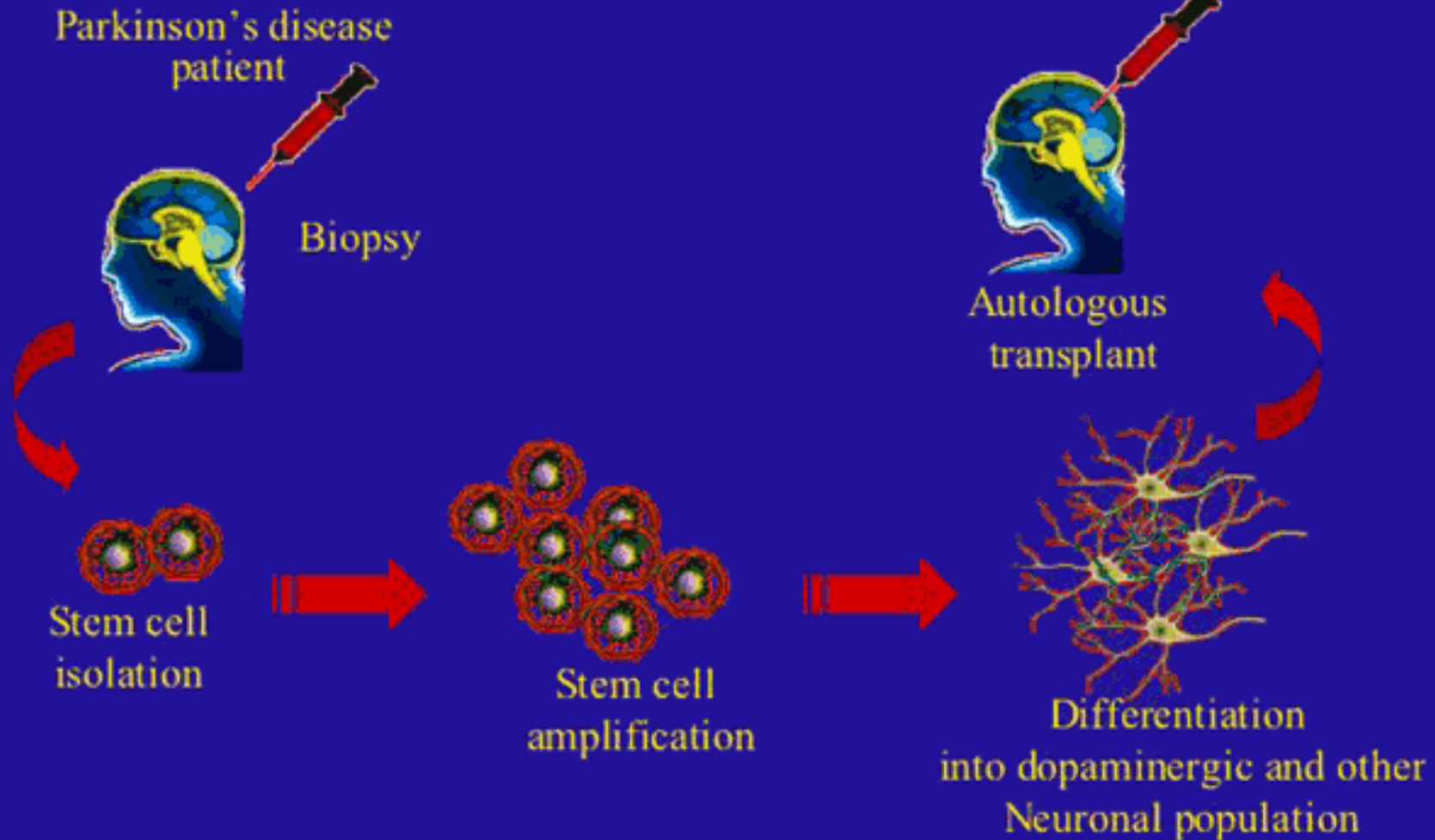
*Russell H. Morgan Dept. of Radiology and Radiological Science
Cellular Imaging Section, Institute for Cell Engineering
The Johns Hopkins University School of Medicine*



Potential uses of **Stem cells**



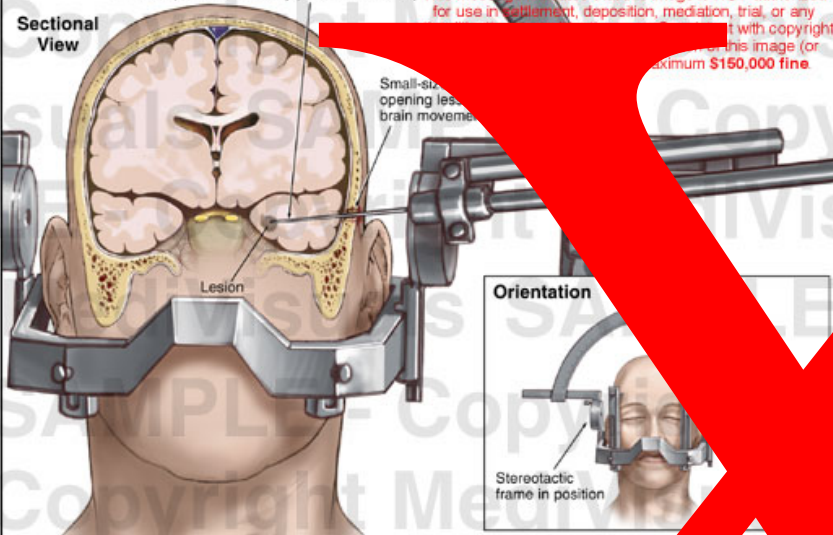
NeuroGeneration Parkinson's Treatment



Frame-Based Stereotactic Biopsy

Biopsy needle guided according to MRI taken with frame in place immediately prior to craniotomy. **MediVisuals • 800-899-2154**
This message indicates that this image is NOT authorized for use in replacement, deposition, mediation, trial, or any other legal proceeding without copyright owner's prior written consent. This image (or any part of this image) may be used for a maximum \$150,000 fine.


Sectional View



Small-slice opening lessens brain movement

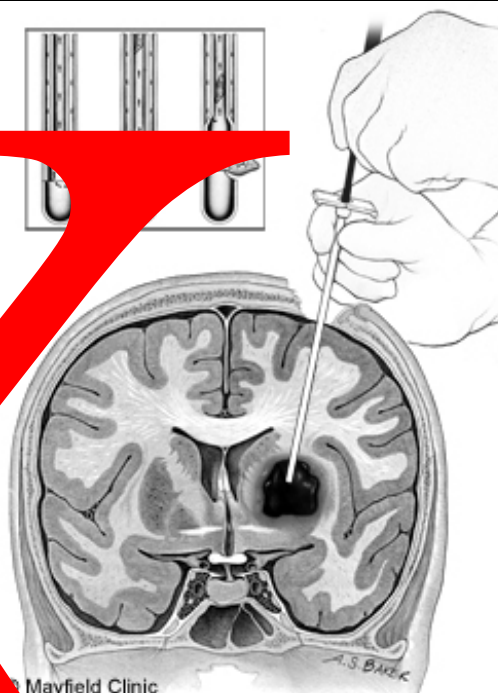
Lesion

Orientation



Stereotactic frame in position

Exhibit# 204060_04XG



Mayfield Clinic

A.S. BARK



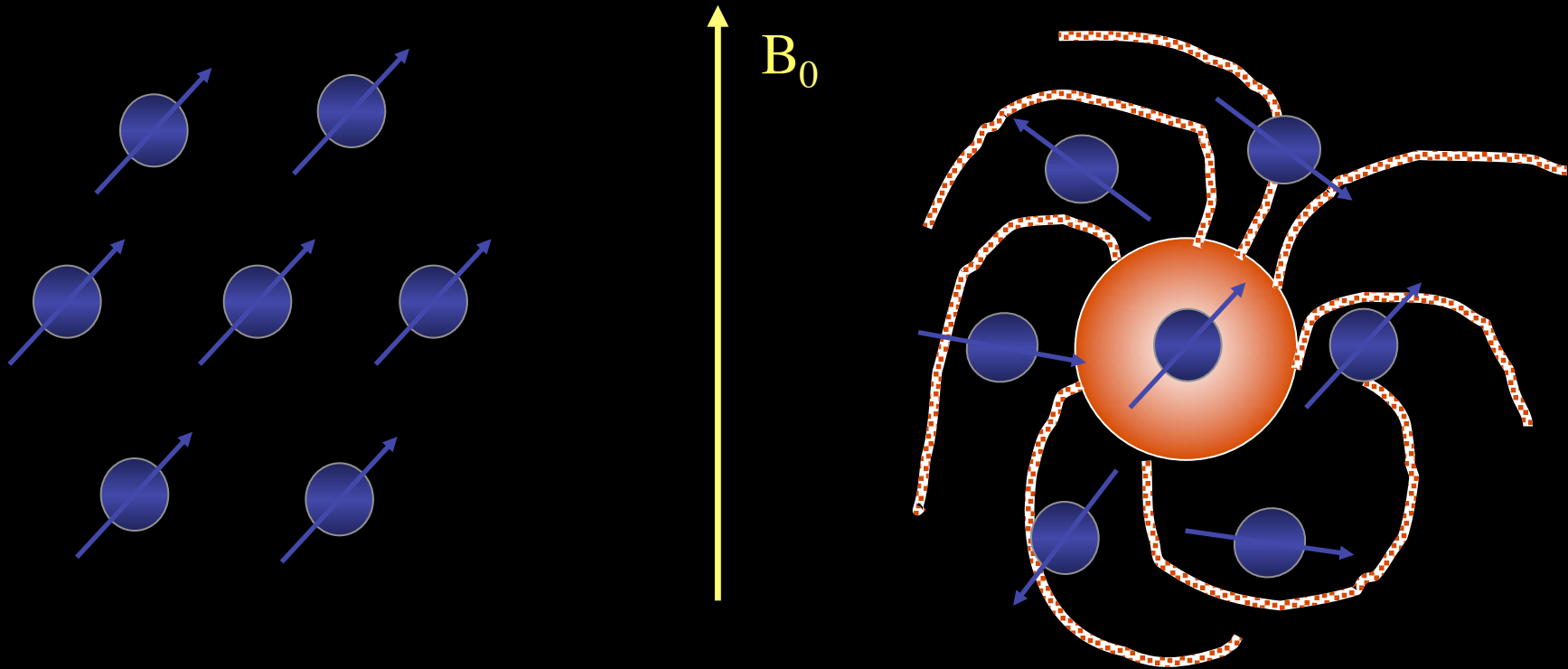


Non-Invasive Whole Body Cell Tracking

- 1) Are stem cells being delivered/injected correctly?
- 2) How many stem cells have been correctly delivered/homed into the target organ?
- 3) For how long do stem cells survive?
- 4) Do stem cells replicate following administration including the formation of unwanted neoplasms/teratomas?
- 5) Do stem cells differentiate *in vivo*, and if so, when does this occur?

