Tracking ES cells after administration: Are they delivered correctly, where do they go, and what do they become?

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Professor of Radiology, Biomedical Engineering, and Chemical & Biomolecular Engineering

Director, Cellular Imaging Section
Institute for Cell Engineering
The Johns Hopkins University School of Medicine

www.hopkins-ice.org/vascular/int/bulte.html

THE JOHNS HOPKINS INSTITUTE FOR CELL ENGINEERING

inbt Institute for NanoBioTechnology

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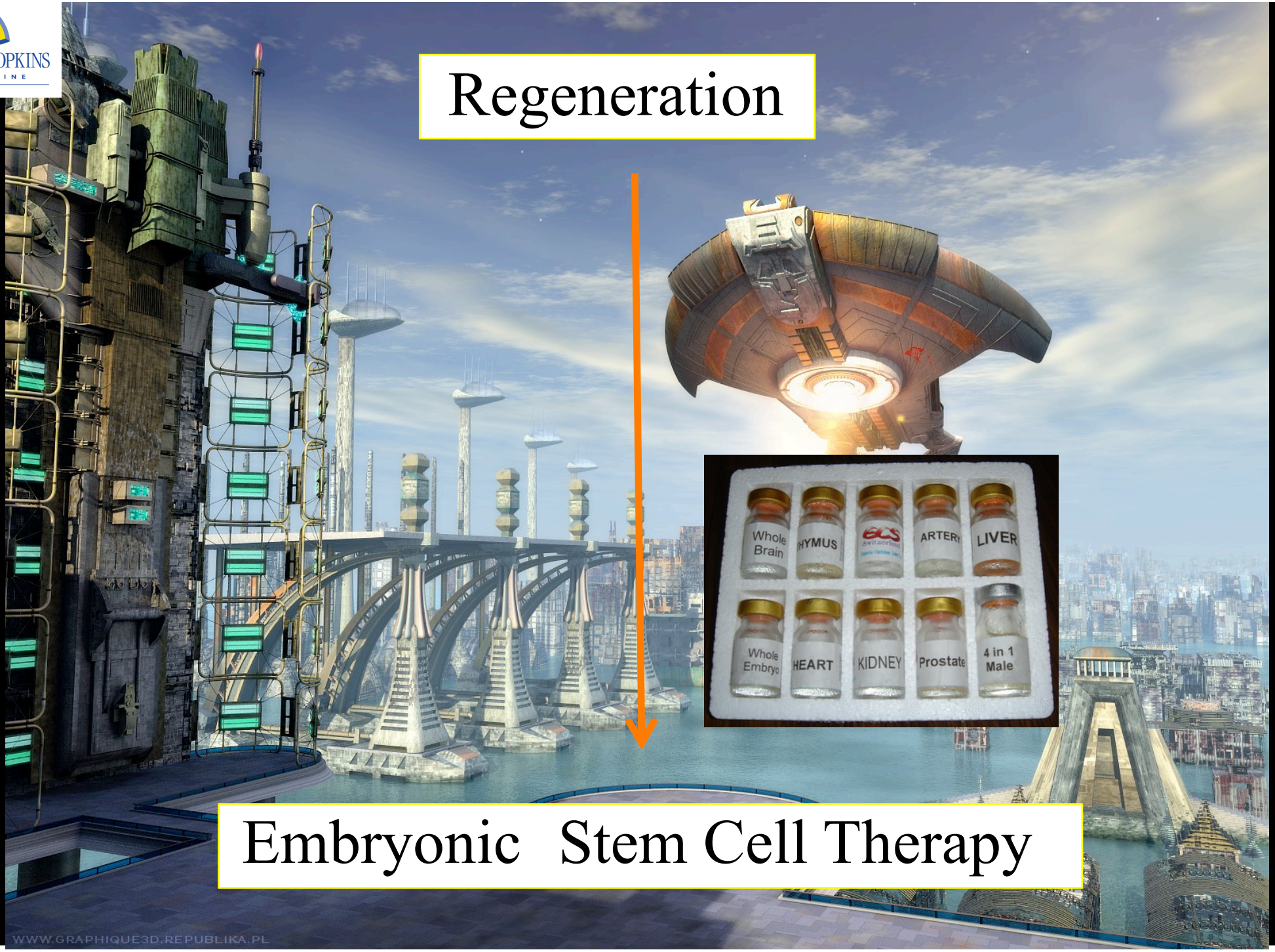
Organ Failure

Transplantation


Regeneration
Whole Brain
THYMUS
ARTERY
LIVER
Whole Embryo
HEART
KIDNEY
Prostate
4 in 1 Male
Embryonic Stem Cell Therapy
WWW.GRAPHIQUE3D.REPUBLIKA.PL

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The majority of examples that will be shown do not involve the use of human embryonic stem cells,

HOWEVER

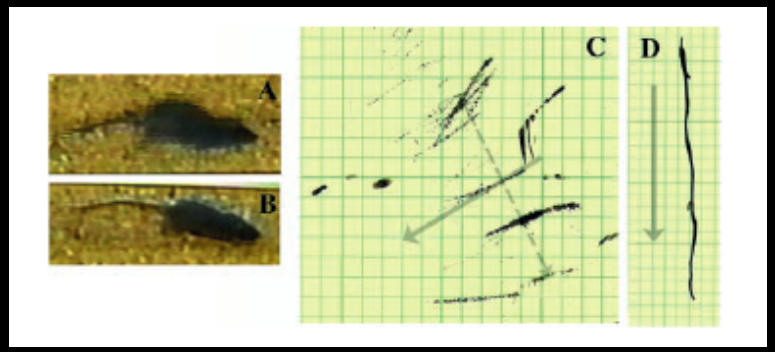
all cases directly apply to them

Neural Stem Cells: The Case of the Shiverer Dysmyelinated Mouse Brain

90 days, untreated

300 days, stem cell injection

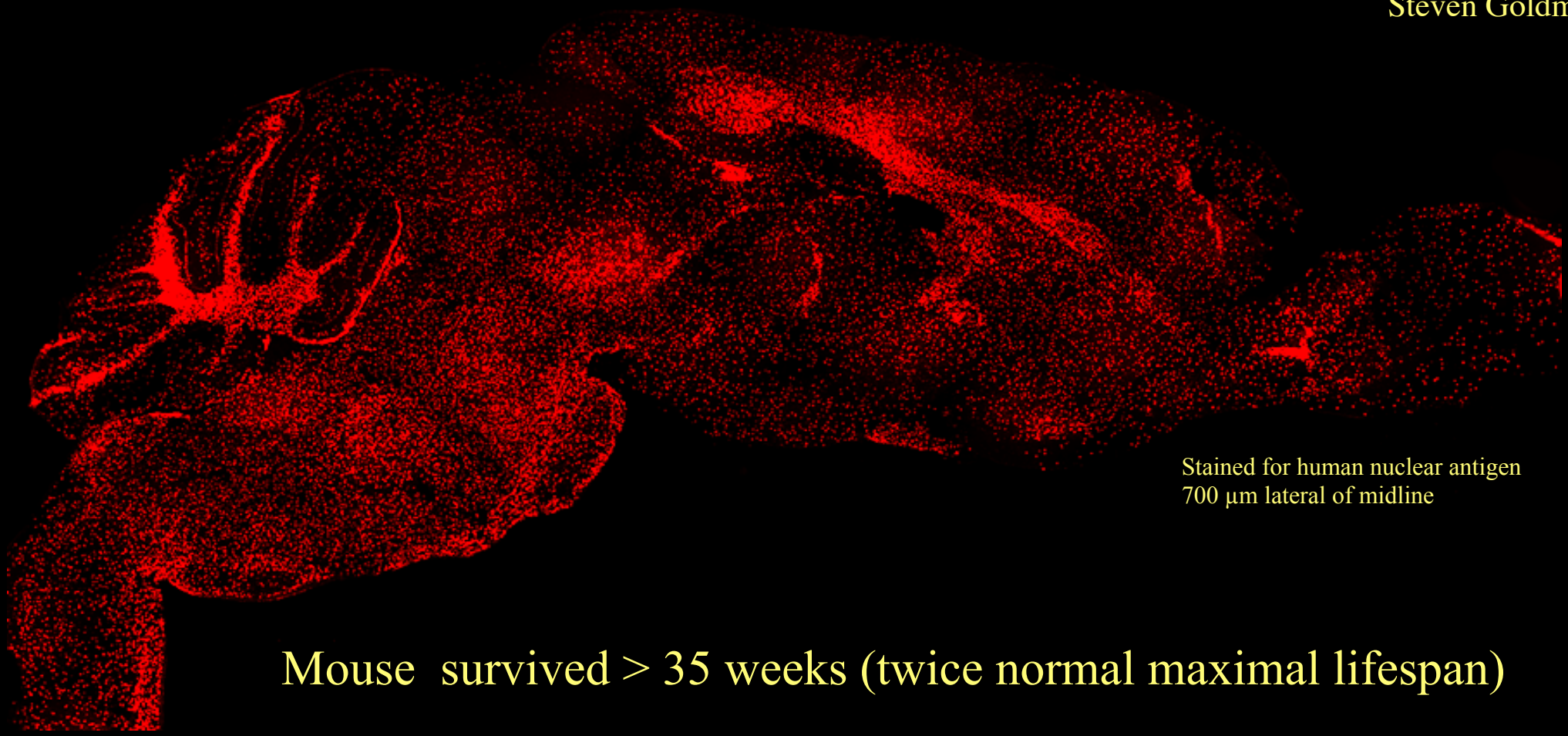
Windrem & Goldman, Cell Stem Cell, in press



Yandava, Snyder et al. PNAS 1999

Human fetal glial progenitor cells engrafted at birth into shiverer mice: What are the limits of cell migration and cell proliferation?

Steven Goldman



Stained for human nuclear antigen
700 µm lateral of midline

Mouse survived > 35 weeks (twice normal maximal lifespan)

Windrem & Goldman, Cell Stem Cell, in press

Stem Cell Therapy

AMELIORATION OF DISEASE? (CURE?)

Perform clinical trial

Prove safety of cell therapy, no adverse effect of MR cell labeling on therapeutic outcome

Observe therapeutic effect in animals

Define Outcome Measures

Identify proper cells and animal model

Find target for stem cell therapy

Identify pathological tissue

Focus on one disease

Visualize Cell Delivery

Visualize Cell Migration and Trafficking,

Visualize Cell Fate (Survival, Different).

Correlate with Therapeutic Effect,

Optimize Delivery Routes, Timing, Dose

Imaging

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Non-invasive cellular imaging modalities: What are the current available choices?

1. Optical Imaging (GFP, intravital microscopy)
2. Bioluminescent imaging
3. Near-infrared imaging
4. PET imaging
5. SPECT/radionuclide imaging
6. ^{1}H MR imaging using metal-based (SPIO) contrast agents
7. ^{19}F MR hot spot MR imaging
8. CEST MR imaging
9. X-ray/CT imaging
10. Ultrasound imaging

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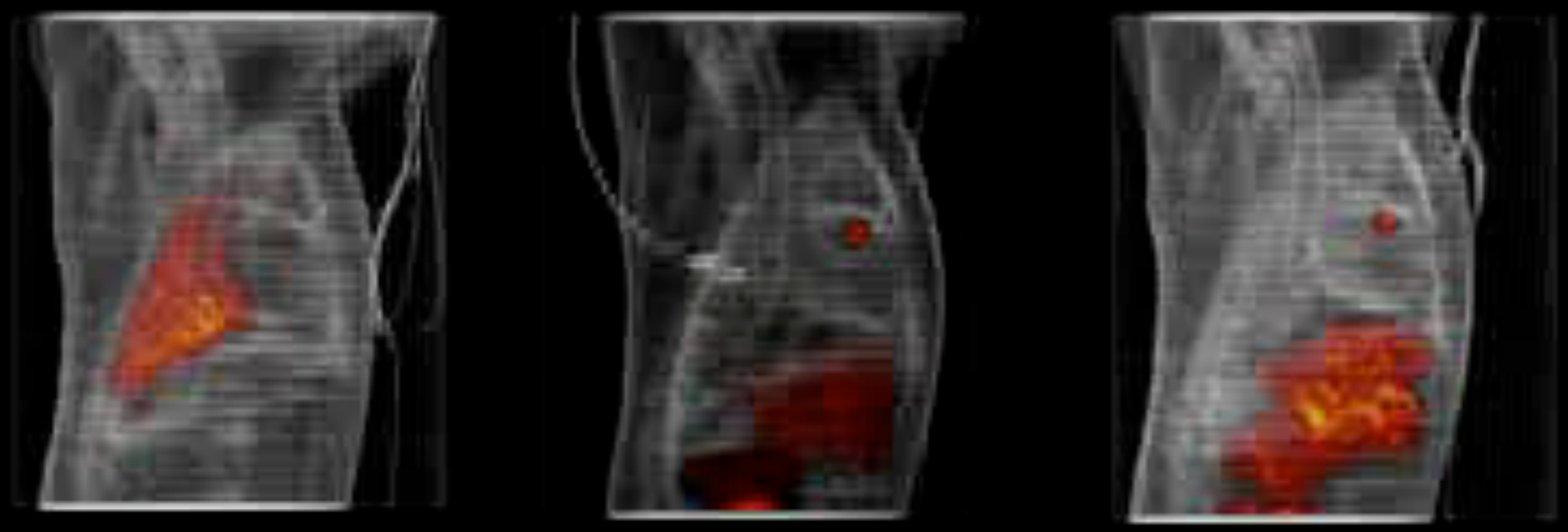
Only FDA-approved cell tracker as of today:
^{111}In-oxine (1970s)

