

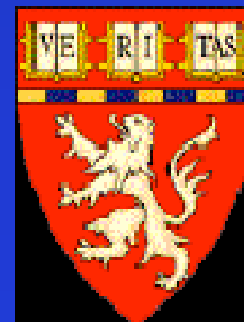
In vivo multimodal imaging of transplanted islets

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Why do we want to image transplanted islets?

- **Difficult to image endogenous islets**
 - Lack of knowledge about specific beta-cell surface markers
 - Nonexistent target-specific agents
- **Easy to label exogenous islets**
- **In vivo imaging as a way to monitor transplantation efficiency and graft survival**

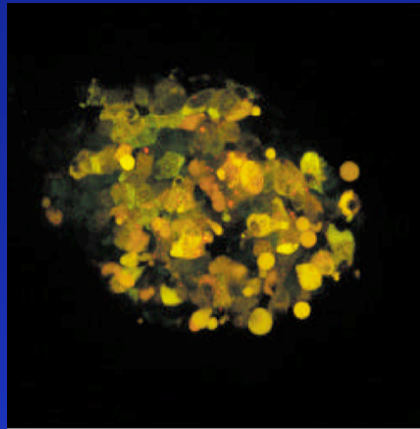
Table 1 | Overview of high-resolution, small-animal imaging systems

Technique	Resolution	Depth	Time	Imaging agents	Target*	Cost‡	Primary small-animal use	Clinical use
MR	10–100 μ m	No limit	Minutes–hours	Gadolinium, dysprosium, iron oxide particles	A, P, M	\$\$\$	Versatile imaging modality with high soft-tissue contrast	Yes
CT	50 μ m	No limit	Minutes	Iodine	A, P	\$\$	Lung and bone imaging	Yes
Ultrasound	50 μ m	Millimetres	Minutes	Microbubbles	A, P	\$\$	Vascular and interventional imaging	Yes
PET	1–2 mm	No limit	Minutes	^{18}F , ^{11}C , ^{15}O	P, M	\$\$\$	Versatile imaging modality with many different tracers	Yes
SPECT	1–2 mm	No limit	Minutes	$^{99\text{m}}\text{Tc}$, ^{111}In chelates	P, M	\$\$	Commonly used to image labelled antibodies, peptides and so on	Yes
FRI	2–3 mm	<1 cm	Seconds–minutes	Photoproteins (GFP), NIR fluorochromes	P, M	\$	Rapid screening of molecular events in surface-based tumours	Development
FMT	1 mm	<10 cm	Seconds–minutes	NIR fluorochromes	P, M	\$\$	Quantitative imaging of targeted or 'smart' fluorochrome reporters in deep tumours	Development
BLI	Several millimetres	Centimetres	Minutes	Luciferins	M	\$\$	Gene expression, cell and bacterial tracking	No
Intravital microscopy (confocal, multiphoton)	1 μ m	<400 μ m	Seconds–minutes	Photoproteins (GFP), Fluorochromes	P, M	\$\$\$	All of the above at higher resolutions but at limited depths and coverage	Limited development (skin)

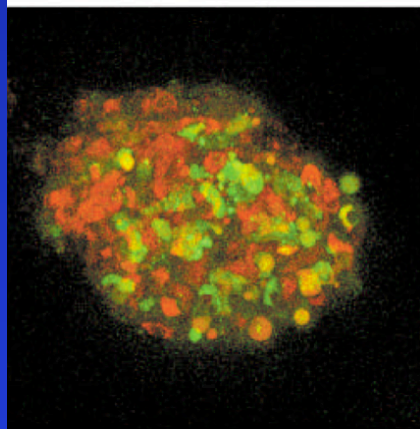
*Primary area that a given imaging modality interrogates: A, anatomical; M, molecular; P, physiological. ‡Cost of system: \$ <100,000; \$\$ 100–300,000; \$\$\$ >300,000. BLI, bioluminescence imaging; CT, X-ray computed tomography; FMT, fluorescence-mediated molecular tomography; FRI, fluorescence reflectance imaging; GFP, green fluorescent protein; NIR, near-infrared; MR, magnetic resonance; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Massoud and Gambhir, 2003