Labeling Stem Cells with a “MAGNETIC “DYE”

Superparamagnetic Iron Oxide Particles (SPIO):
Nanoscale Magnets Disturb MRI Signal,
Leading to Loss of Imaging Signal

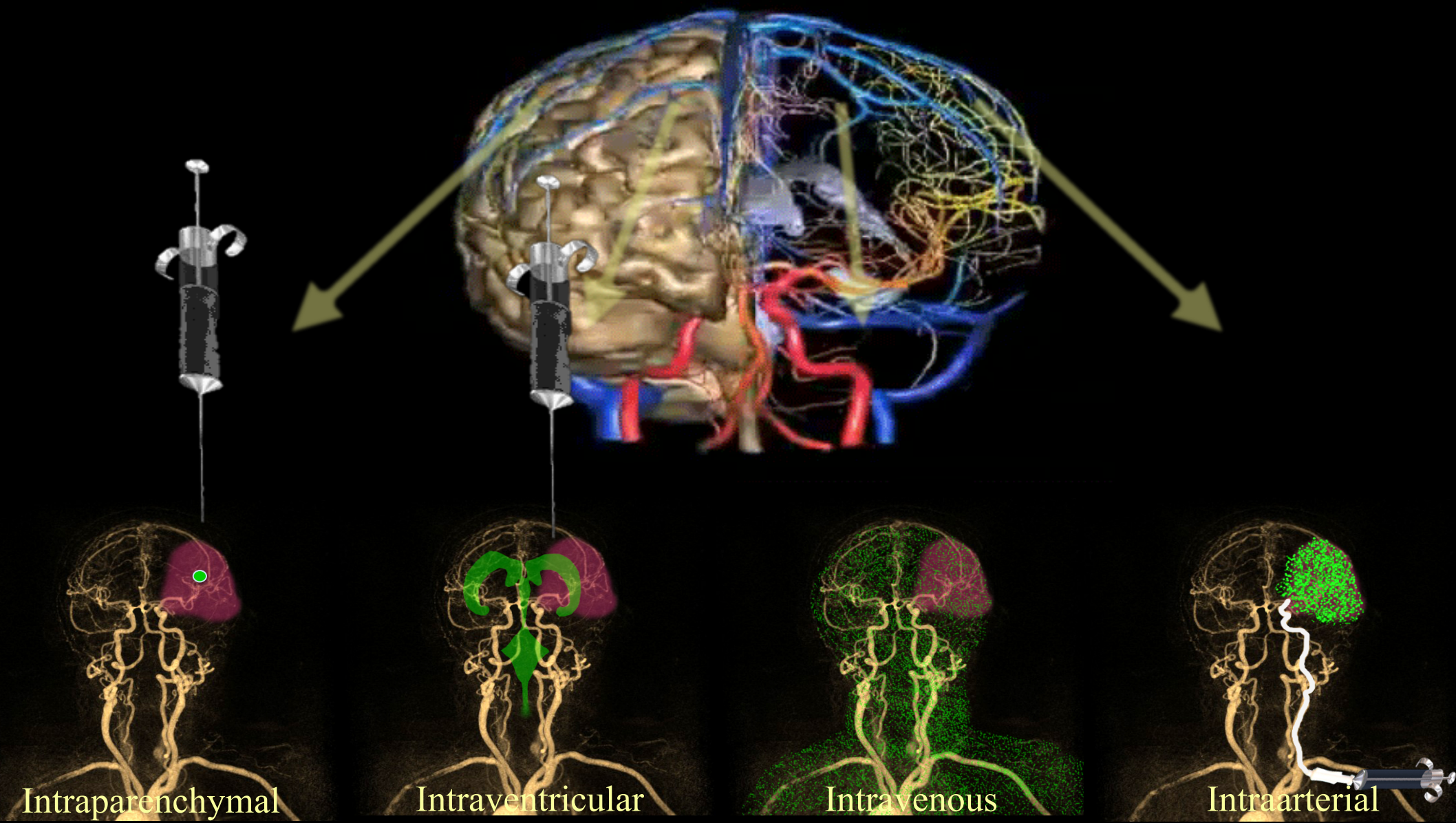


Diameter: ~80 nm (size of a virus)

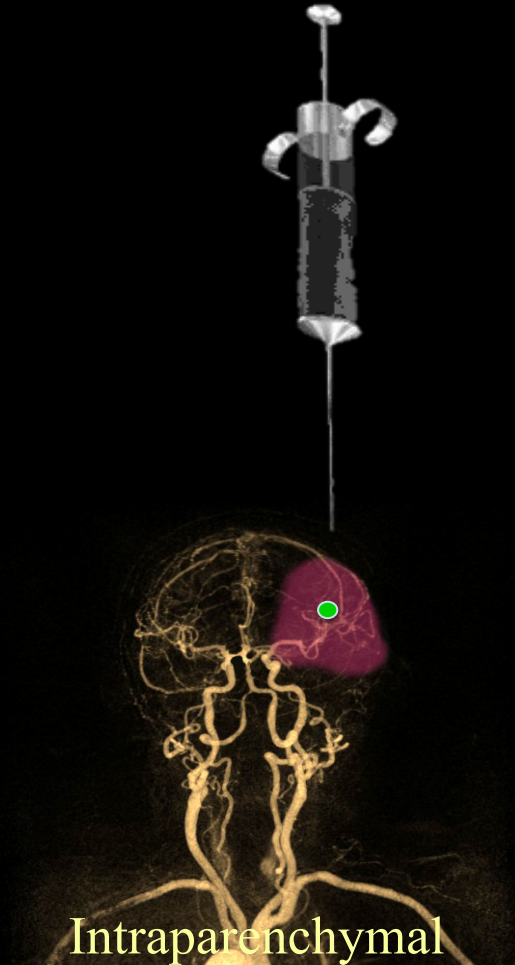
Labeling of Stem Cells with Superparamagnetic Iron Oxide (SPIO)



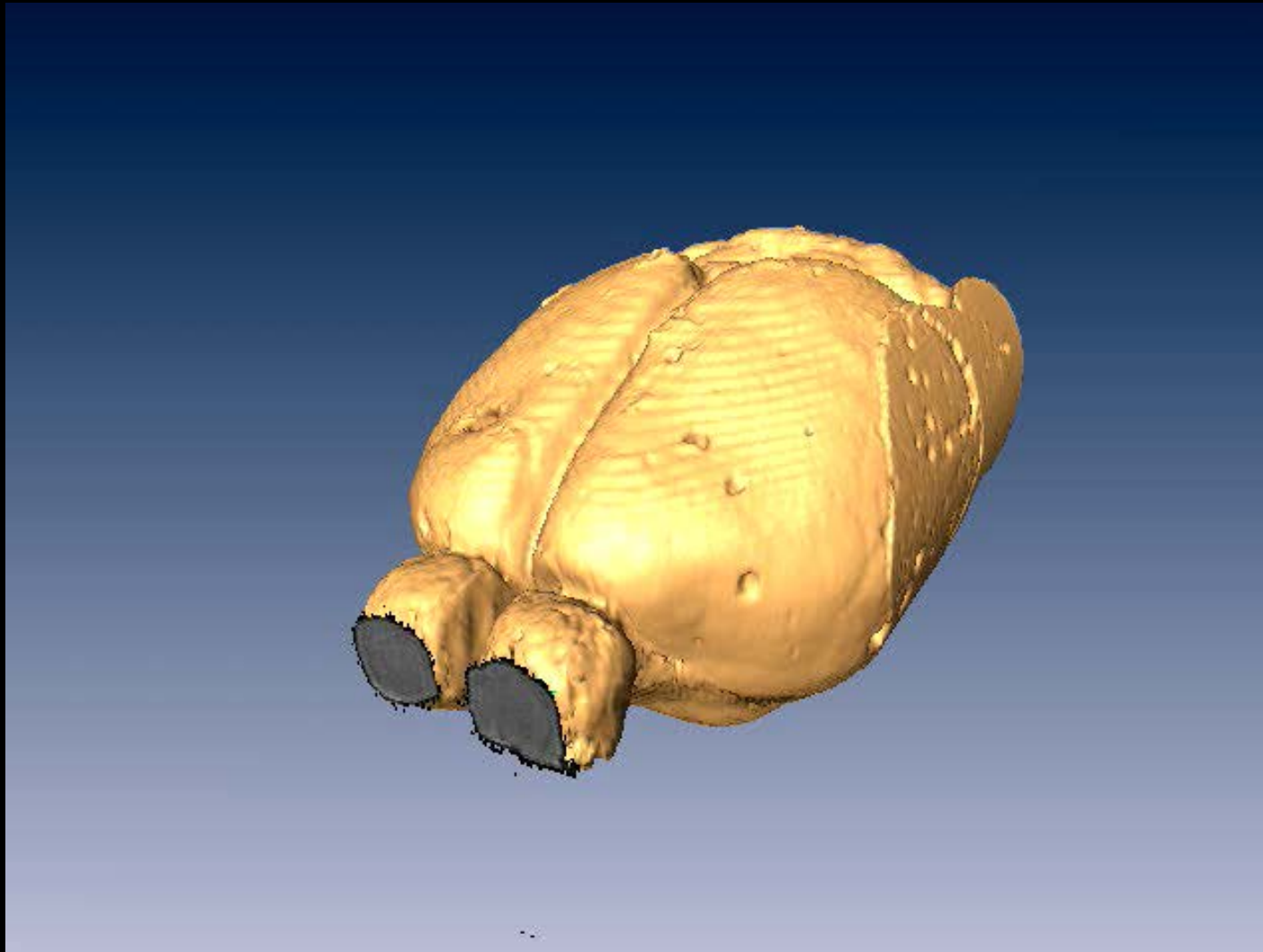
Routes of Stem Cell Delivery to the Brain



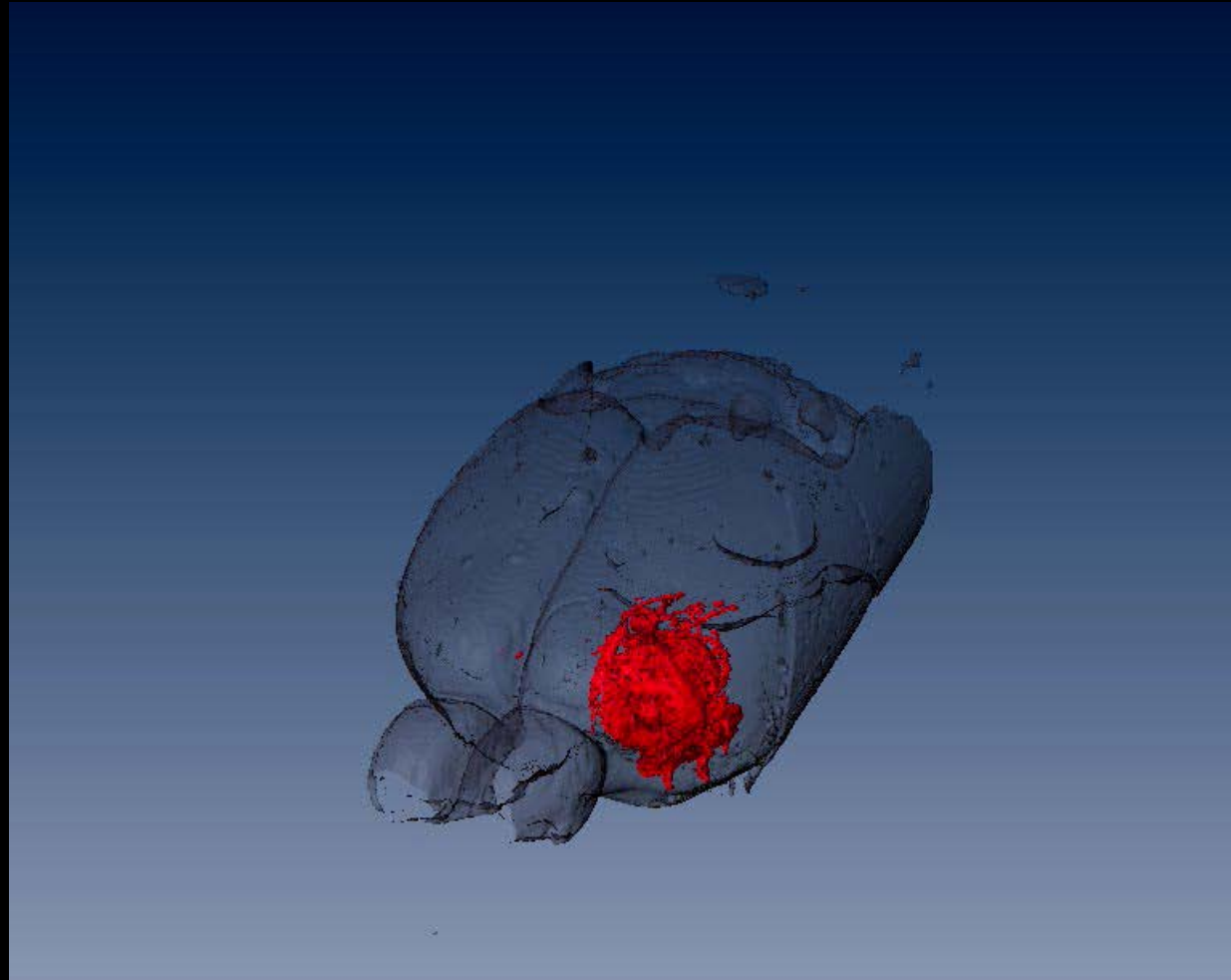
Routes of Stem Cell Delivery to the Brain