Half-life = 2.8 days

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

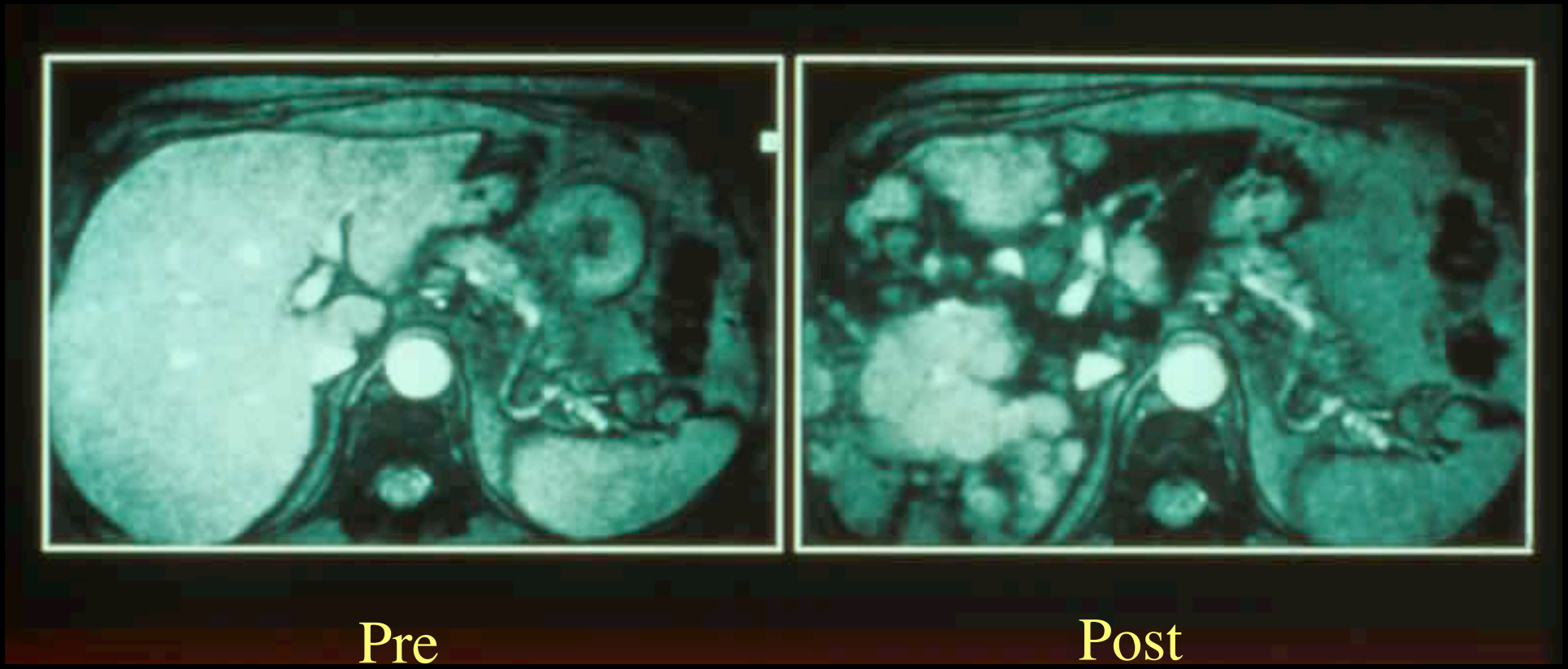
Day 1 Day 2 Day 5



SPECT/CT

D.L. Kraitchman et al, Circ. 112, 1454-1464 (2005).

MR Imaging
Feridex®: FDA-approved SPIO since 1996
(as Liver Agent, not for Cell Tracking)



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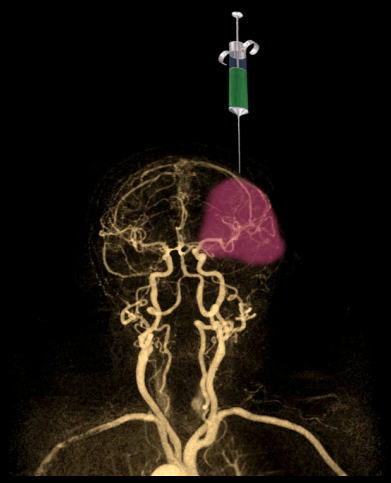
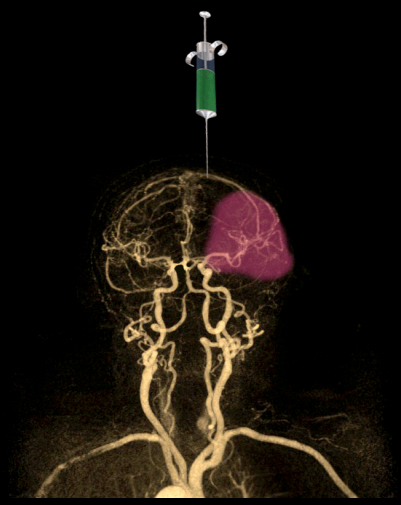
Tracking cells after administration:
1) Are they delivered correctly?

Routes of Stem Cell Delivery



Stereotactic parenchymal injection

Intravenous infusion



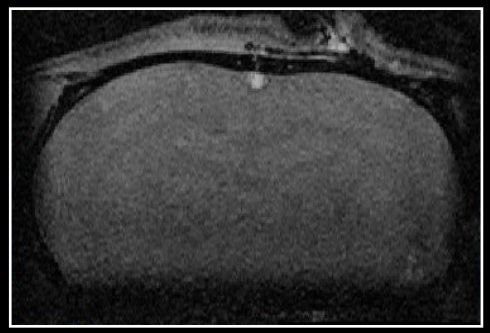
Intraventricular injection

Targeted intra-arterial infusion

Dual-Modality (MRI + Laser Doppler Flow) Monitoring of MSC Engraftment in Stroke (MCAO) n=17

Pre Tx

MRI in vivo

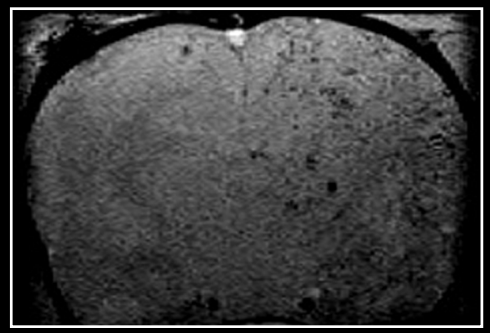


Moderate engraftment

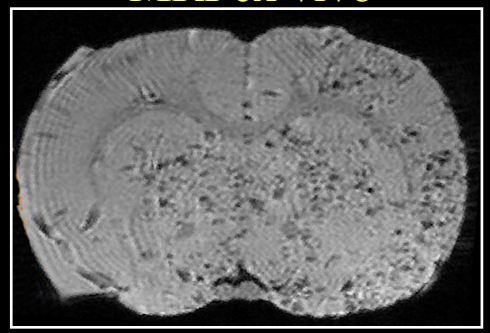
8/17

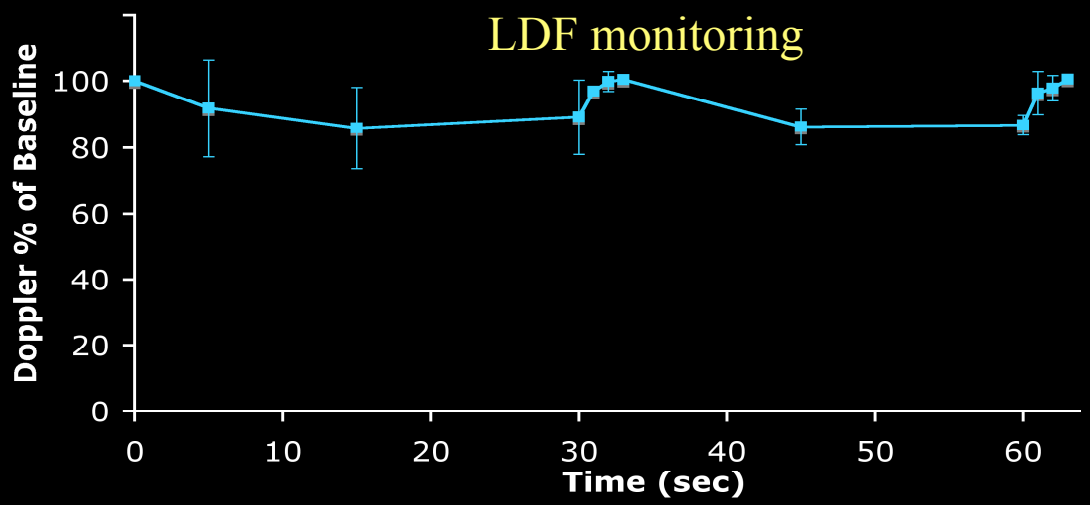
Post Tx

MRI in vivo



MRI ex vivo



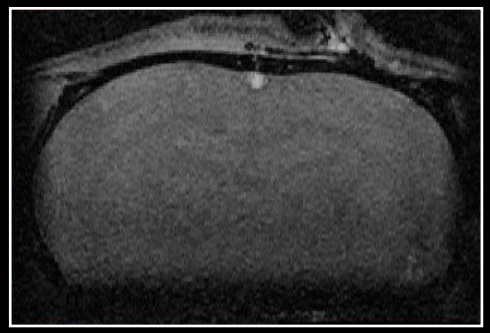


P. Walczak et al.
Stroke, in press

Dual-Modality (MRI + Laser Doppler Flow) Monitoring of MSC Engraftment in Stroke (MCAO) n=17