MR Imaging of Magnetically Labeled Neural Stem Cells



MR Imaging of Magnetically Labeled Neural Stem Cells



Routes of Stem Cell Delivery to the Brain

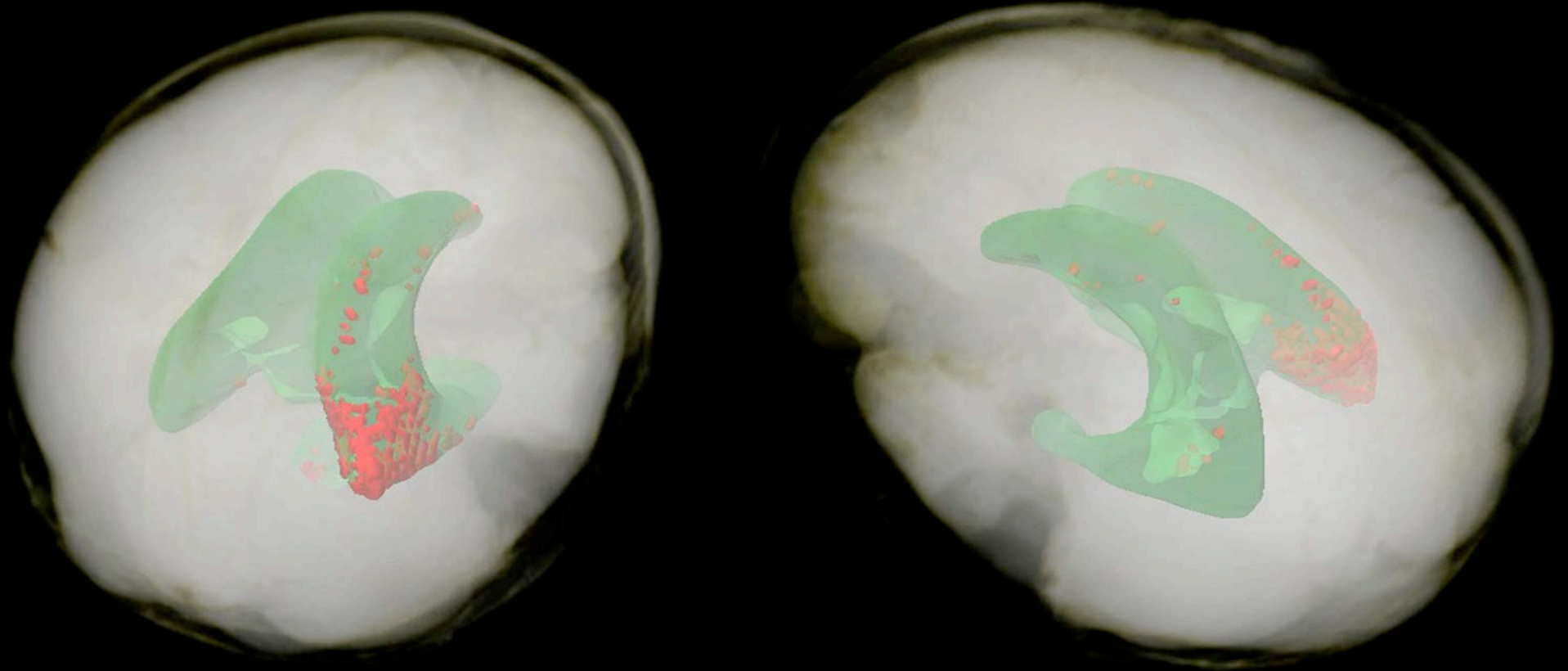


ICV-injected Feridex-labeled NSCs in perinatal hypoxic brain injury



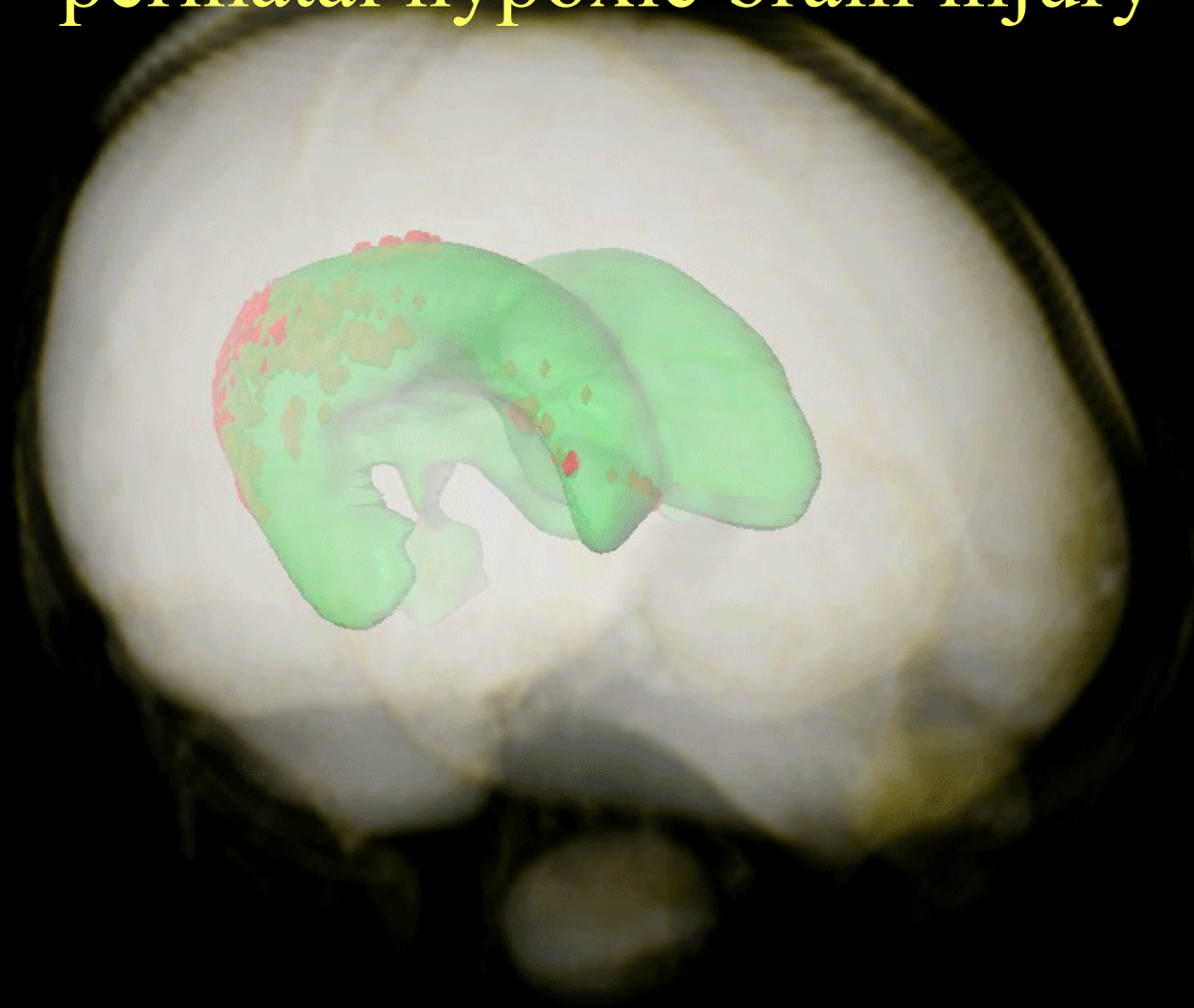
M. Janowski,
P. Walczak et al.

ICV-injected Feridex-labeled NSCs in perinatal hypoxic brain injury



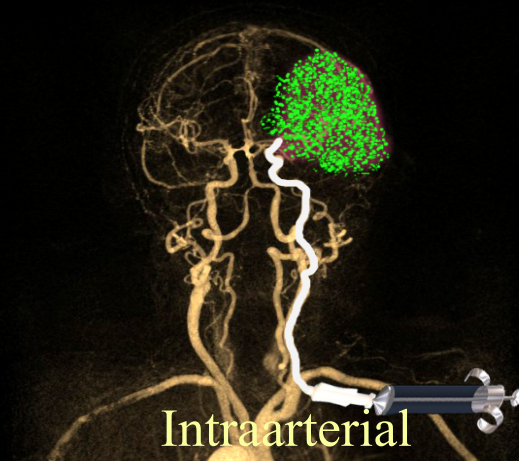
M. Janowski,
P. Walczak et al.

ICV-injected Feridex-labeled NSCs in perinatal hypoxic brain injury



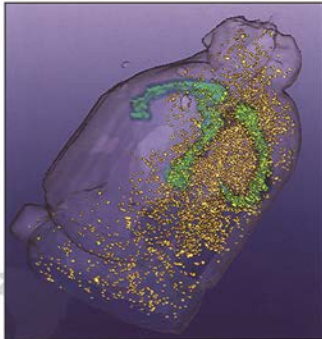
M. Janowski,
P. Walczak et al.

Routes of Stem Cell Delivery to the Brain



Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Targeted Intracarotid Delivery of Magnetically Labeled Mesenchymal Stem Cells

■ Editorials

Leukoaraiosis: Ancient Term to Actual Marker
Ultrasound-Enhanced Thrombolysis
Balance Between Stroke Prevention and Bleeding Risk in AF

■ Original Contributions

Leukoaraiosis and Susceptibility to Infarct Growth
Progression of Small Vessel Disease
Unrecognized MI, Dementia, and Small Vessel Disease
Stroke and Cognitive Decline After Cardiac Surgery
Genome-Wide Linkage Screen for Intracranial Aneurysm
Circulating EPC in Acute Stroke
Lp-PLA₂ and LysoPC in Symptomatic Carotid Plaques
Progression of Intracranial Atherosclerosis
Microspheres for Sonothrombolysis
Sonothrombolysis in MCA Main Stem Occlusion

Microspheres in Brain Vessels
Oral Anticoagulation in Atrial Fibrillation
Thrombolysis for Cerebral Sinus Thrombosis
Thrombosis Caused by Angiography
IV Thrombolysis and Thrombectomy in BAO
Intraoperative Rupture During Aneurysm Treatment
fMRI Correlates of Lower Limb Function in Stroke
Outcomes in Stroke
Structural Brain Changes From CI Therapy After Stroke
Psychiatric Morbidity and Return to Work After Stroke
Socioeconomic Disparities in Stroke at Old Age
MRI of Secondary Thalamic Damage
Induced Hypertension in Acute Focal Ischemia
Albumin Augments Thrombolysis in Arteriolar Thrombosis
T2*WI Detected Angiogenesis Poststroke in Rats
Monitoring Intraarterial Stem Cell Delivery in Stroke
Preventing CNS Autoimmunity After Stroke

■ Research Letters

Need for Church-Based Stroke Health Promotion
Ischemic Stroke and Chr9p21
Androgen Receptor Variation and Risk of MI and Stroke
EPHX2 and Stroke in a Central European Population
Carotid Atherosclerosis and Coronary Artery Disease
Diabetes and Brain MRI in Vascular Patients
Microvascular Imaging Using 7.0T MRA
Metabolic Syndrome and Silent Brain Lesions
CSF Tenascin-C in Hydrocephalus After SAH
Selective MCA Occlusion in a Rabbit Stroke Model
Response to IV-tPA in Tandem ICA/MCA Occlusion
Stroke Benchmarks

■ Special Report

Acute Stroke Imaging Research Roadmap

■ Topical Review

Hypoxia Imaging in Ischemic Stroke

■ Emerging Therapies

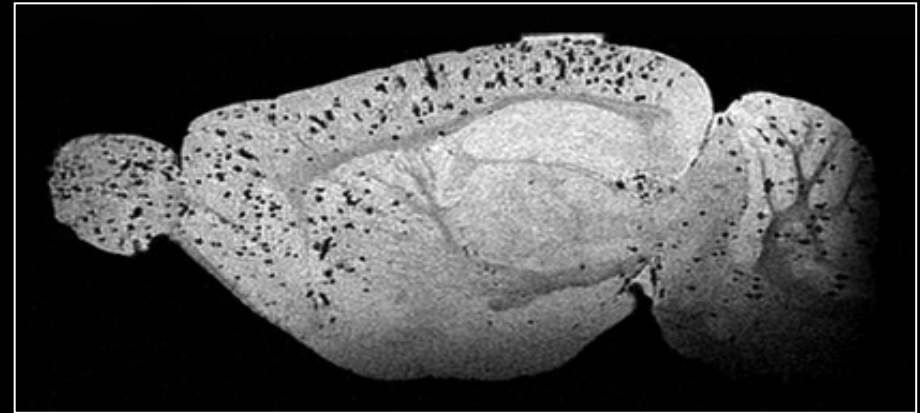
Antiplatelet Therapy for Ischemic Stroke **CME**

■ Letters to the Editor*

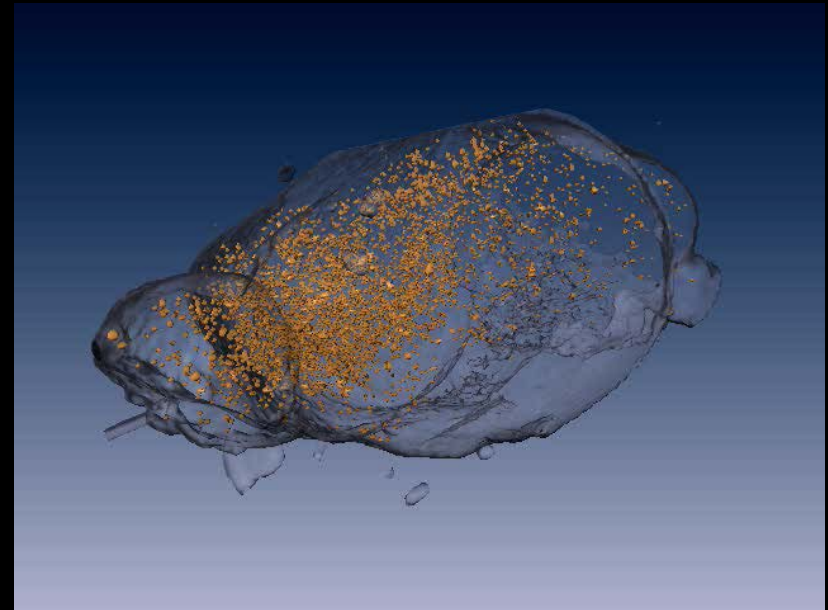
■ AHA/ASA Science Advisory

■ Correction*

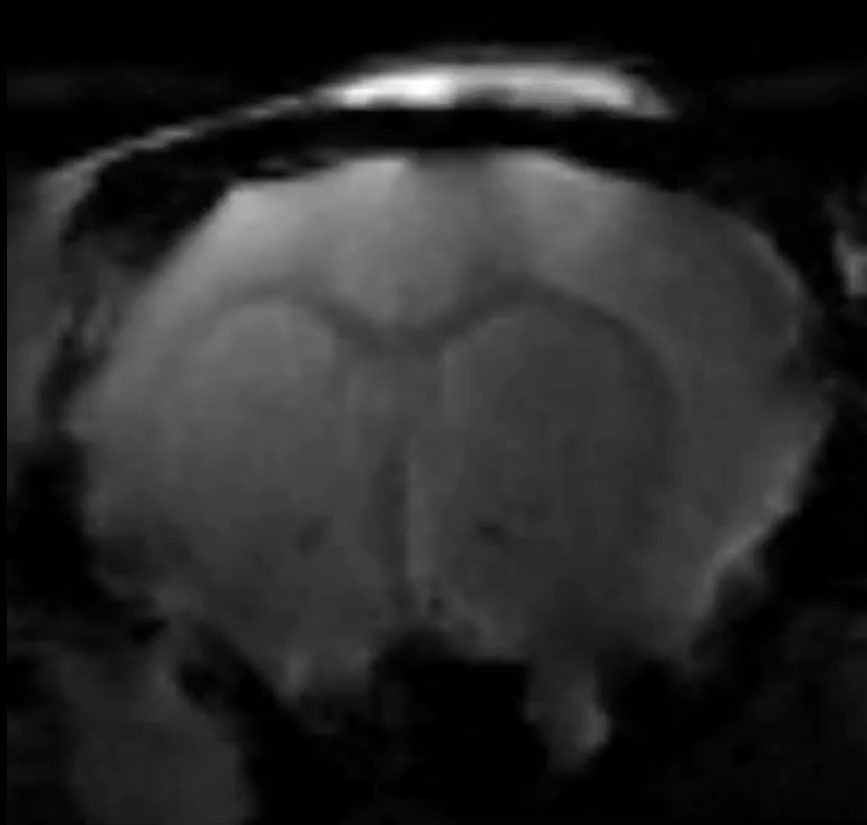
2D



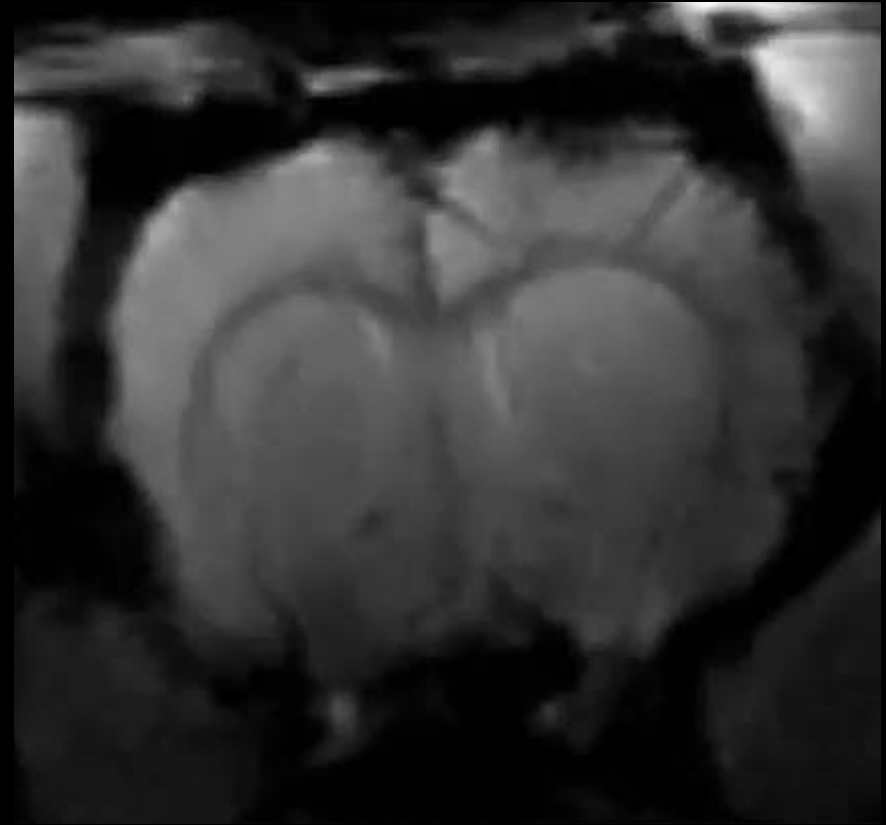
3D



Effect of Cell Size

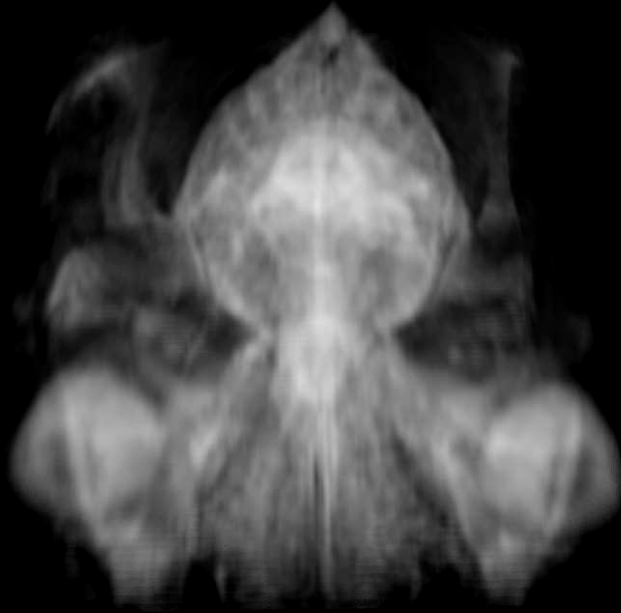


GRPs – 15 μm

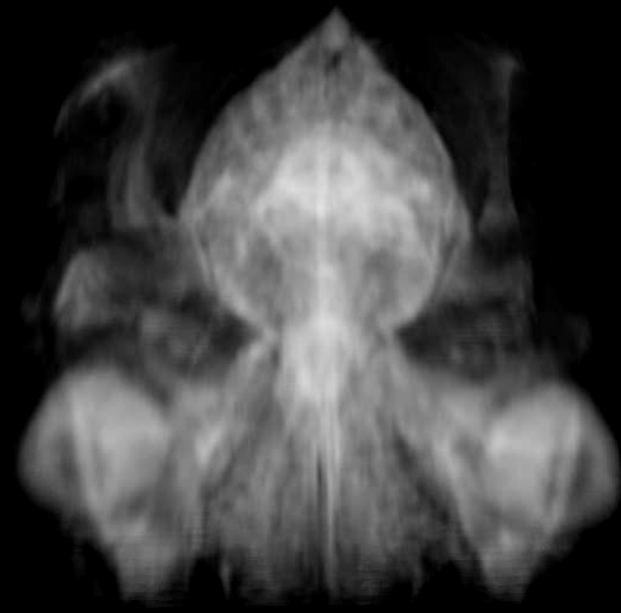


MSCs – 25 μm

Feraheme® Injection Compared to SPIO-MSC Injection

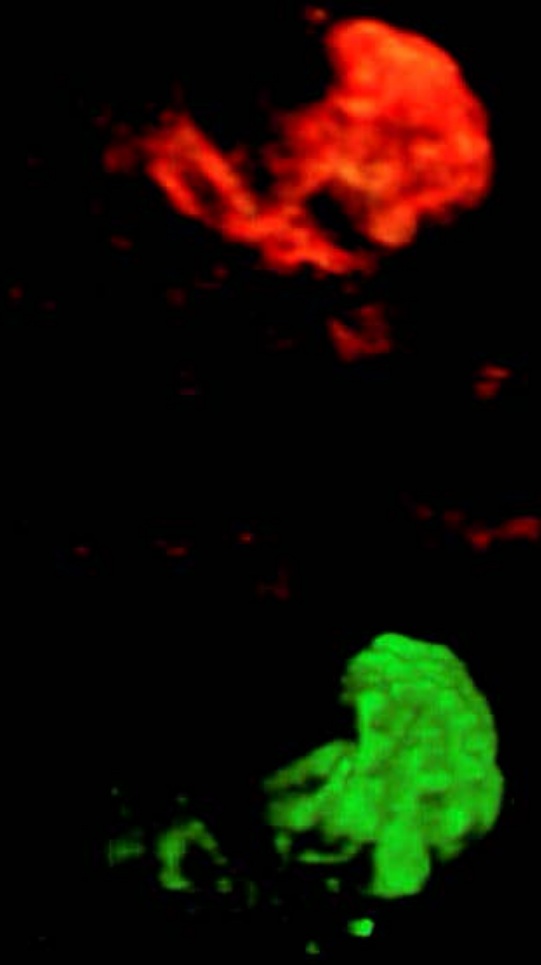


Feraheme®
(Perfusion agent)