Pre Tx

MRI in vivo

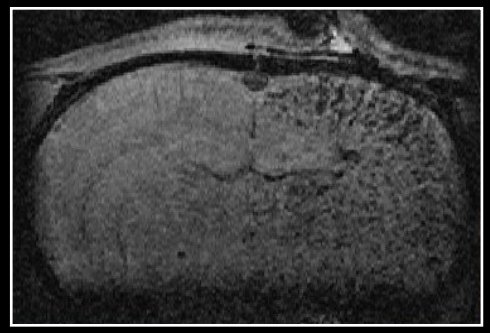


High engraftment

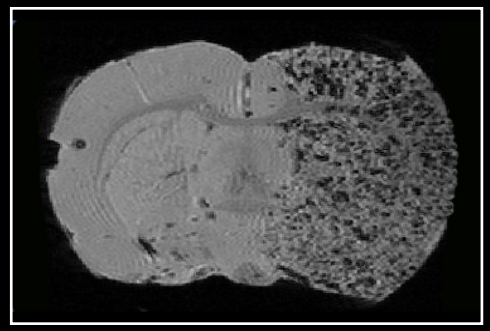
6/17

Post Tx

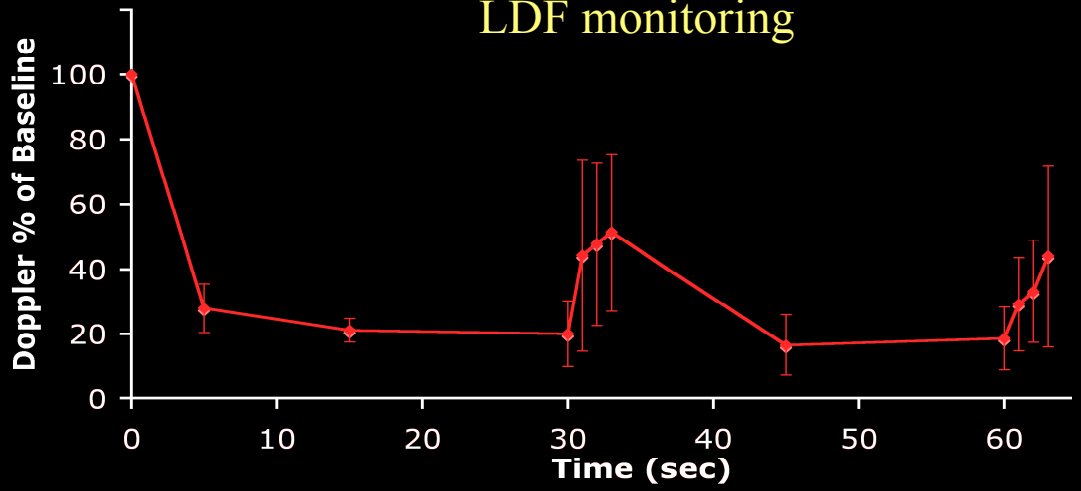
MRI in vivo



MRI ex vivo



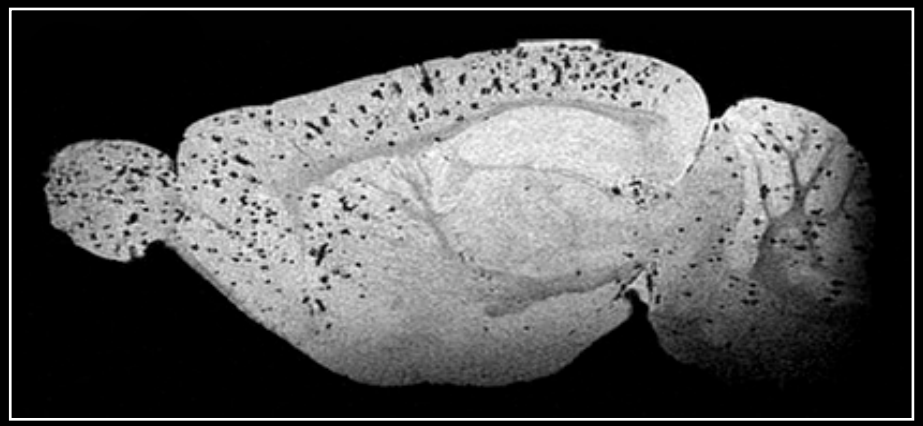
LDF monitoring



P. Walczak et al.
Stroke, in press

3D Reconstruction of graft distribution

2D



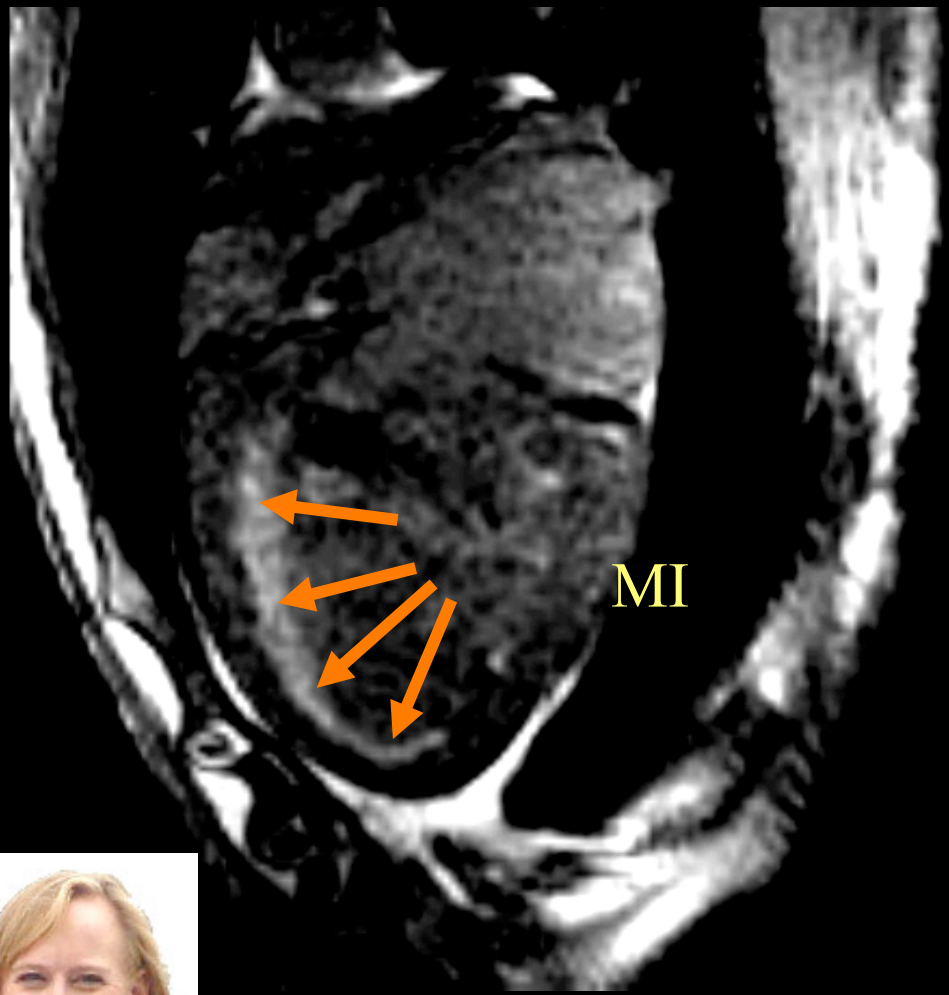
3D

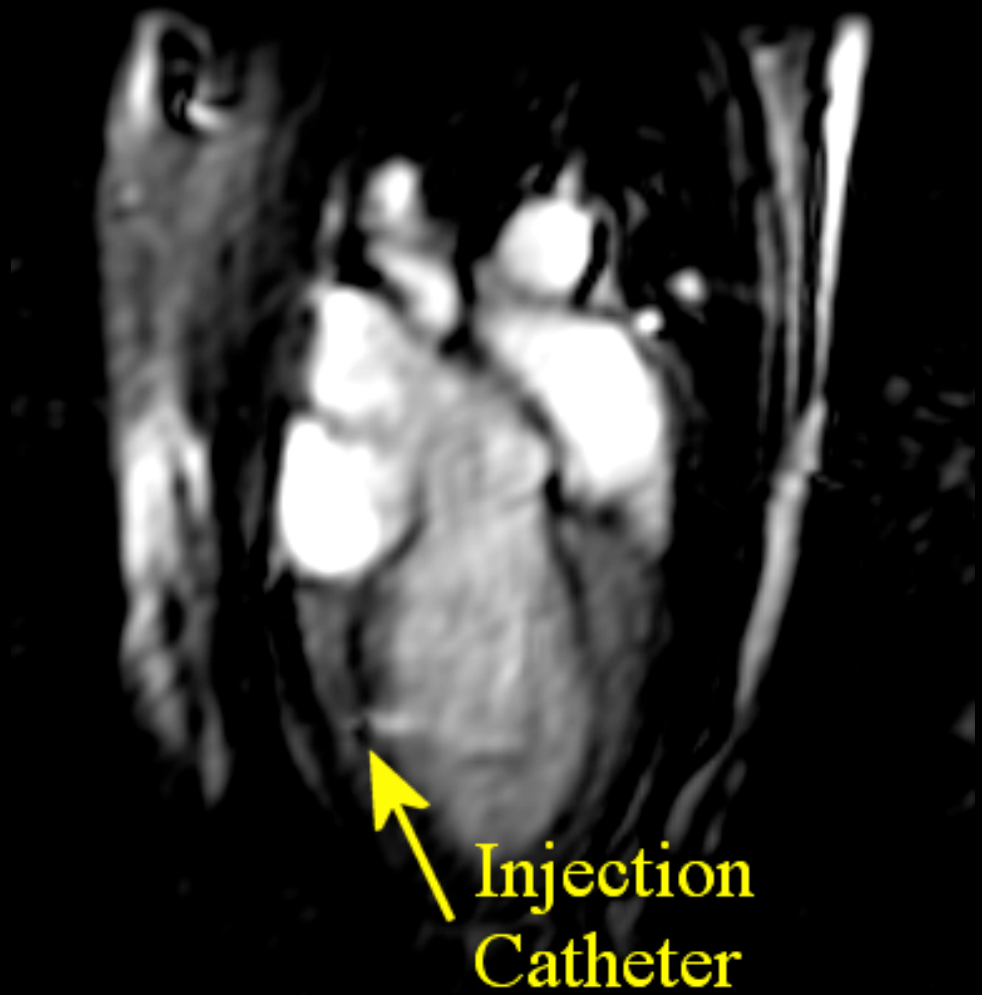
MR-Guided Real-Time Injections Using MR Compatible Injection Catheters

- Modified loopless antenna design
- Matching, tuning, and decoupling circuitry
- Steerable guide catheter via nitinol pull wire
- 26 gauge nitonol injection needle

P. Karmarkar et al., MRM 51, 1163-1172 (2004).

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





DL Kraitchman et al., Curr Pharm Biotech 5, 567-584, 2004.

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MEDICINE

April 2006 • Volume 16, Number 4

RSNA News

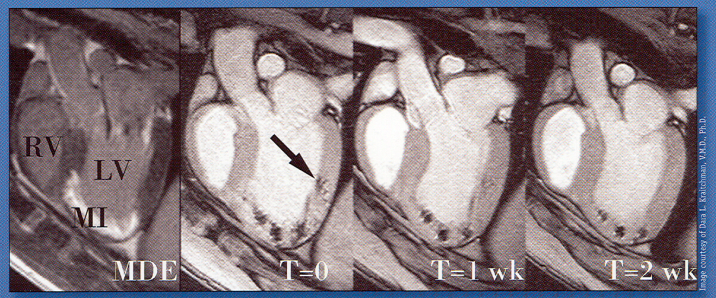


Image courtesy of Dara L. Kraitchman, V.M.D., Ph.D.

MR Imaging Used to Track Accuracy and Effectiveness of Stem Cell Injections

Also Inside:

- RSNA Workshop Addresses Need for Clinical Trials Training
- Adjuvant Radiation for Endometrial Cancer Increases Survival, Study Shows
- Long-Term Survival Possible After Radiosurgery for Brain Cancer
- Leaders Look to Establish Teleradiology Standards

Advance Registration for RSNA 2006 Begins April 24

April 2006

First Clinical Trial Using MR Tracking of Magnetically Labeled Cells

First patient injected on April 26, 2004
(Collaboration between JHU and U of Nijmegen, NL)

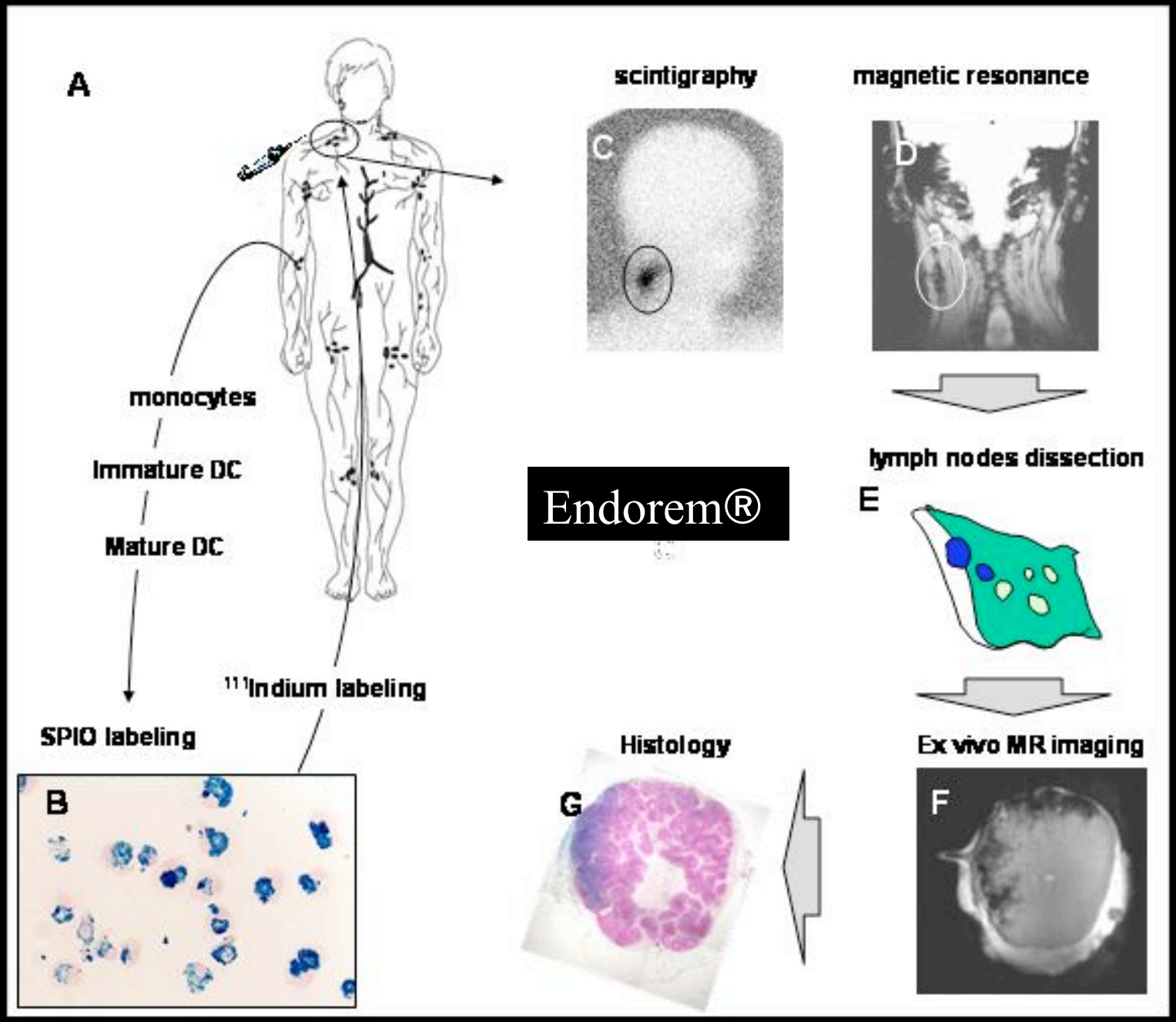
ARTICLES

nature biotechnology

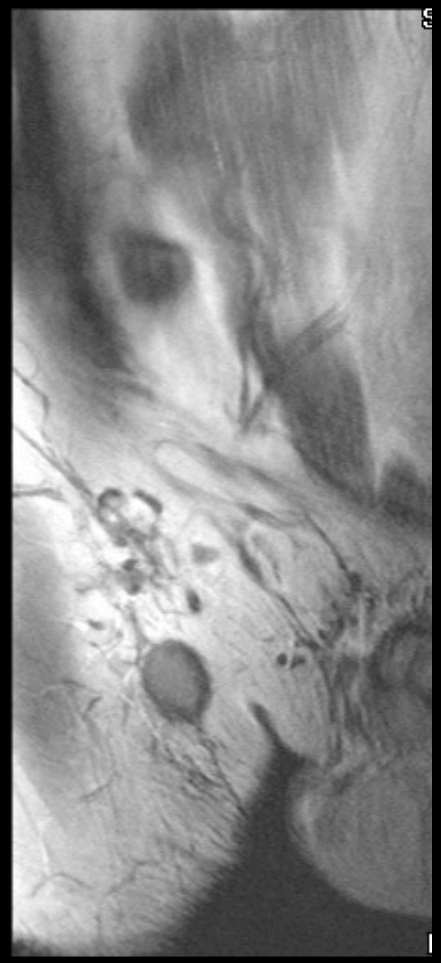
Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy

I Jolanda M de Vries[1,2], W Joost Lesterhuis[3], Jelle O Barentsz[4], Pauline Verdijk[1], J Han van Krieken[5], Otto C Boerman[6], Wim J G Oyen[6], Johannes J Bonenkamp[7], Jan B Boezeman[8], Gosse J Adema[1], Jeff W M Bulte[9], Tom W J Scheenen[4], Cornelis J A Punt[3], Arend Heerschap[4] & Carl G Figdor[1]

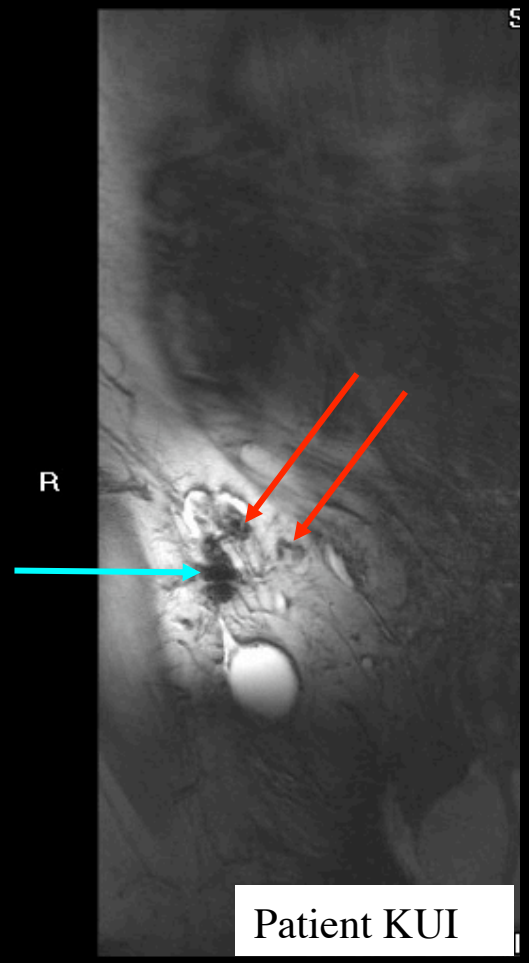
NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 11 NOVEMBER 2005


A
scintigraphy
magnetic resonance
C
D
monocytes
Immature DC
Mature DC
Endorem®
lymph nodes dissection
E
111Indium labeling
SPIO labeling
Histology
Ex vivo MR imaging
B
G
F

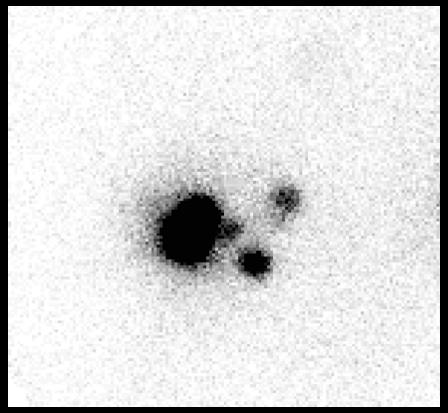
What Did We Learn:
1) MR Imaging of Cell Migration to Nearby Lymph Nodes