SPIO-MSC

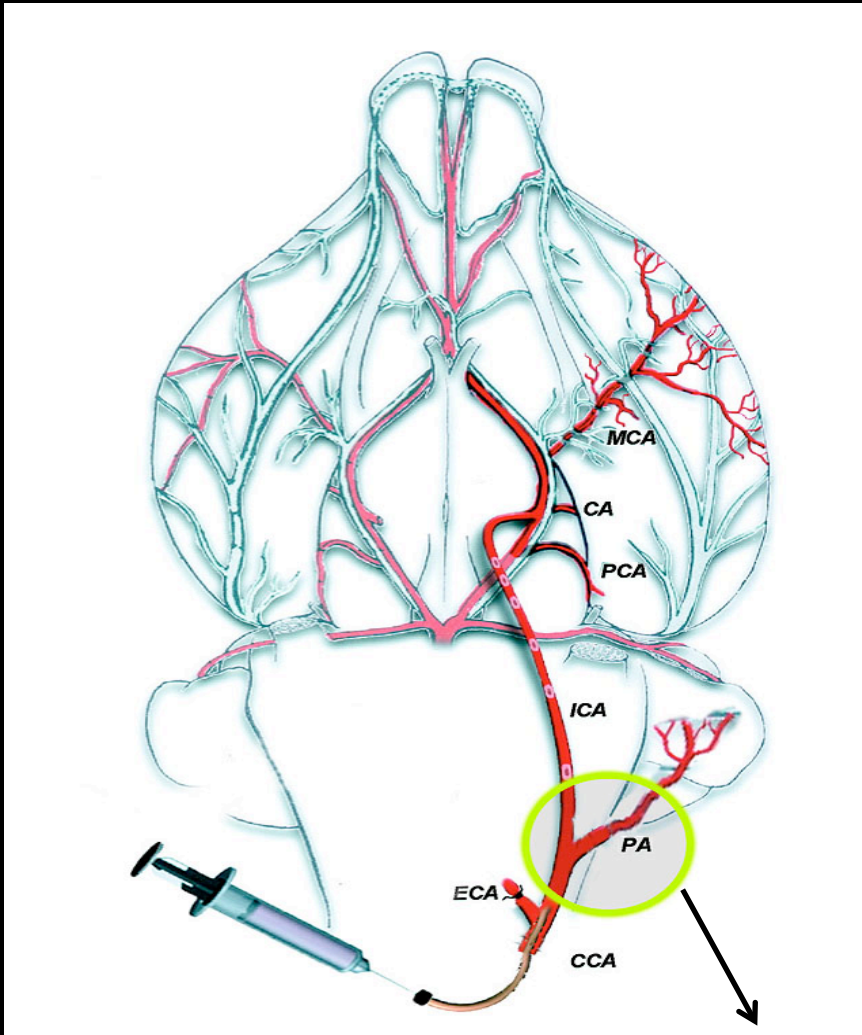
Feraheme® Injection Compared to SPIO-MSA Injection



Feraheme®

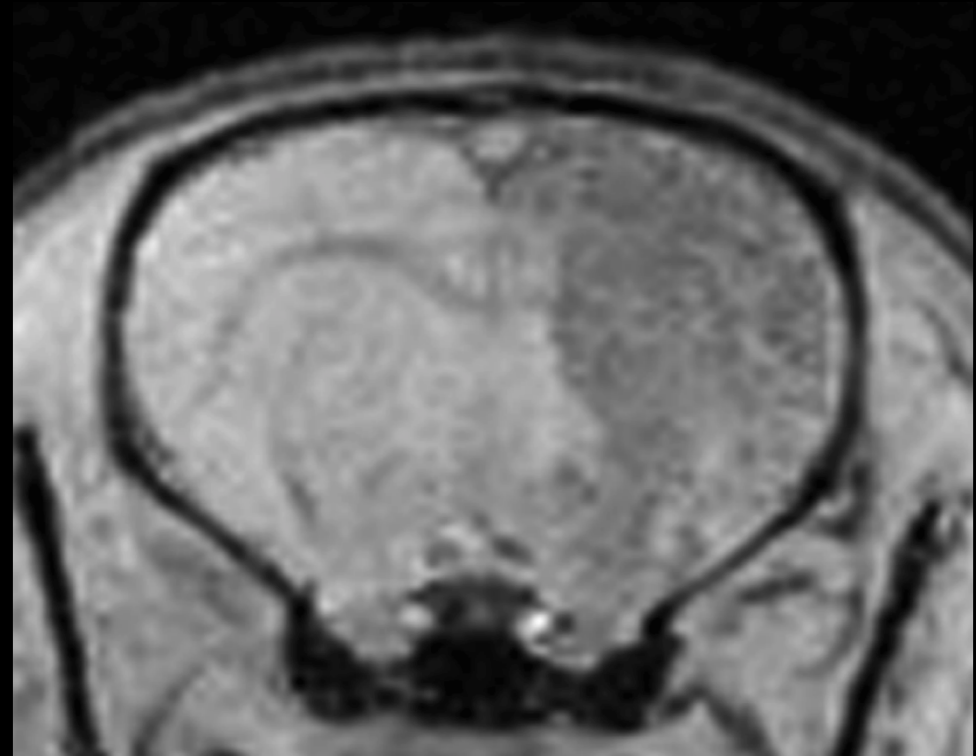
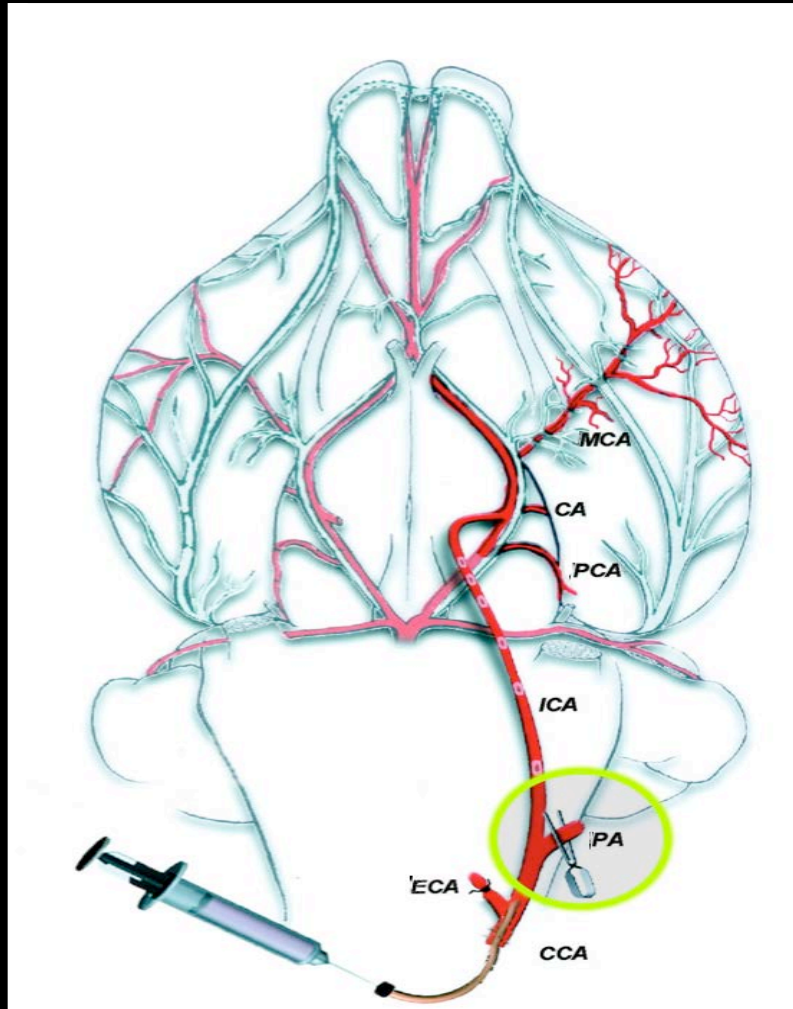
SPIO-MSA

MR Monitoring of Cell Delivery



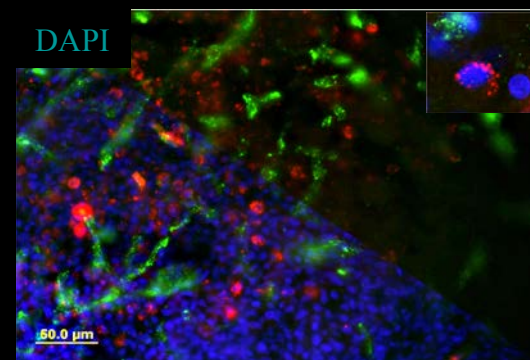
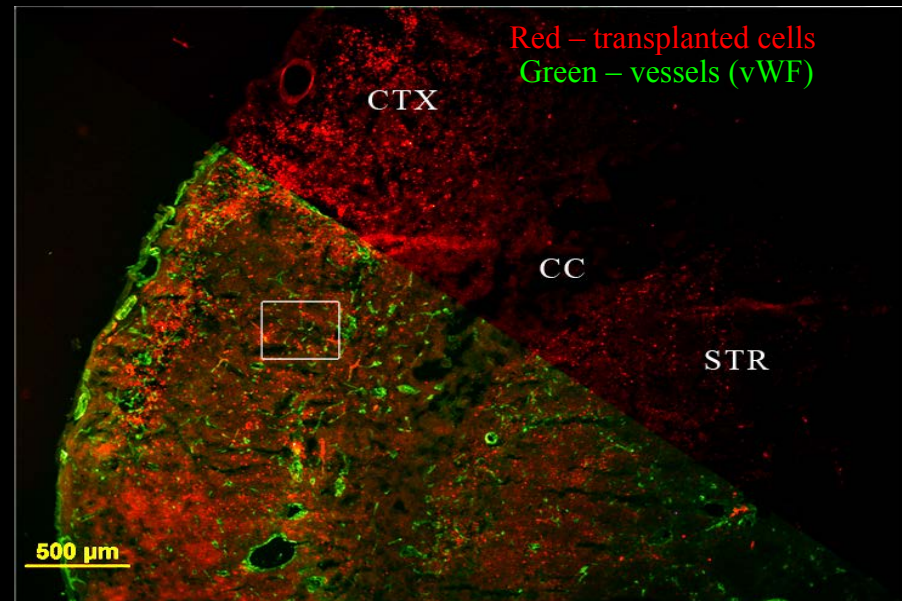
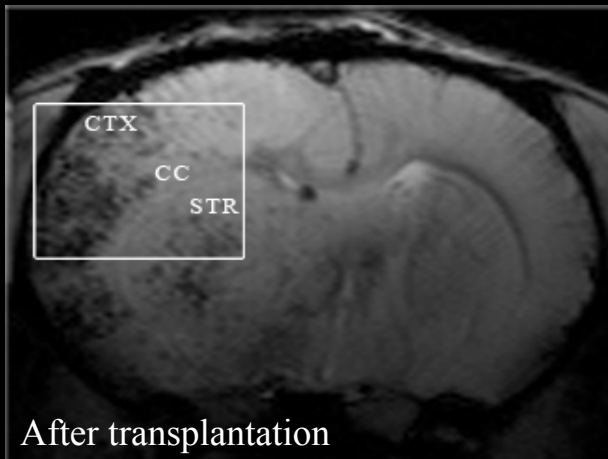
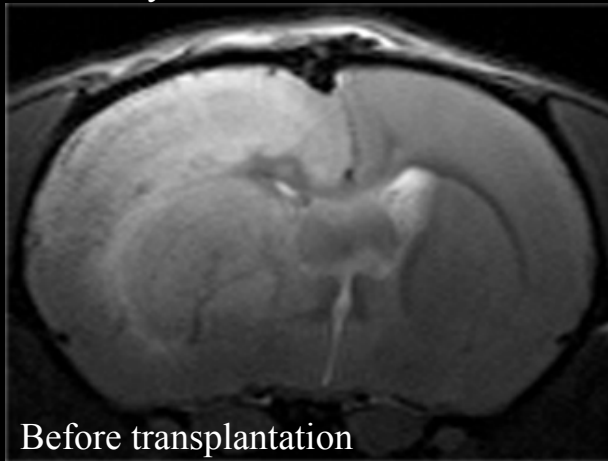
Pterygopalatine artery