TSE post



MEDIC post



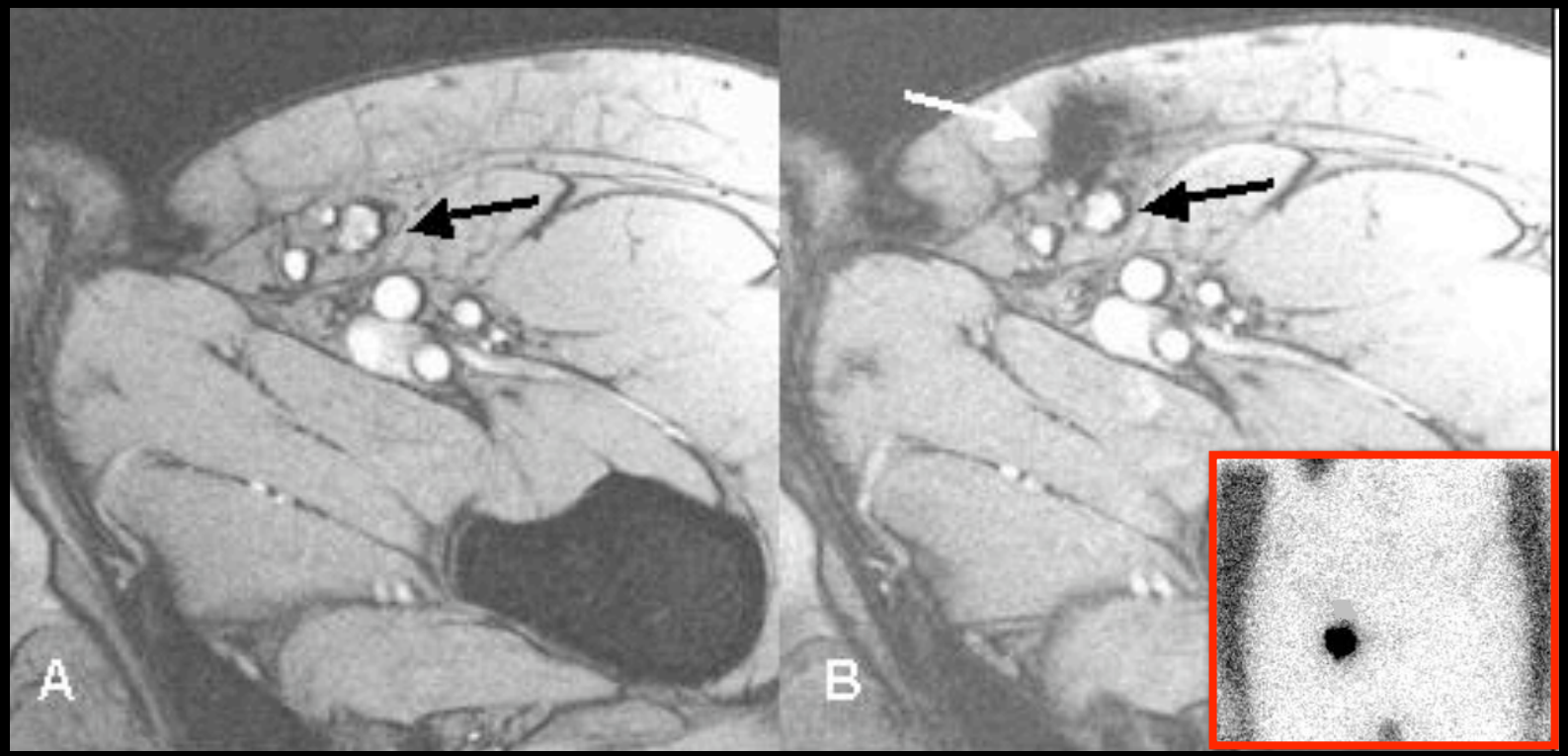
Scintigraphic imaging (^{111}In-oxine):

3 positive nodes

I. de Vries, et. al., Nat. Biotechnol. 23, 1407-1413 (2005).

What Did We Learn:
2) Accidental Misinjection in 4 out of 8 Patients

(Injections performed under US, not MR-Guided)



Pre Post

NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 11 NOVEMBER 2005

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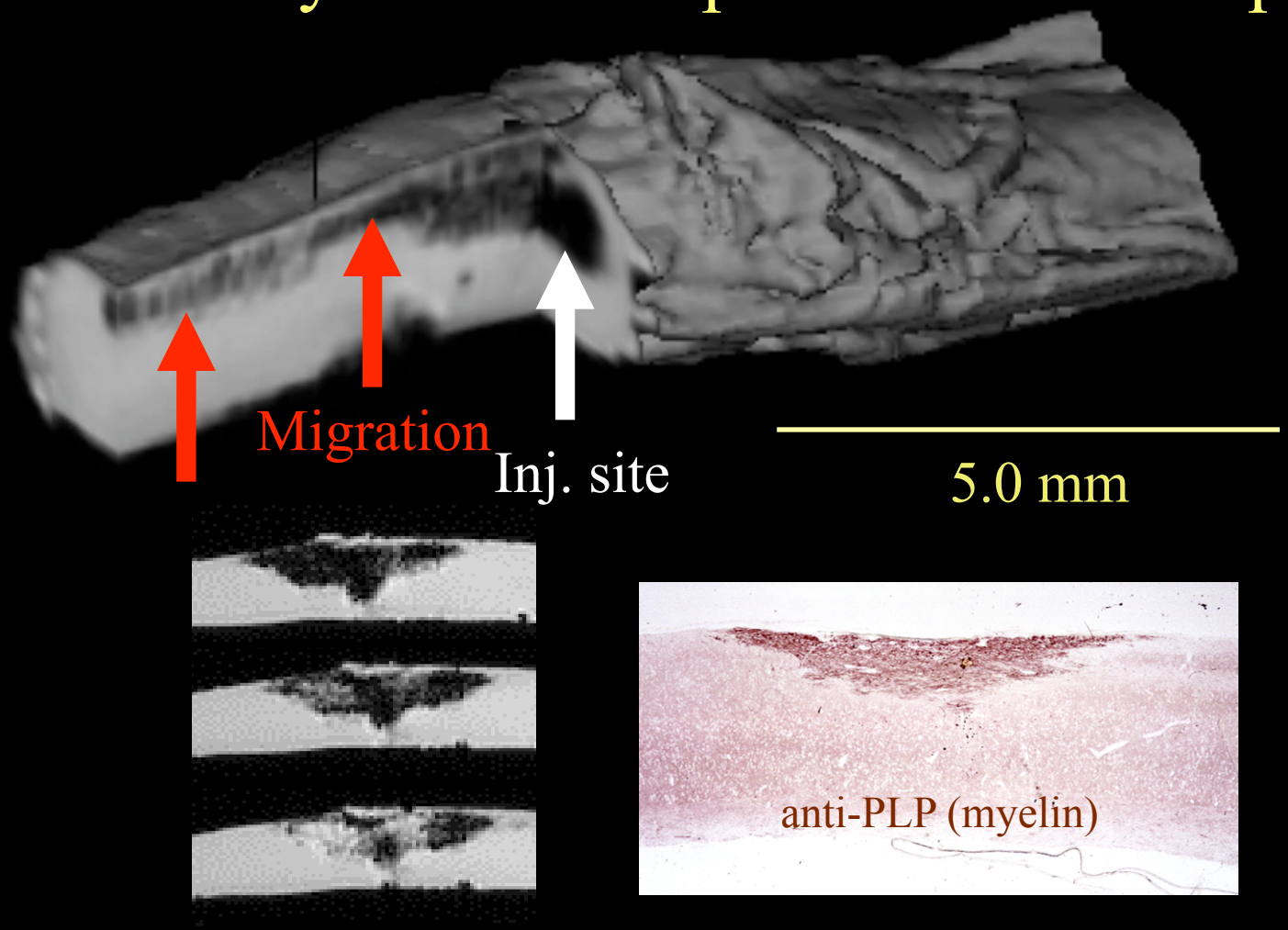
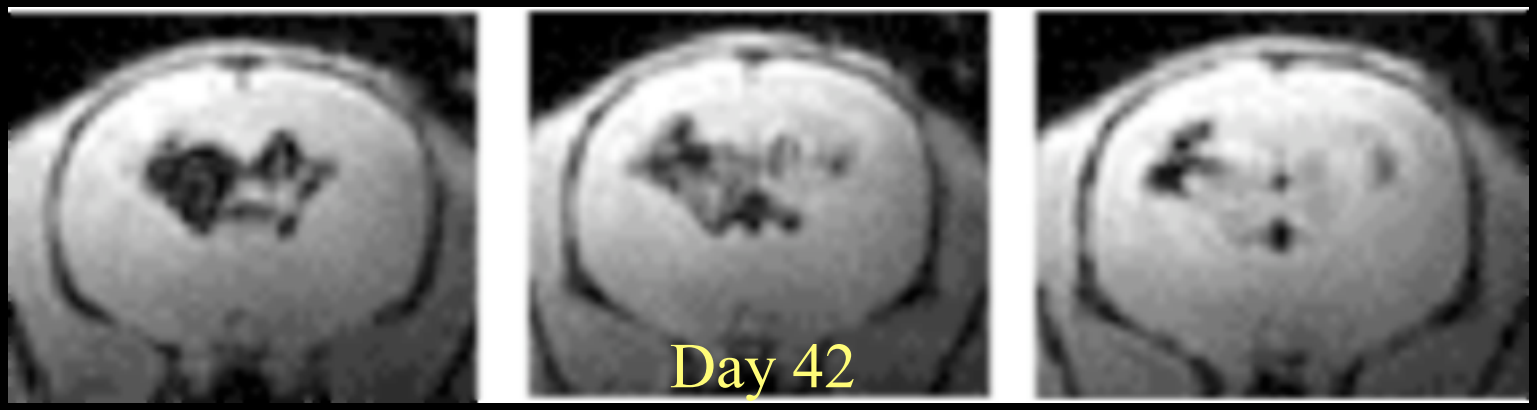
Tracking cells after administration:
2) Where do they go?

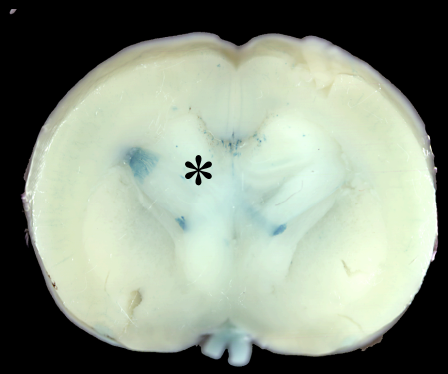
MR tracking of magnetically labeled oligodendrocyte progenitors 10 days after transplantation in rat spinal cord



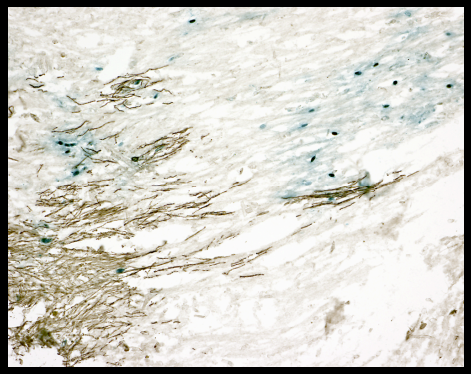
J.W.M. Bulte et al., PNAS 96, 15256-15261 (1999).