MR Monitoring of Cell Delivery



Can IA-Injected GRPs Extravasate?

3-day old ouabain stroke



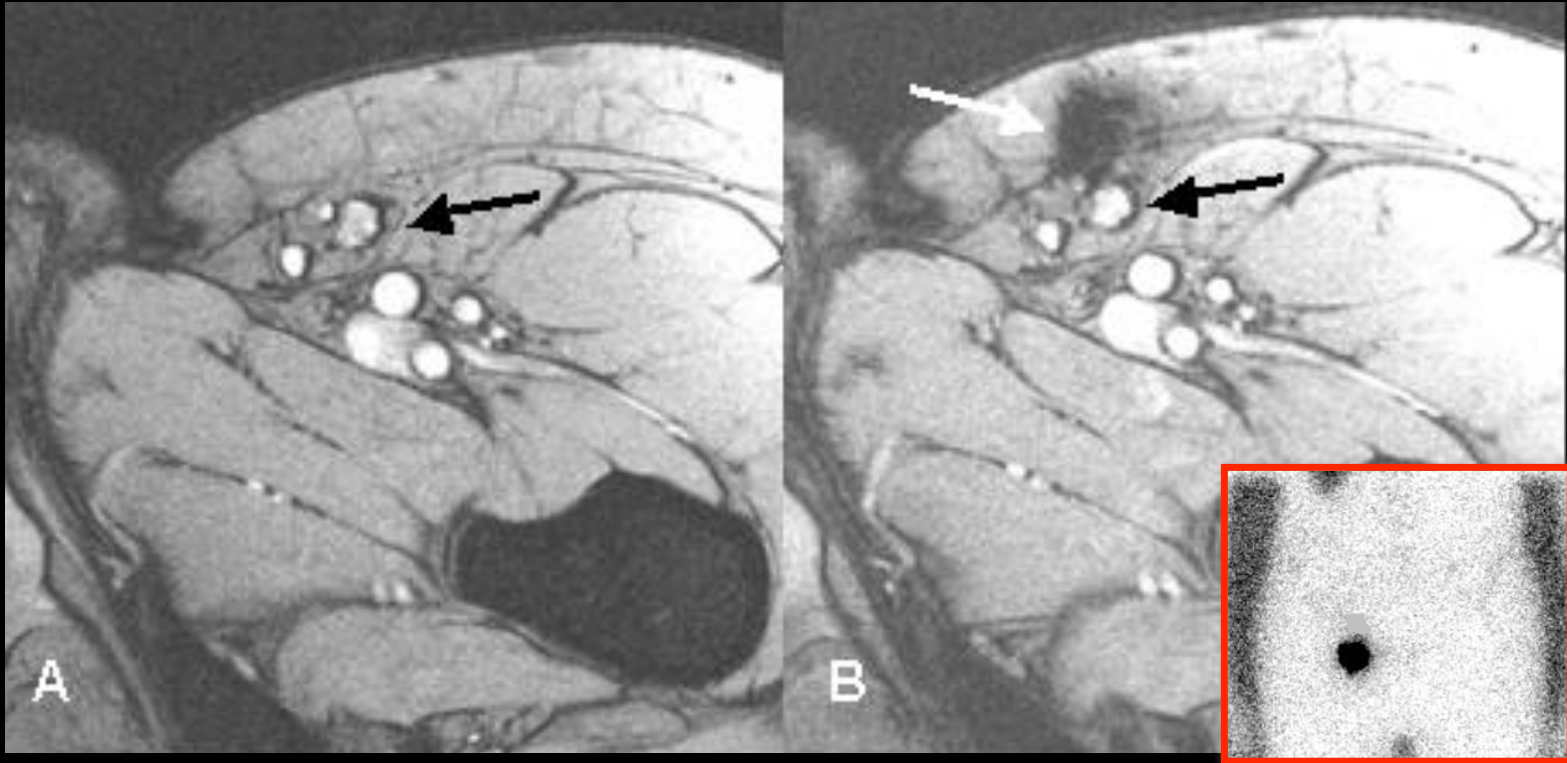
M. Janowski,
P. Walczak et al.

1. De Vries et al. 2005 Nature Biotechnology. 23:1407-1413
2. Zhu et al. 2006 New England Journal of Medicine. 355;22:2376-2378
3. Callera et al. 2007 Stem Cells and Development. 16:461-466
4. Toso et al. 2008 American Journal of Transplantation. 8:701-706
5. Saudek et al. 2010 Transplantation. 90;12:1602-1606
6. Karussis et al. 2010 Archives of Neurology 67(10):1187-1194
7. Jozwiak et al. Cell Medicine 2010;1:71-80
8. Richards et al. Circ Cardiovasc Imaging 2012;5:509-17

As of today there are 8 published clinical MRI cell tracking trials



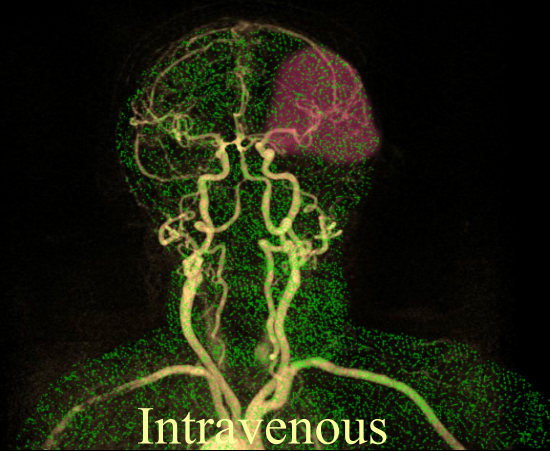
Accidental Misinjection in 4 out of 8 Patients (Injections performed under US guidance, **not** MR-Guided)



Pre

Post

Routes of Stem Cell Delivery to the Brain



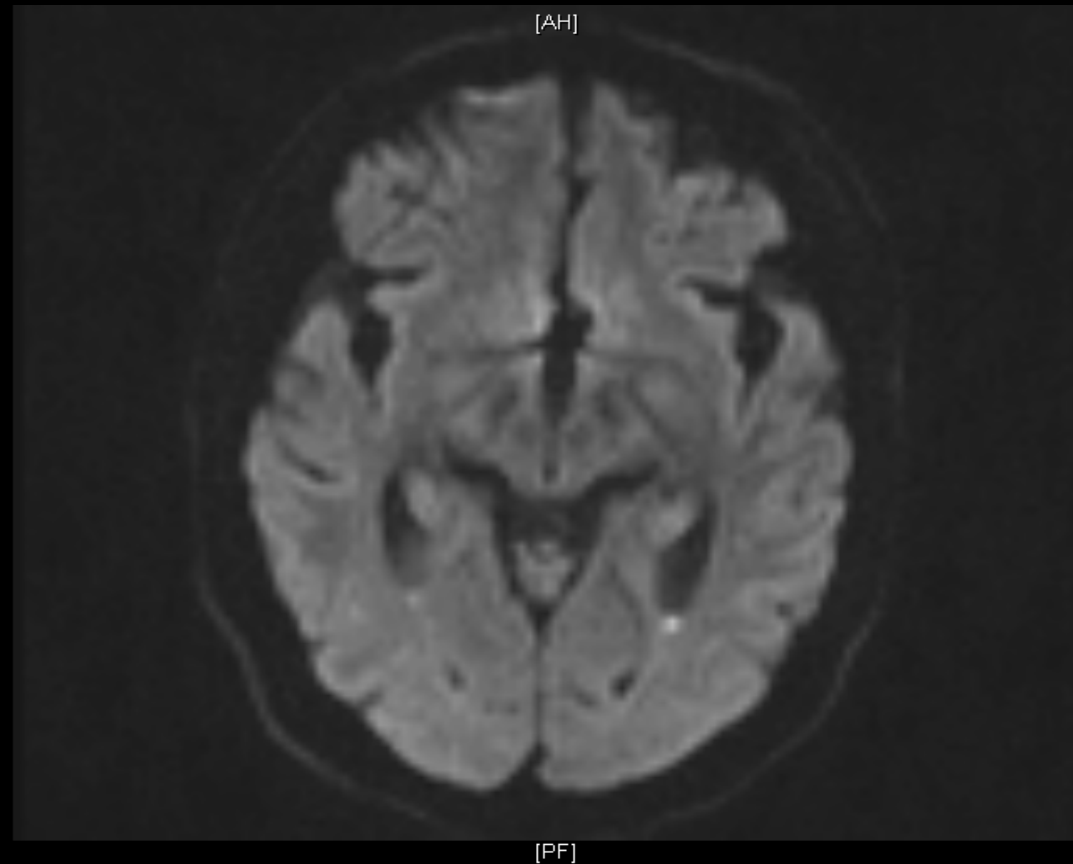
PRE-MSC

POST MSC



Suppression of inflammation

IV-injected SPIO-labeled MSCs localize in the occipital horns



Only FDA-approved cell tracker as of today:
 ^{111}In -oxine (1980s)

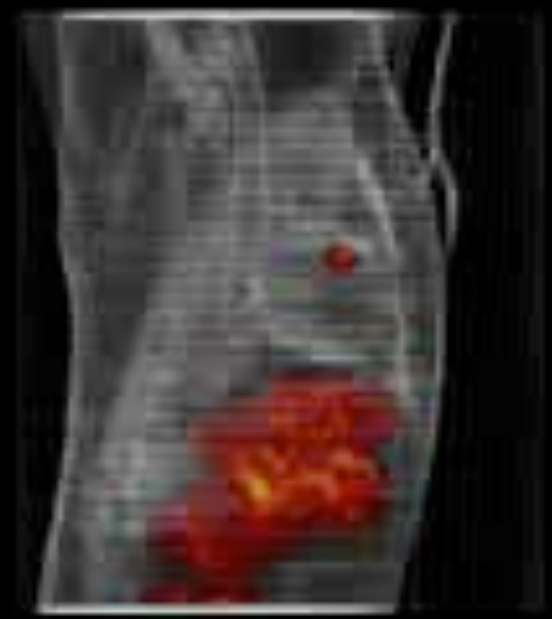
Half-life = 2.8 days

^{111}In -Oxine Labeled MSCs following IV injection in a Canine Myocardial Infarct Model