In Vivo Tracking of Magnetically Labeled Neural Stem Cells

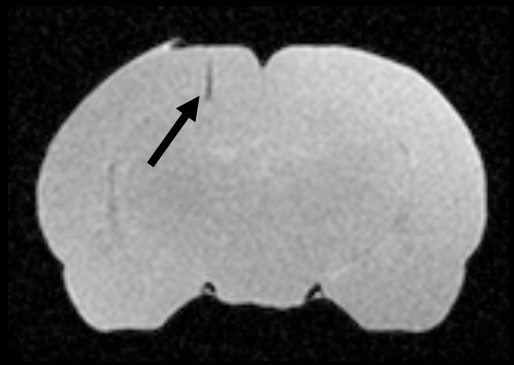




LacZ



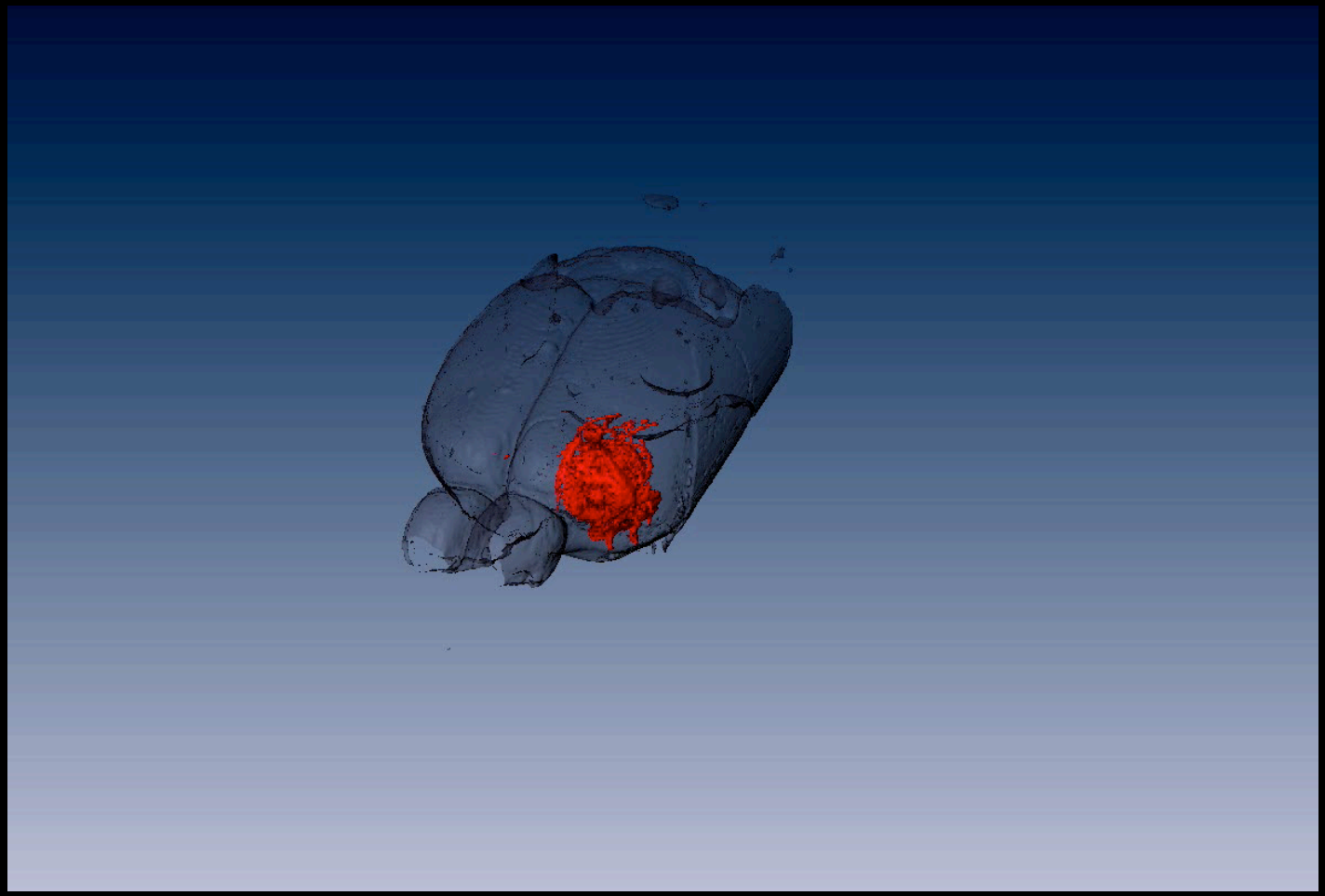
Anti-MBP



Unlabeled cells

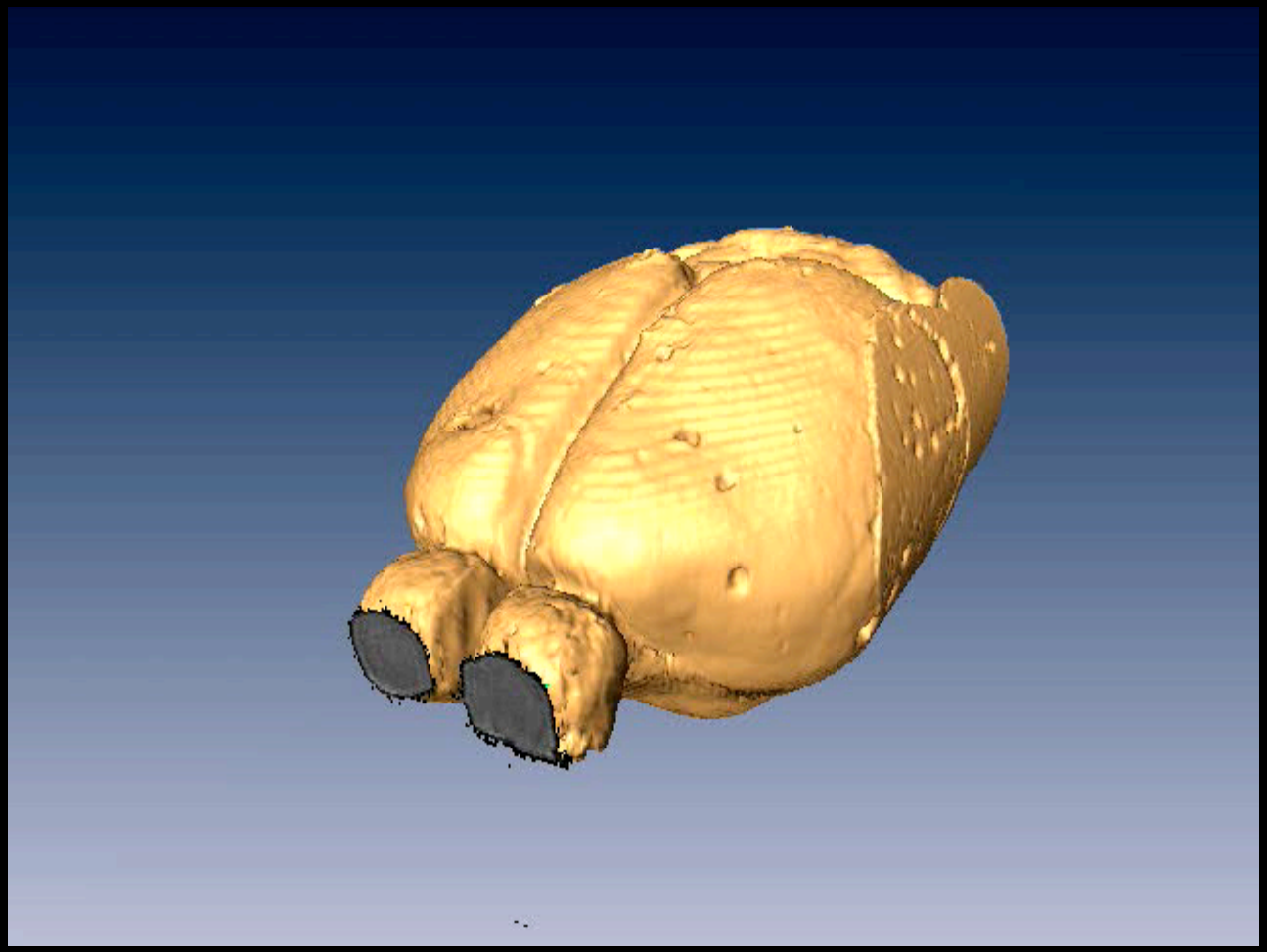
J.W.M. Bulte et al., Nature Biotechnol. 19, 1141-1147 (2001).

MR Imaging of Magnetically Labeled Neural Stem Cells



P. Walczak et al. Nanomedicine 2, 89-94, 2006

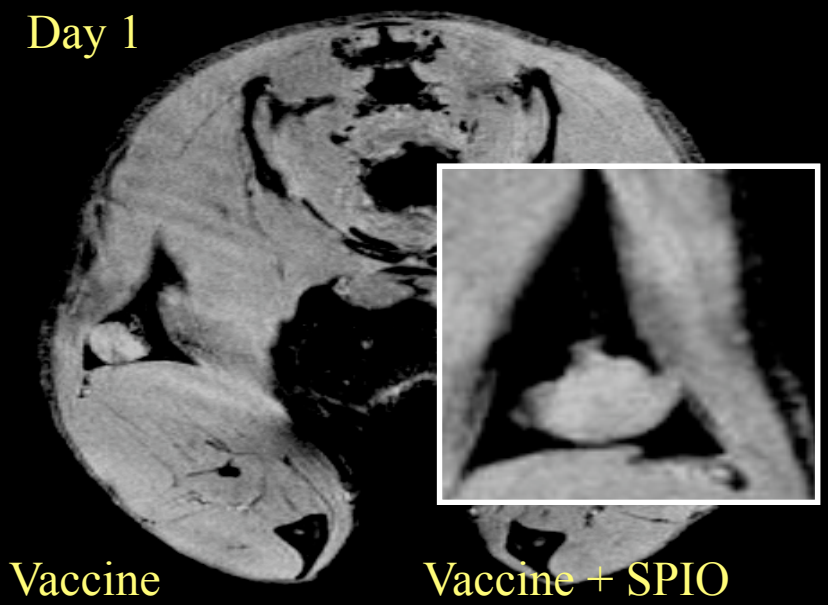
MR Imaging of Magnetically Labeled Neural Stem Cells

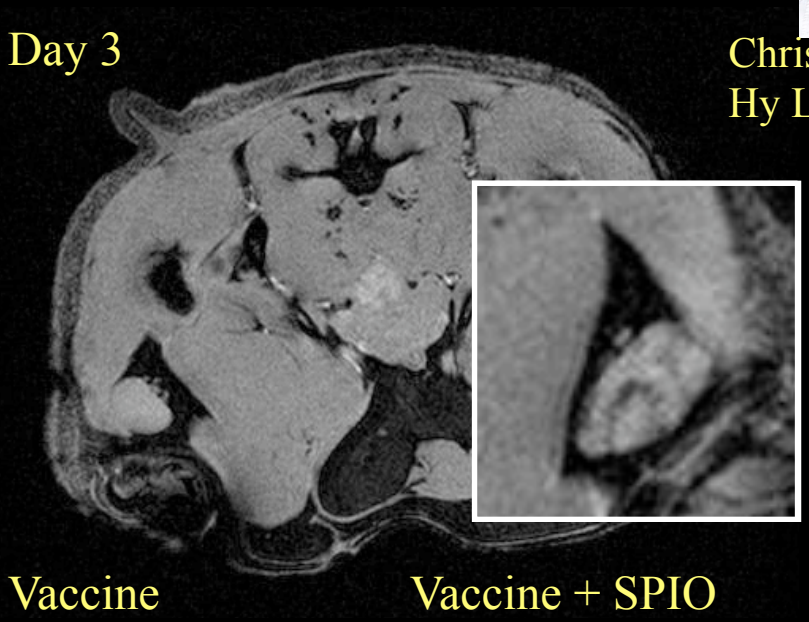


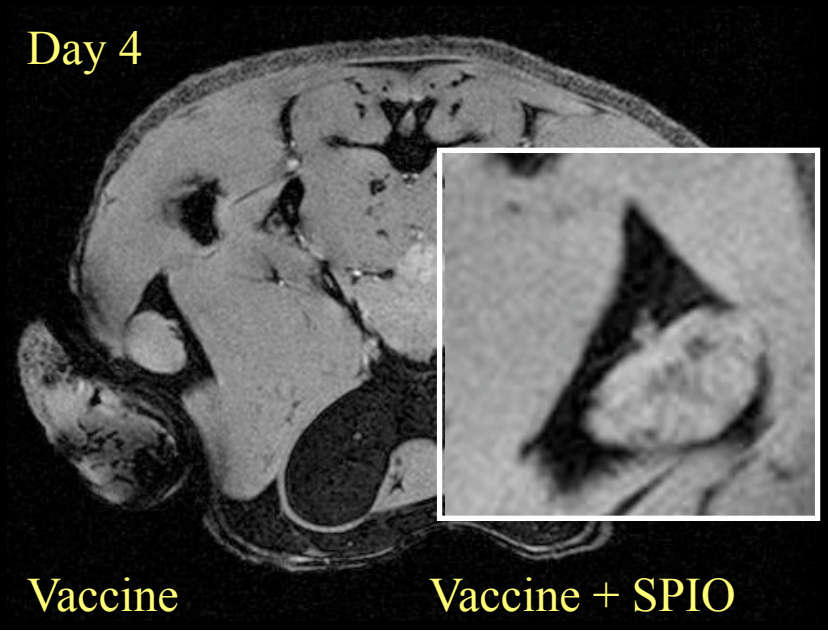
P. Walczak et al. MRM 54, 769-774, 2005.

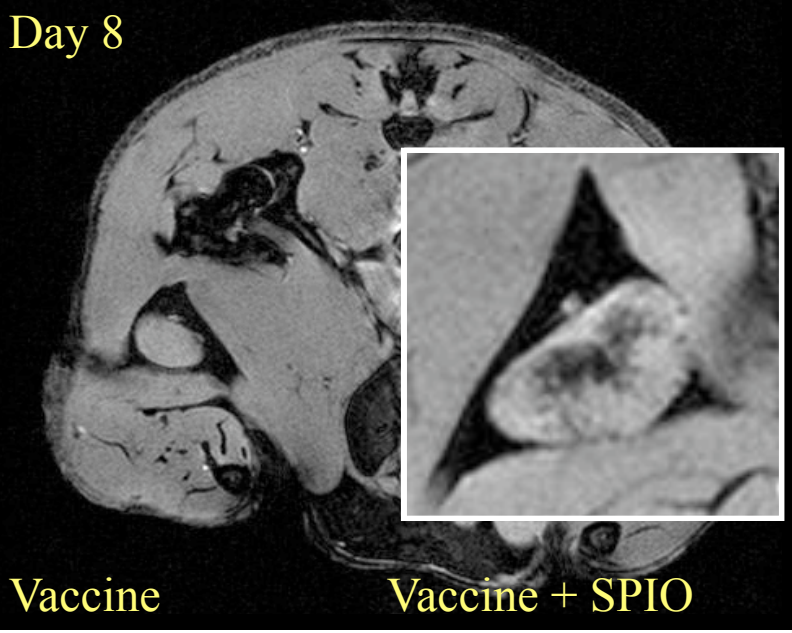
In vivo MR Studies of Cancer Vaccines

Chris Long
Hy Levitsky









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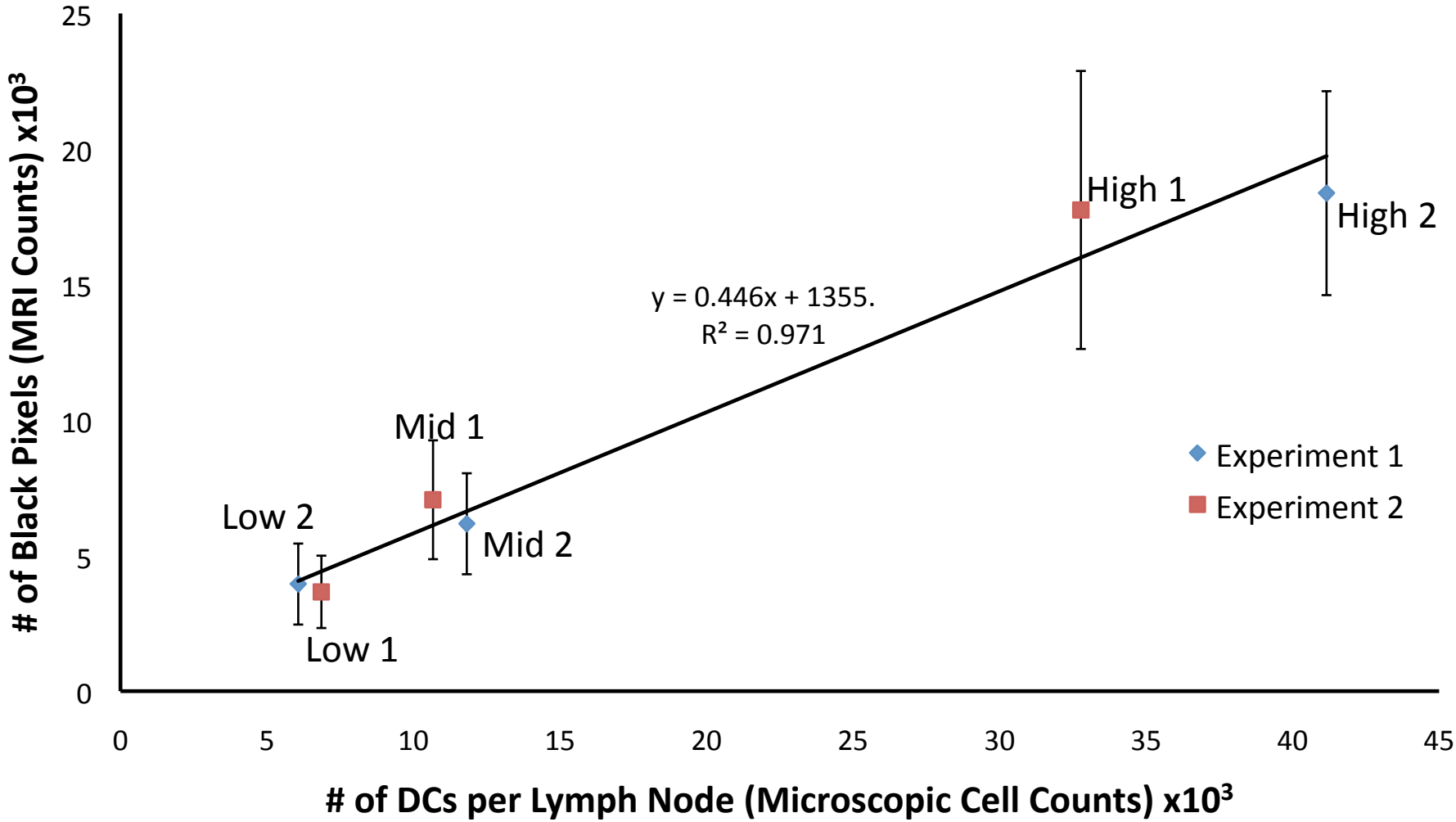
MEDICINE

What about Quantifying the Local Number of Cells?

Black Pixels and DC Numbers Correlate Throughout Separate Experiments

n=15 mice / 30 lymph nodes



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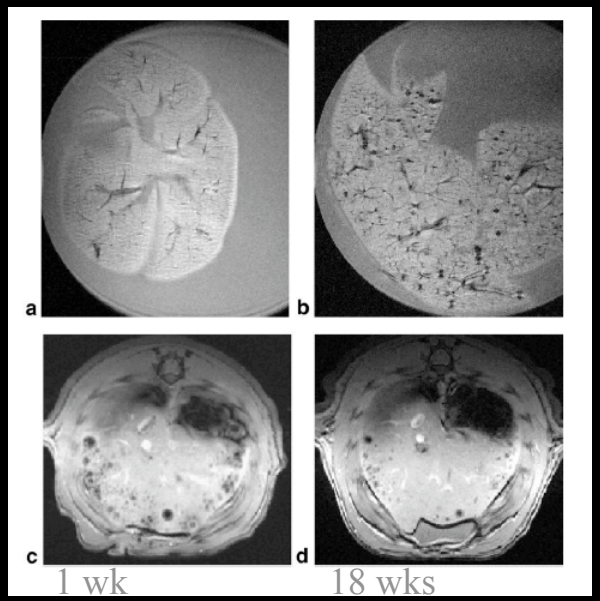
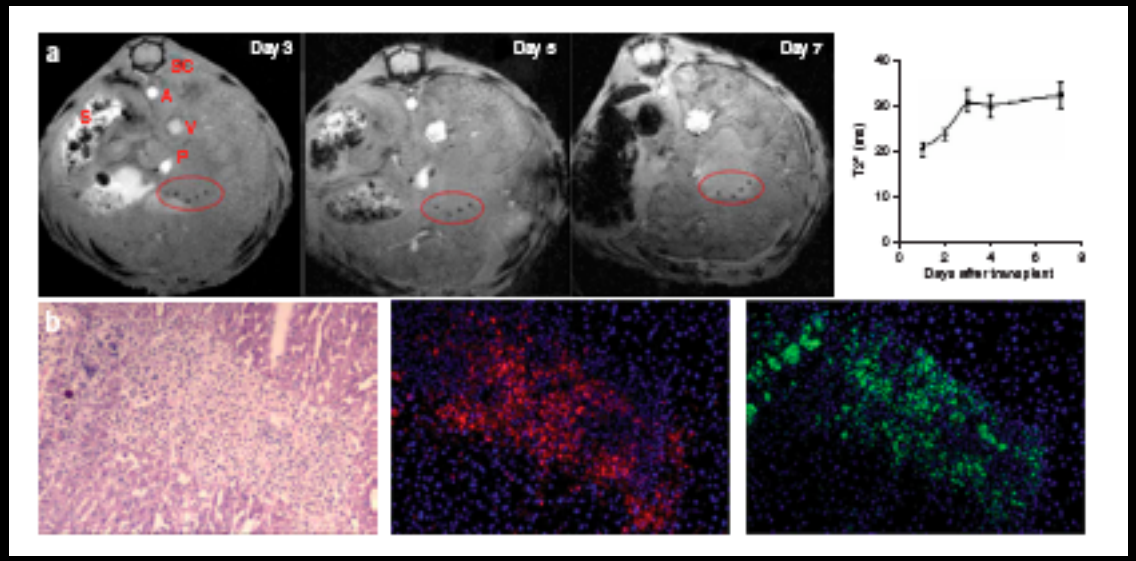
MEDICINE

Transplanting ESCs in humans:
Can we learn from islet transplantation studies?

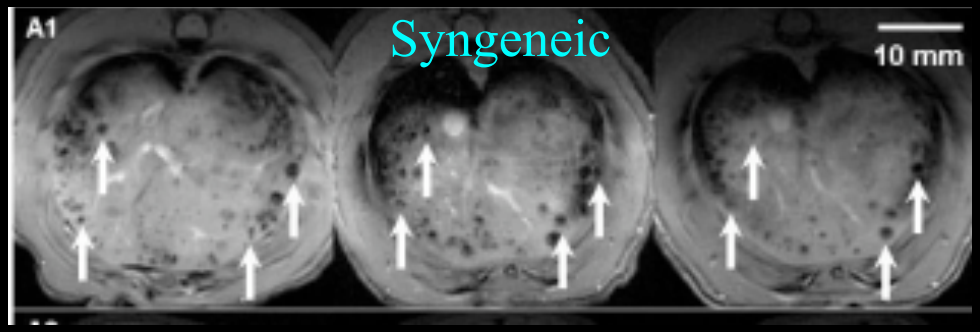
MR Tracking of Pancreatic Islet Cells: Direct SPIO-Labeling of Beta Cells

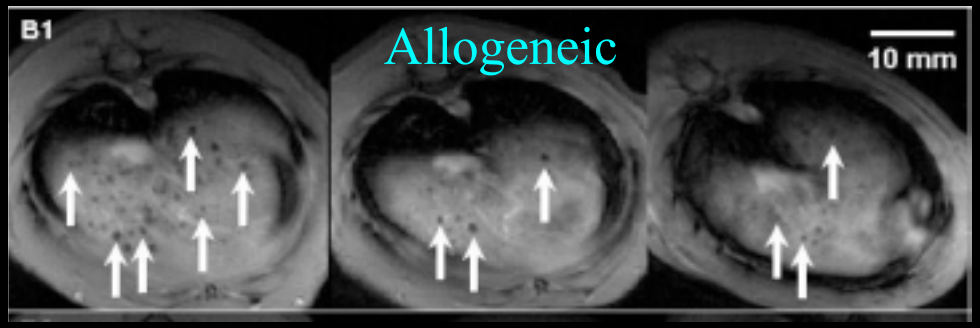


D Jirak, M Hajek et al., MRM 52, 1228-1233 (2004)



NV Evgenov, A Moore et al., Nat. Med. 122, (2006).

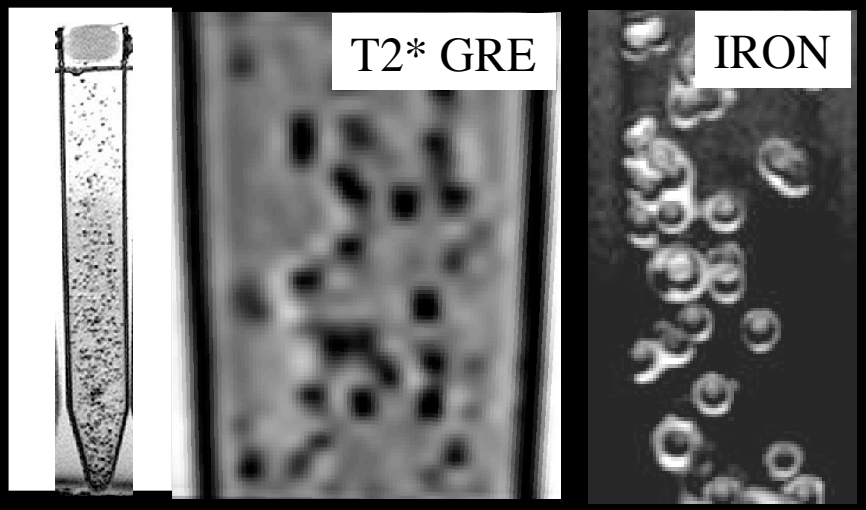




J Kriz, F Saudek et al., Transplantation 80, 1596-1603 (2005).

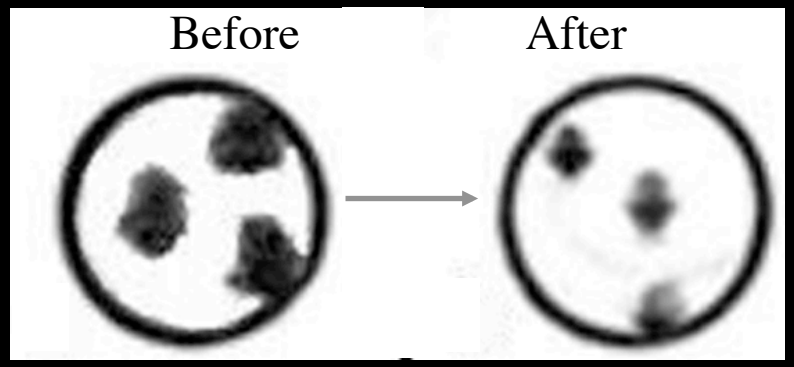
MR Imaging Properties of Magnetocapsules

Single capsule imaging



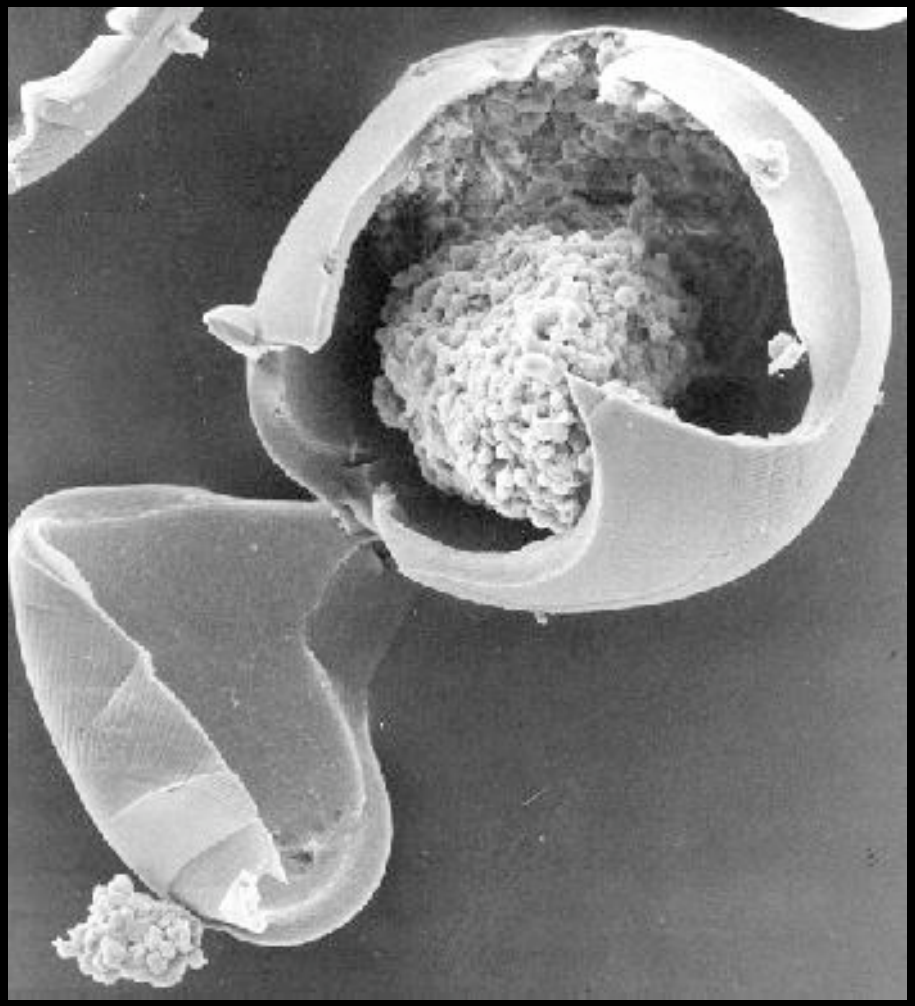
"IRON":
positive contrast
imaging of
capsule surface
M.Stuber et al., MRM 2007

Imaging of capsule rupture



B.P. Barnett, A. Arepally et. al., Nat. Med. 13, 986-991 (2007).

Use of APA Capsules for Immunoprotection of Islet Cells



Courtesy of Ming Chen

MR-Guided Targeted Delivery of MC Human Islets in Swine
(Portal Vein Access from Femoral Vein)

B.P. Barnett, A Arepally et. al., Nat. Med. 13, 986-991 (2007).