Day 1

Day 2

Day 5



SPECT/CT

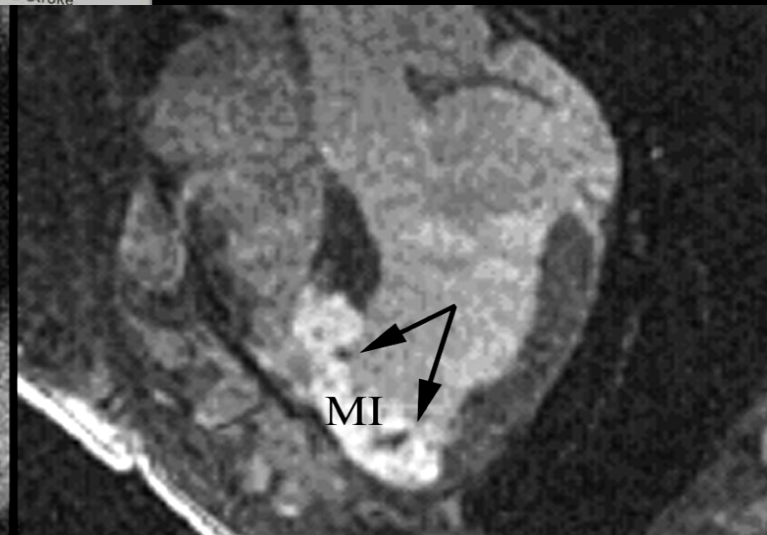
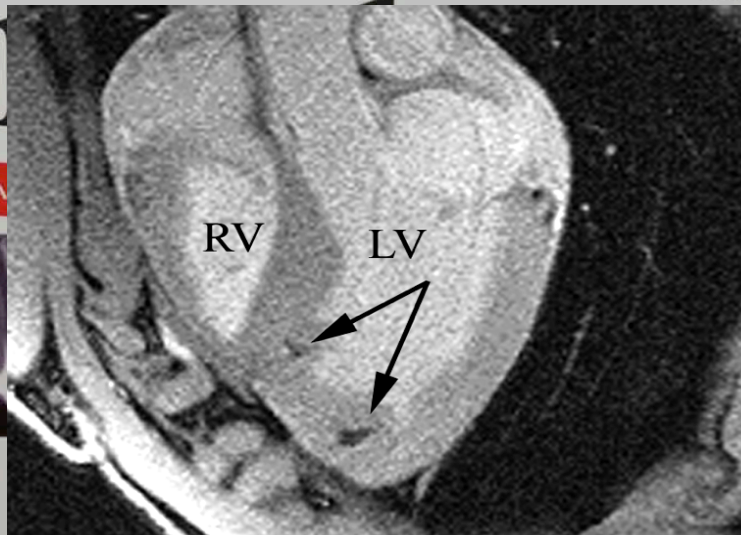
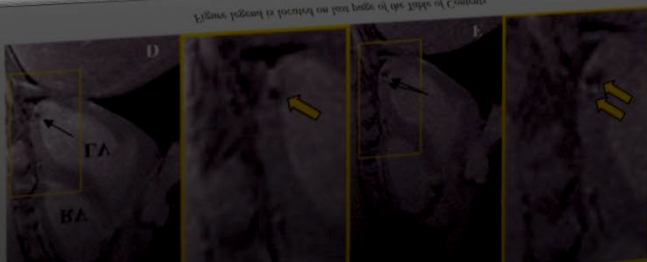


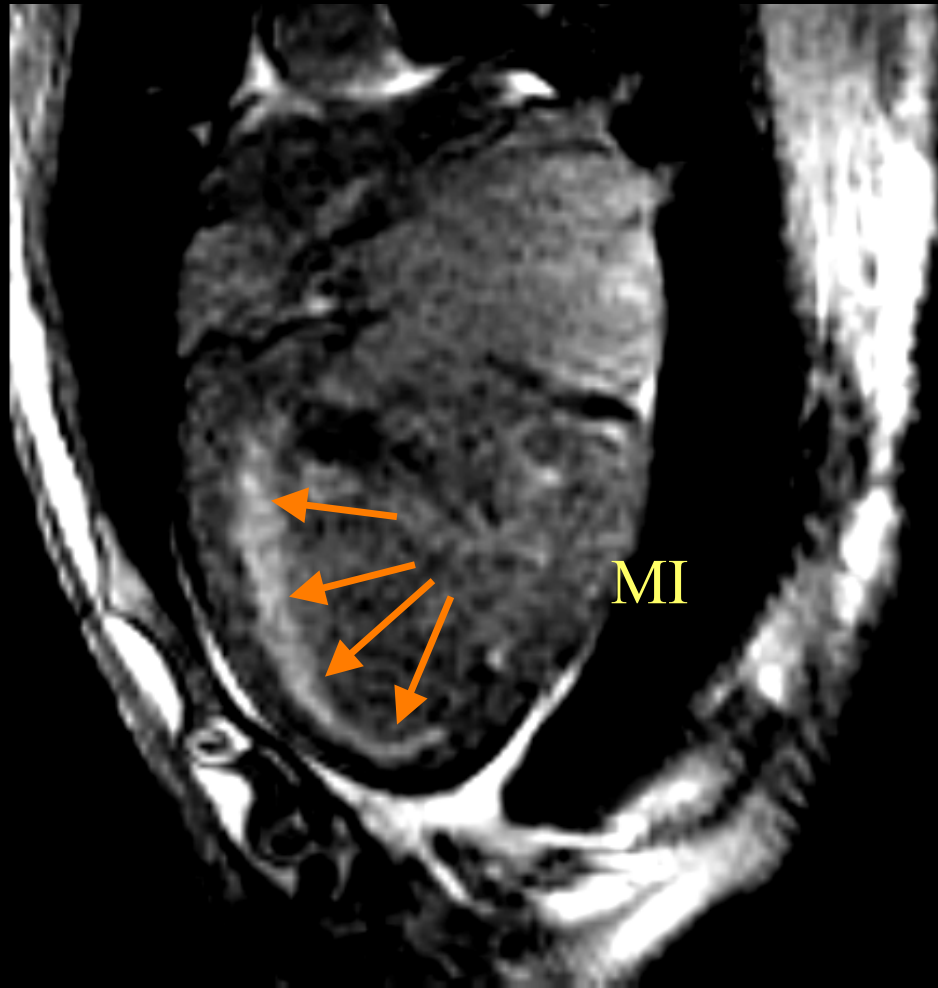
Figure legend is located on last page of the Table of Contents

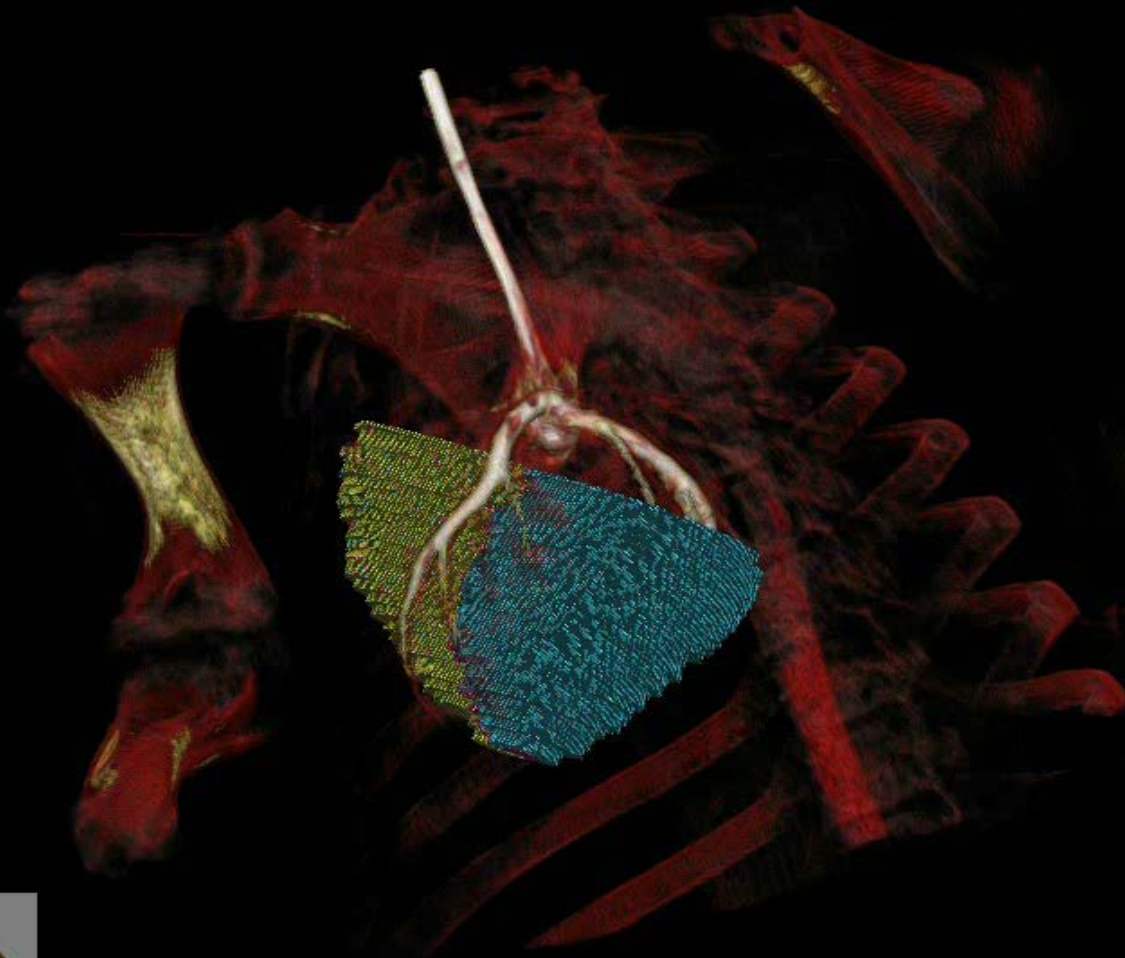
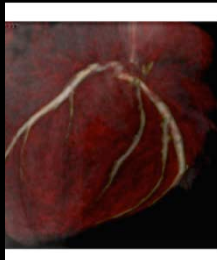
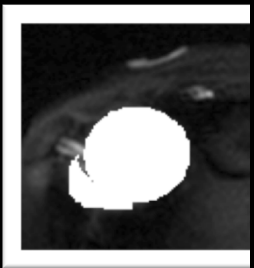
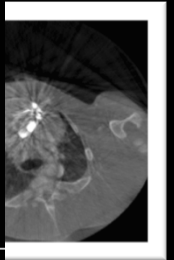
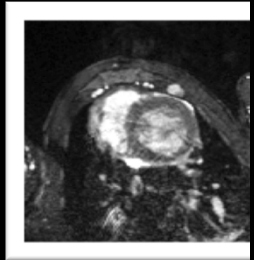