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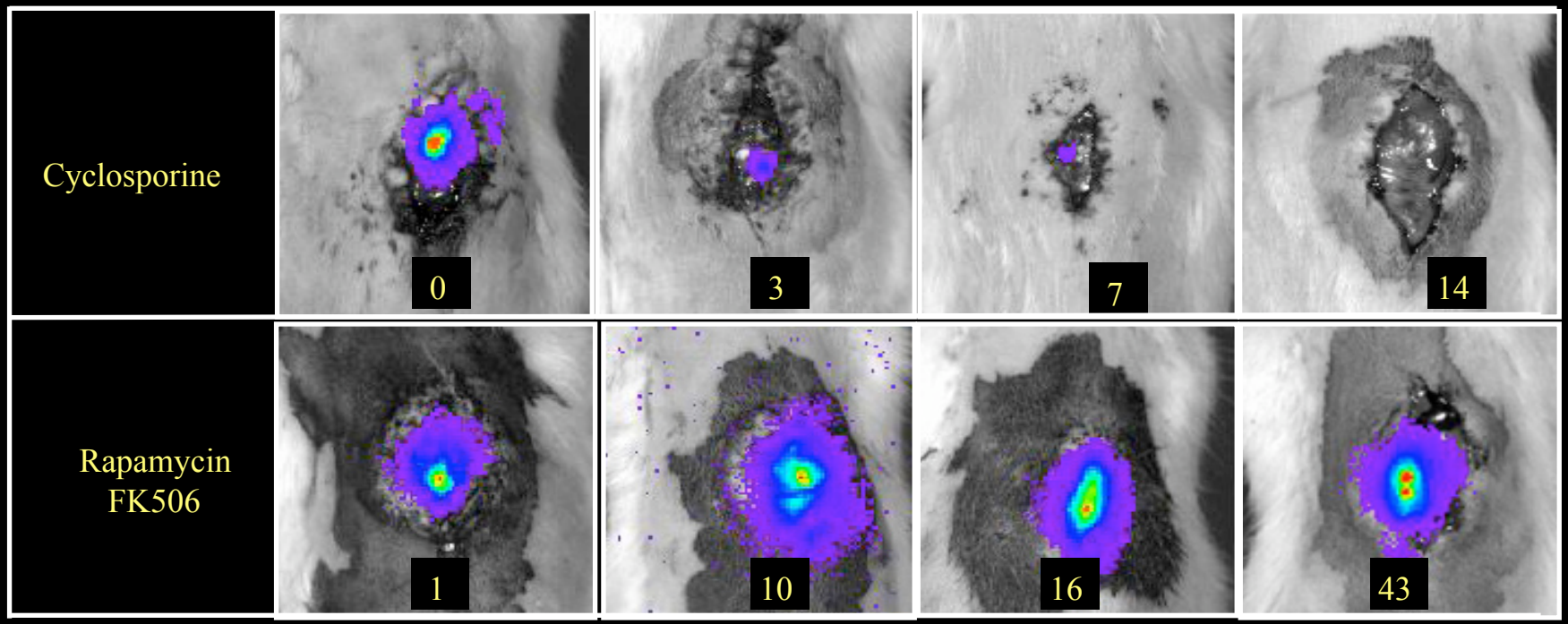
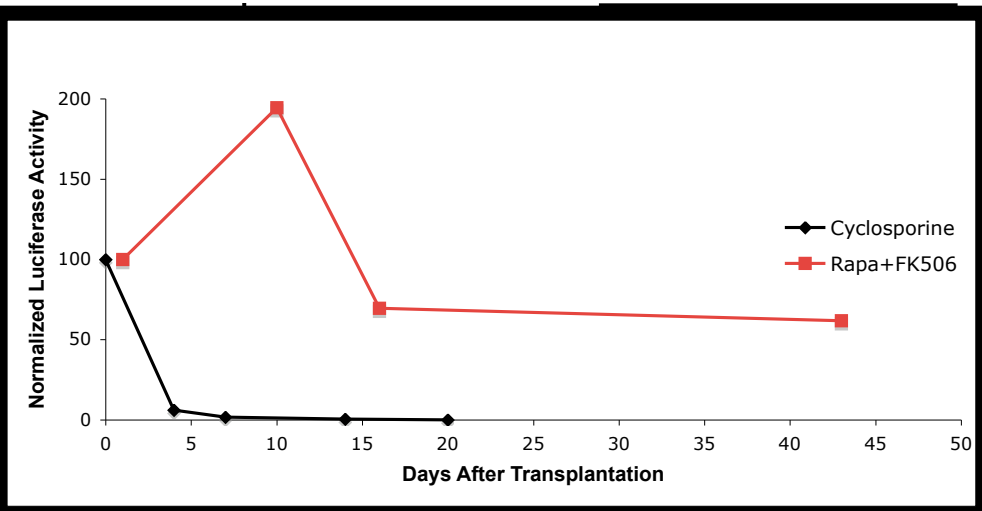
MEDICINE

Tracking cells after administration:
3) What do they become?

→ Need a Reporter Gene

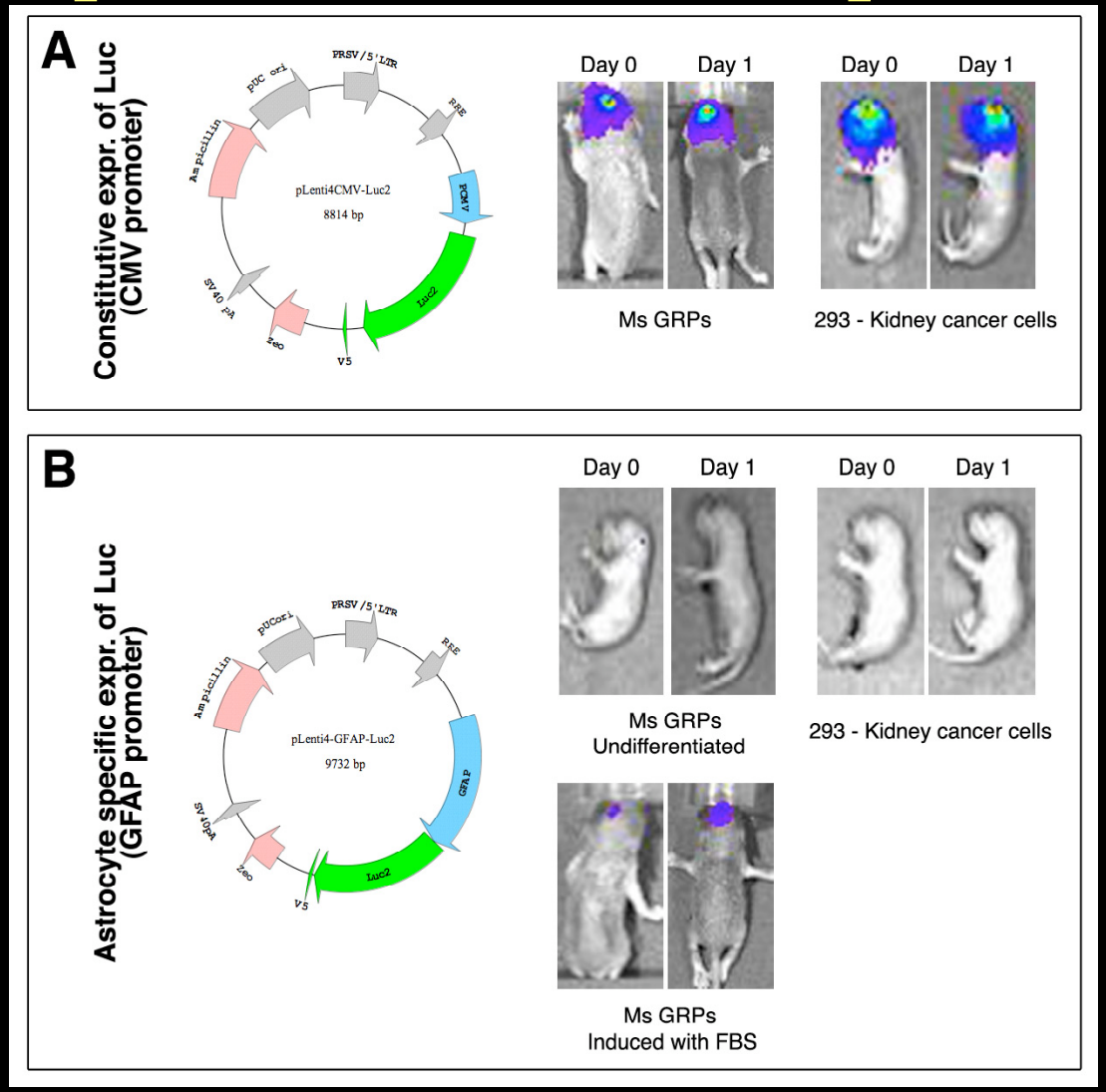
BLI - Monitoring Cell Survival and Determing Optimal Immunosuppressive Regimen





P Walczak et al.
with Doug Kerr

Imaging Cell Differentiation: Placing Reporter Gene under Specific Promotors



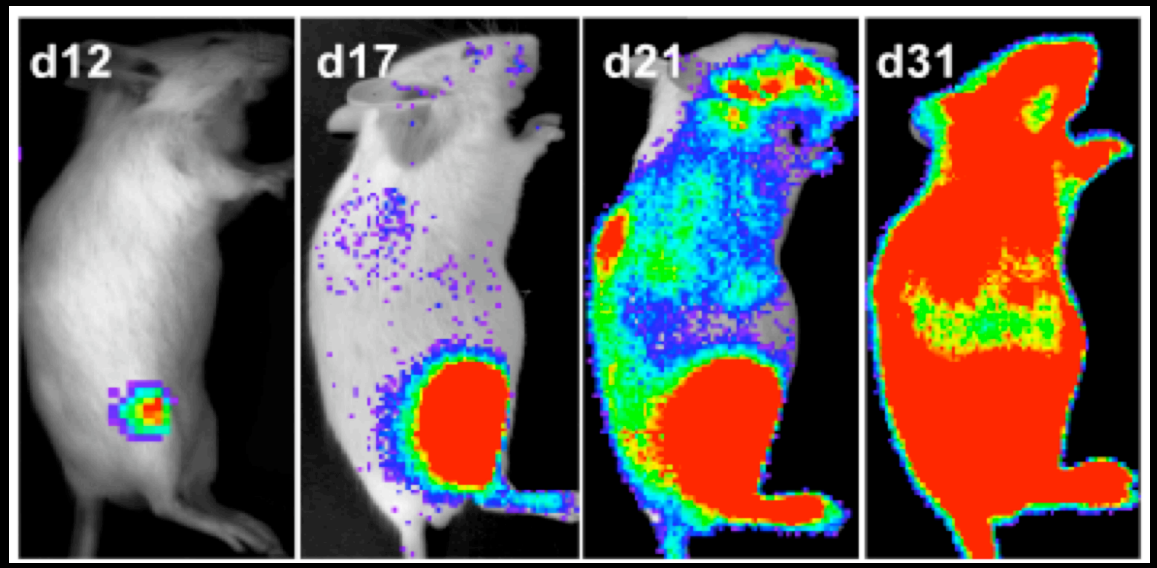
GFAP-Astrocytes

P Walczak et al.

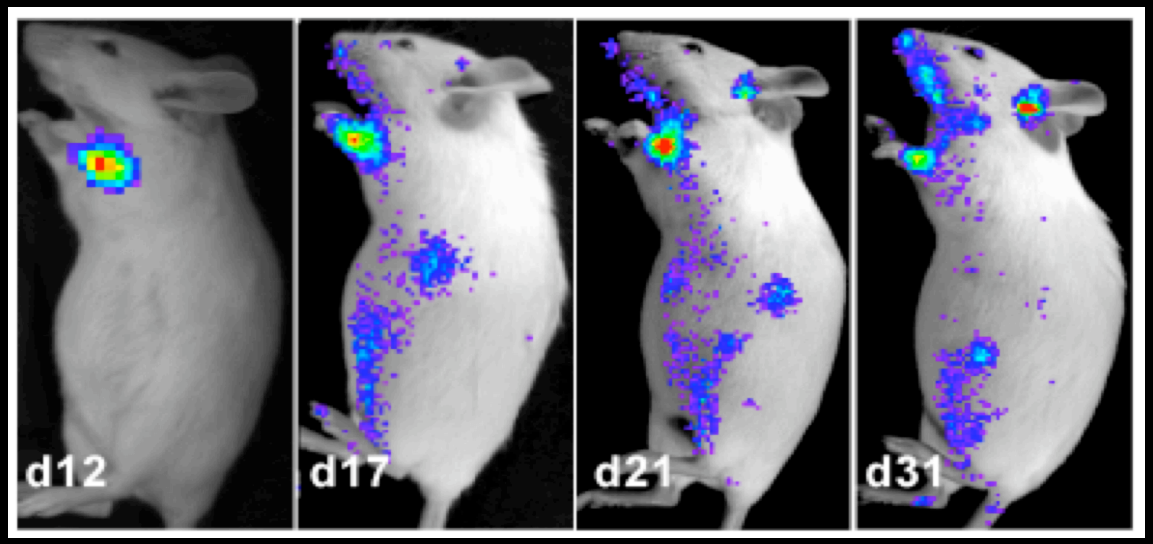
Tissue Regeneration: Visualizing Success and Failure

Rebuilding Tissue from a Single Stem Cell

Success



Failure



Christopher Contag
Stanford University

Cao et al 2004. *PNAS*. 101(1):221-226

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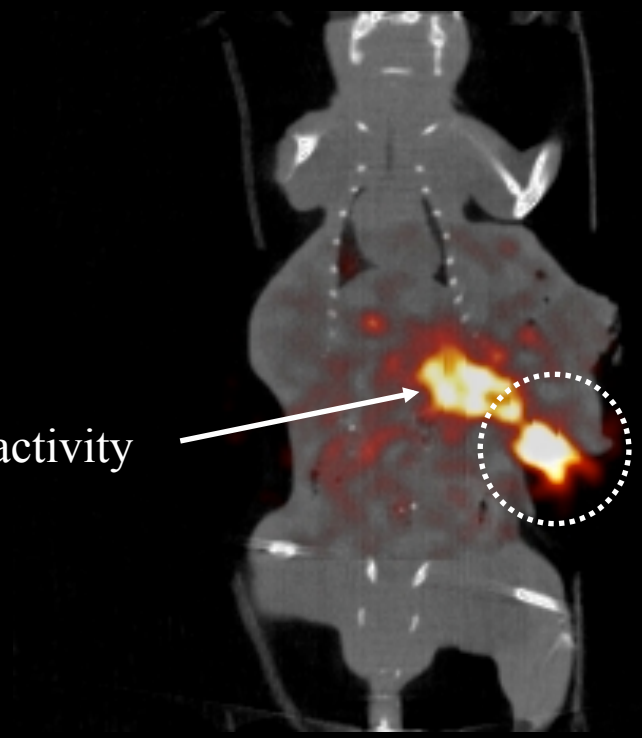
Tracking cells after administration:
4) Do they form teratomas?

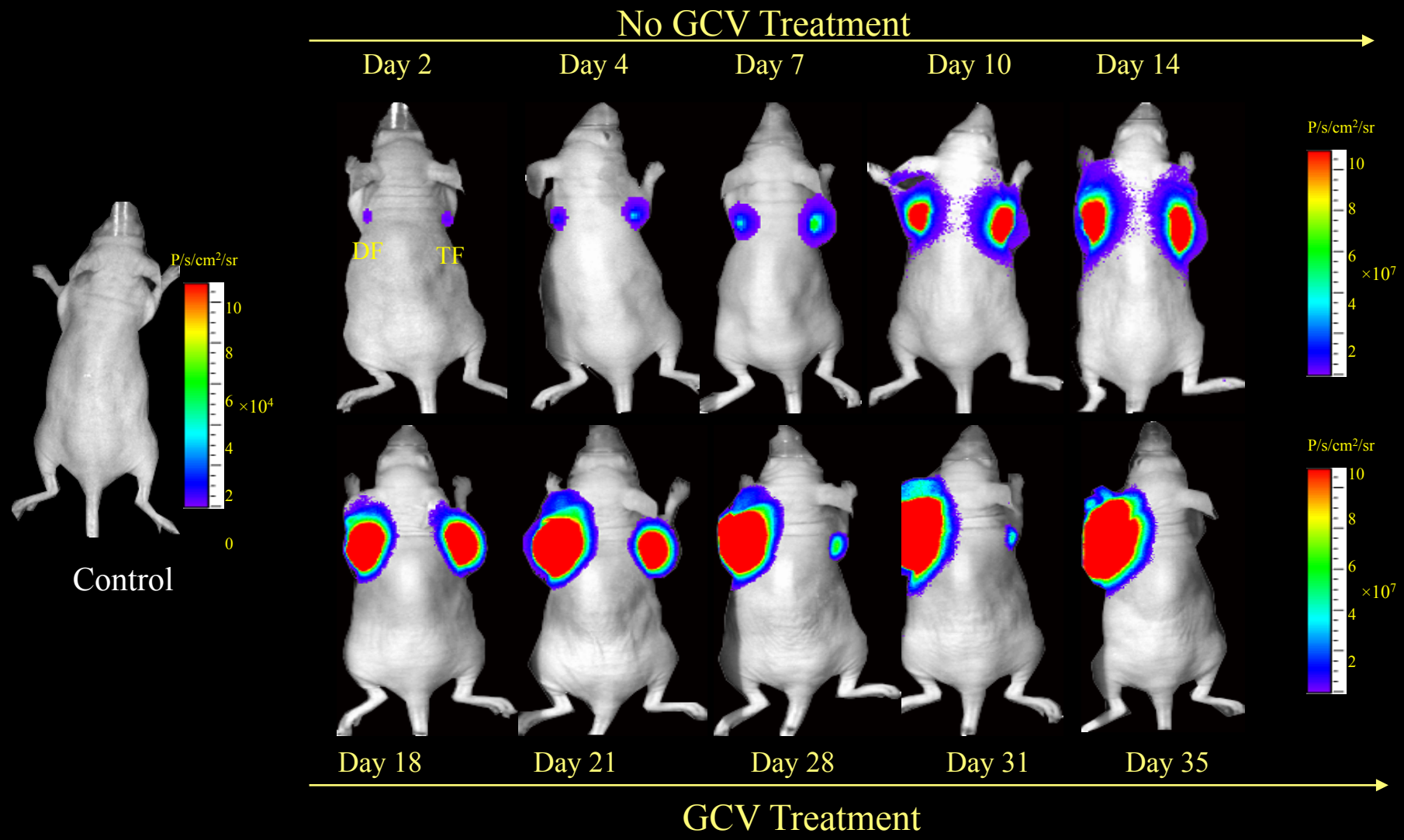
Safety Profiling:
Monitoring of Potential Stem Cell Tumorigenicity
Only need ONE cell for causing trouble

Human embryonic stem cells transfected with
HSV1TK.GFP



Marty G. Pomper,
Linzhao Cheng et al.

Possible Solution: Suicide gene tumor ablation
BLI of murine ES cells



Cao, F. et al. Molecular imaging of embryonic stem cell misbehavior and suicide gene ablation. Cloning and Stem Cells 9, 107–117 (2007).

Possible Solution: Suicide gene tumor ablation
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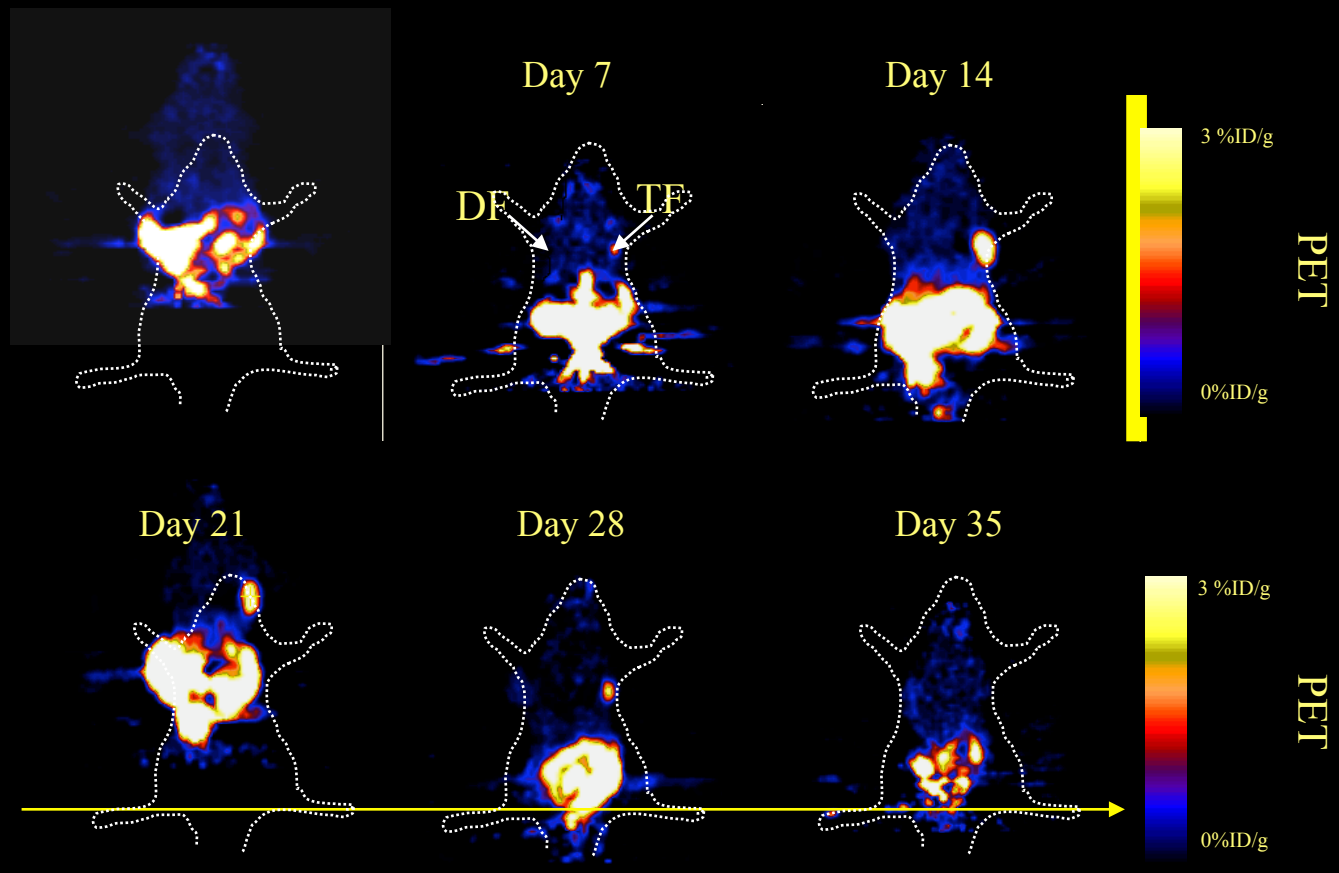
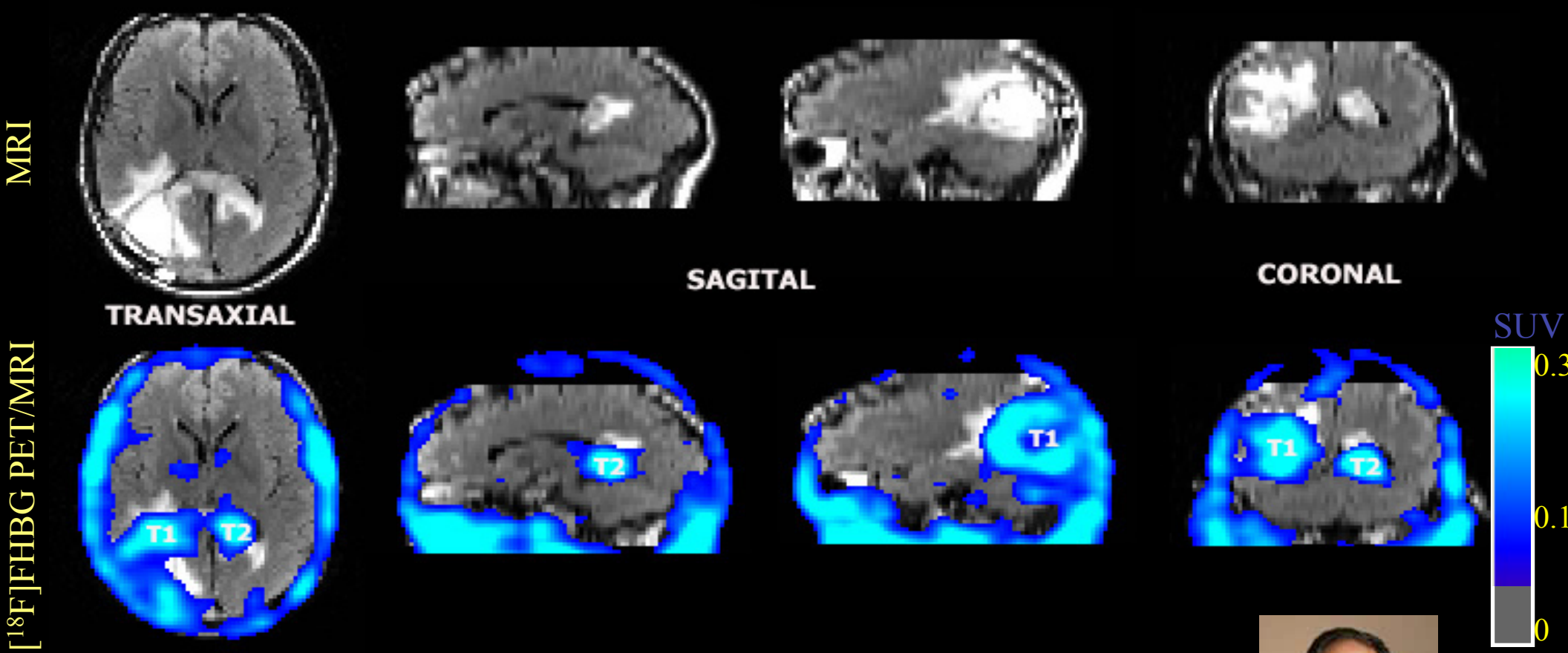


Ganciclovir Treatment start at day 15

Joseph Wu
Stanford

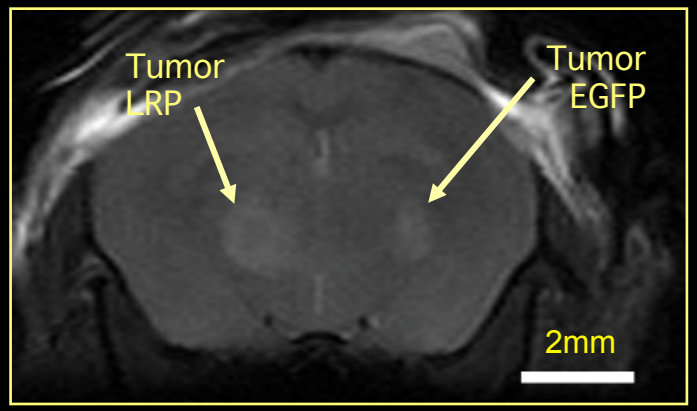
Cao, F. et al. Molecular imaging of embryonic stem cell misbehavior and suicide gene ablation. Cloning and Stem Cells 9, 107–117 (2007).

T Cell Imaging with ^{18}F-FHBG PET in Glioma Patients

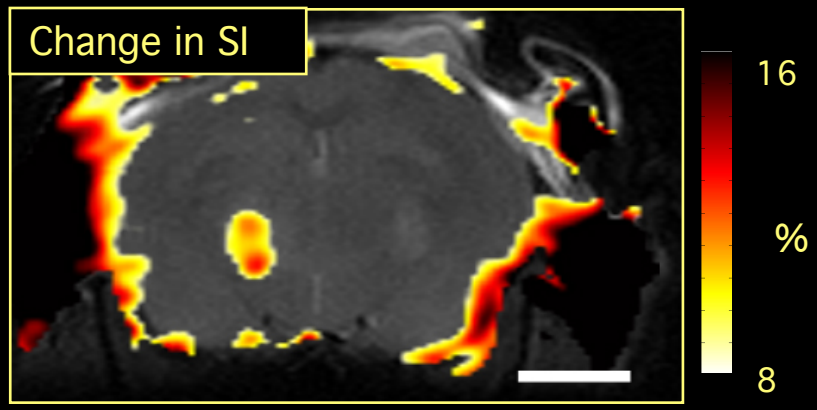


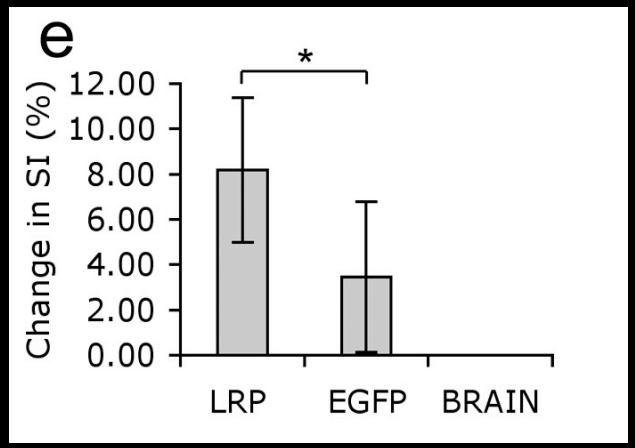
S.S. Gambhir et al.
Stanford University

What is brewing around the corner?
CEST MRI with amide protons: MR artificial reporter gene



CEST





Assaf Gilad

A.A. Gilad et al., Nature Biotechnol. 25, 217-219 (2007).

Summary of Modalities: Pros and Cons

	Clinical Gen/Cells		Resolution	Sensit. n cells	Anatomy	Longevity	Reporter gene	Quant.
Optical	endo	no	+++	?	no	+++	yes	no
NIR	no	no	+	?	no	?	no	no
BLI	no	no	+	10,000	no	+++	yes	~yes
PET	yes	yes	+	50,000	no	+/+/+	yes	~yes
γ-rad	yes	yes	++	?	no	+	~~	YES
^{1}H MRI	yes	yes	++++	1-1000	yes	++	no	~no
^{19}F MRI	no	no	++	7,500	no	++	no	YES
CEST MRI	yes	no	+++	25,000	yes	+++	yes	~yes
X-ray	yes	no	++++	high n	yes	++	no	~yes
US	yes	no	+	1	yes	++	no	~yes

Jeff W.M. Bulte, Johns Hopkins University

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Special Cells, Special Considerations: The Challenges of Bringing Embryonic Stem Cells From the Laboratory to the Clinic

RC Addis[1,2], JWM Bulte[3,4,5] and JD Gearhart[1,2,6]

Clin Ther Exp 83, 386-389 (2008).

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Conclusions

- With iron oxide-labeled cells and local engraftment, the use of MR-compatible catheters allows MR-guided real-time targeted injection of therapeutic cells, allowing accurate cell delivery and its verification (i.e. in myocardial infarct, spinal cord injury, specific brain structures -putamen, etc.)

- After succesful injection or grafting, reporter genes are needed to serve as a beacon for cell survival, uncontrolled cell proliferation (tumor/teratoma), as well as cell differentiation

Conclusions

•Different modalities have different strengths. Combining available techniques? I.e. SPIO-labeled cells transfected with HSV.tk, MRI/PET, ^{19}F MRI/^{1}H MRI, PET/CT, SPECT/CT, etc

•(Interventional) Radiology and Nuclear Medicine will play a key role in bringing hESC-based therapy from pre-clinical to clinical

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