~30% of injections
were unsuccessful
using X-ray delivery

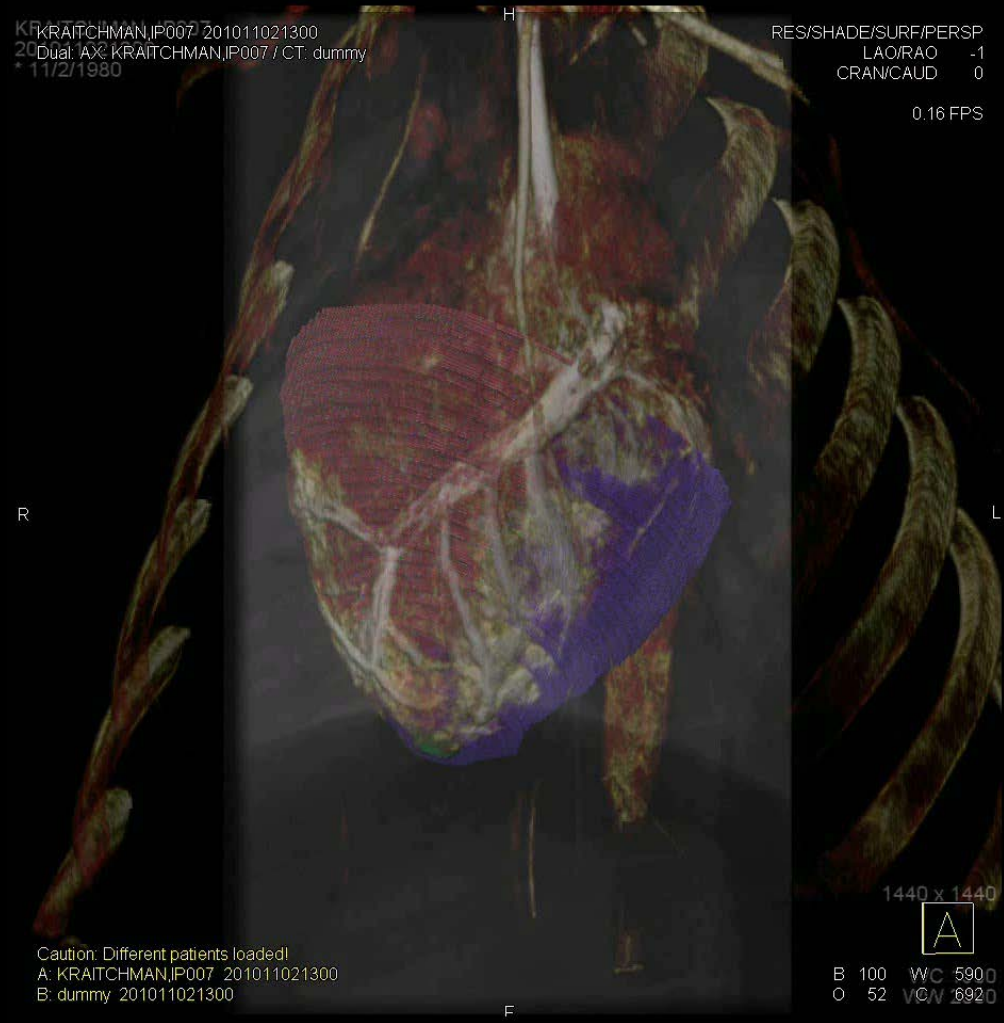
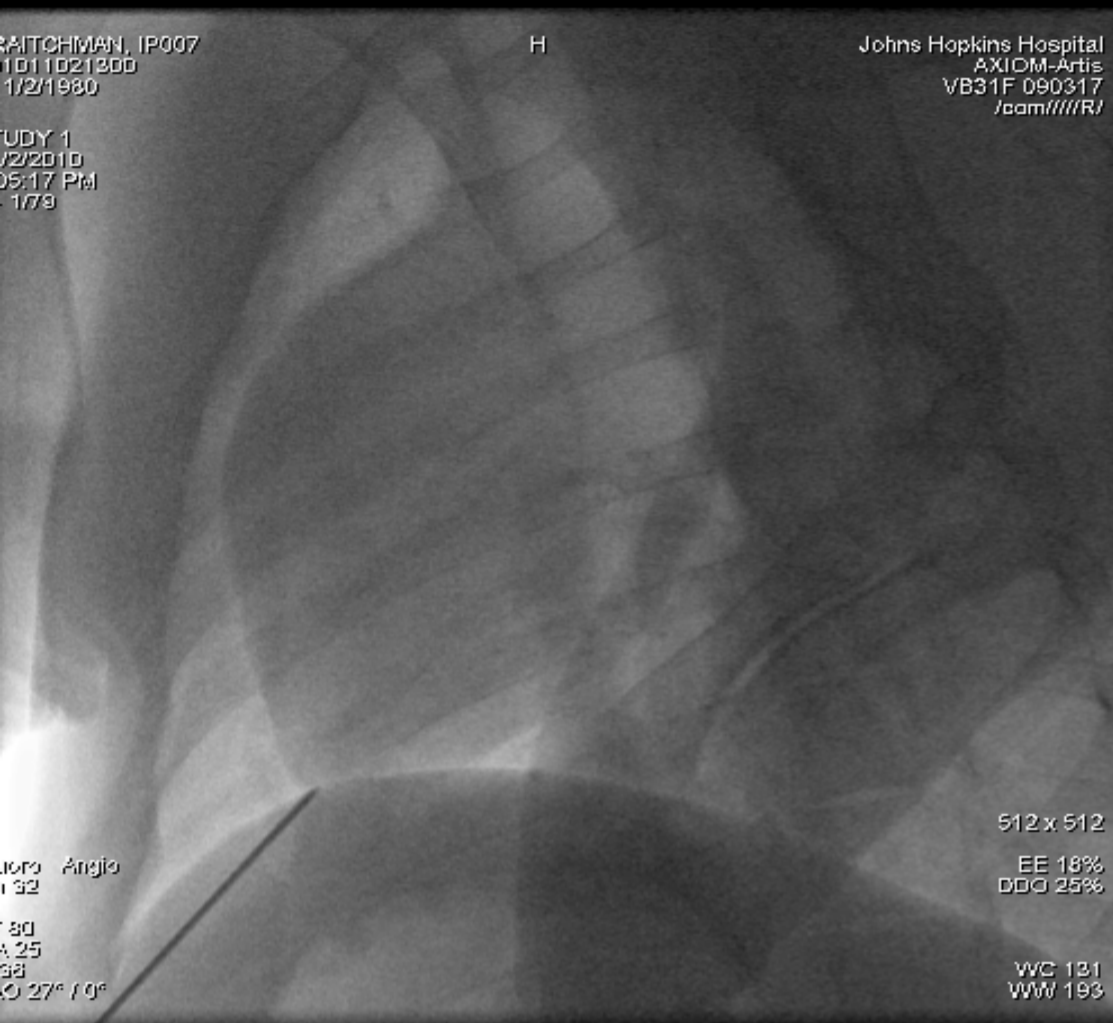
Kraitchman, Bulte et al.

MR-Guided, Real-Time Injection of Magnetically Labeled Canine MSCs in a Dog MI Model





Pericardial Access Using XFM

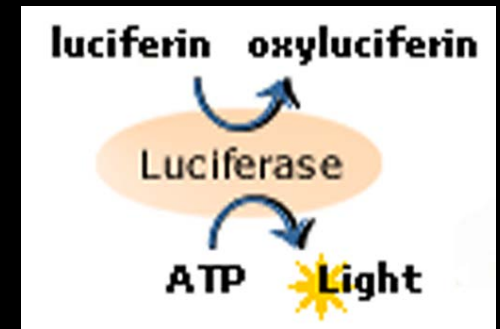




Non-Invasive Whole Body Cellular Imaging

- 1) Are stem cells being delivered/injected correctly?
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American Firefly

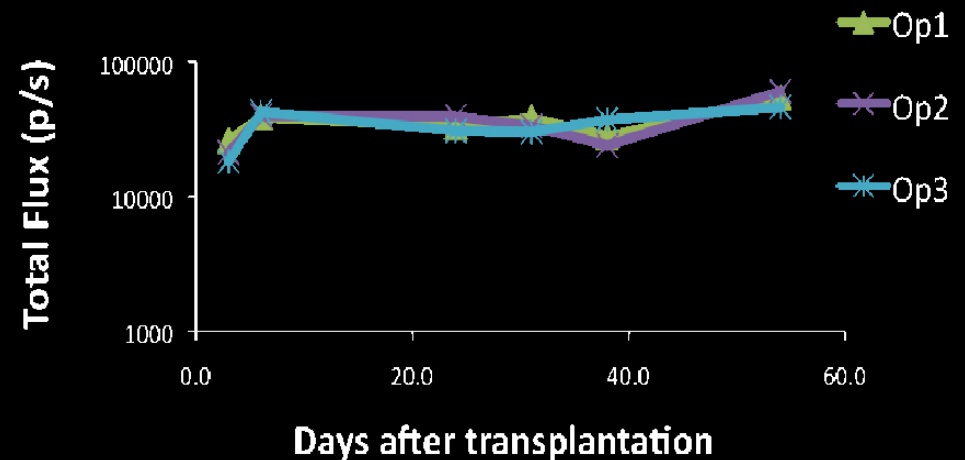
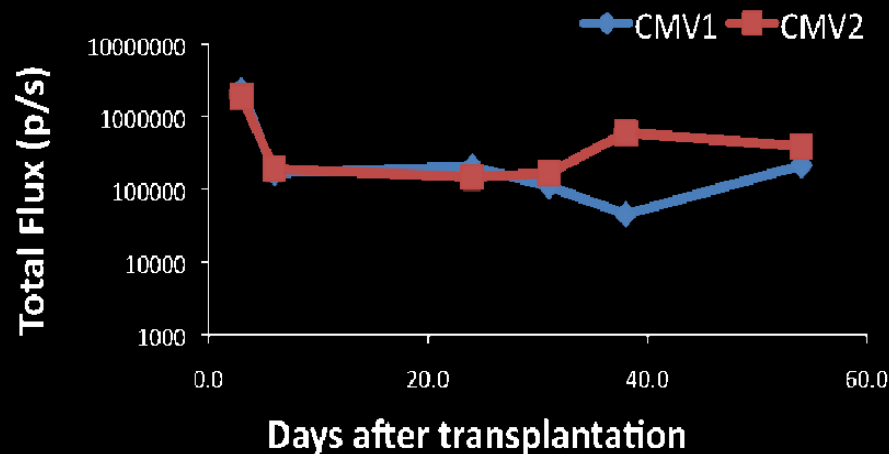
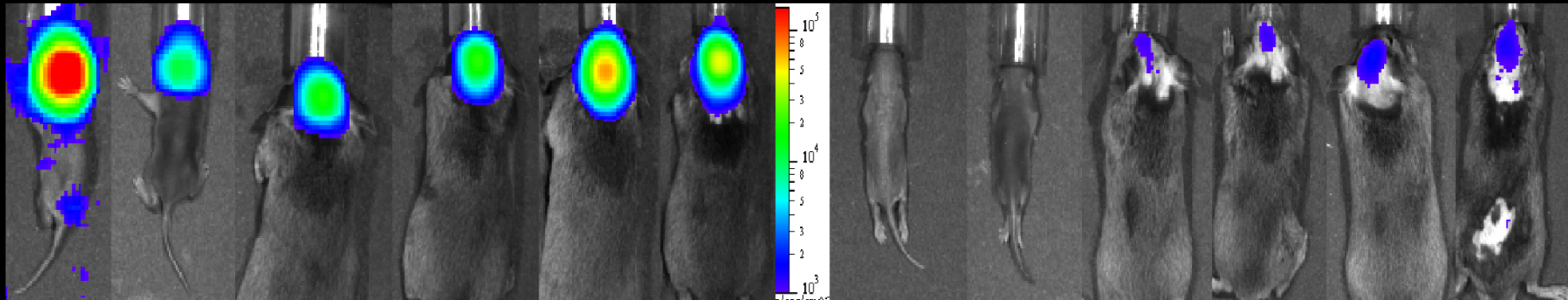


Photinus pyralis

Bioluminescent Imaging of Cell Differentiation

CMV

Opalin





Cellular Imaging Section



THE JOHNS HOPKINS
INSTITUTE FOR CELL ENGINEERING