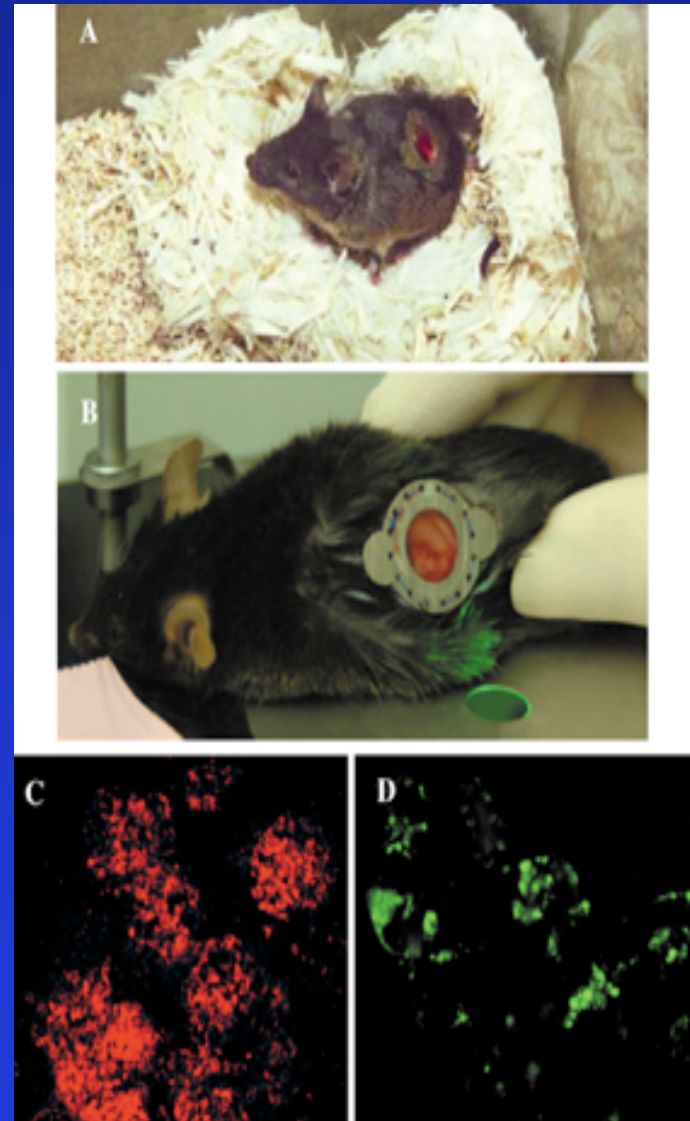
Body window-enabled imaging of transplanted islets expressing an insulin-Timer fusion protein



Ins-C-Timer
islet



Same islet after
24h exposure to
IL-1 β



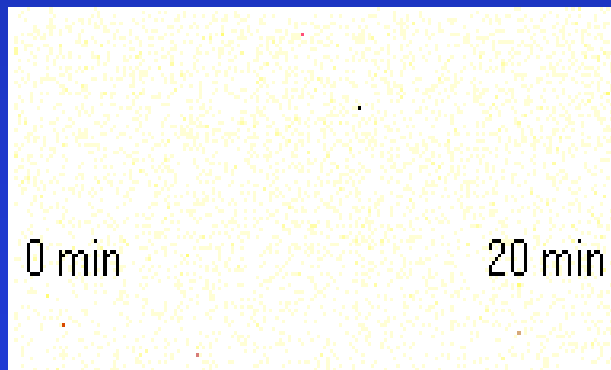
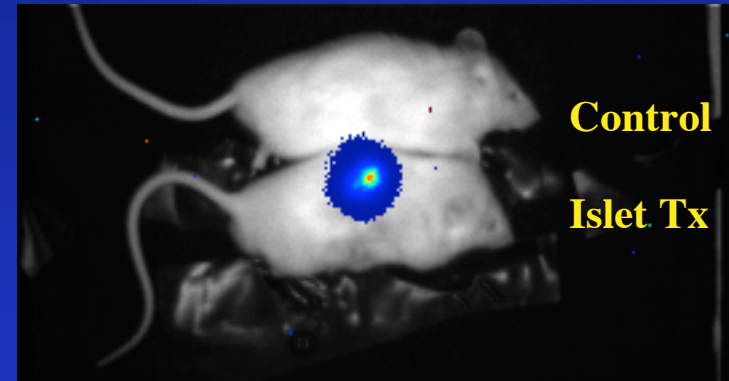
Bertera S et al, BioTechniques,
2003, 35:718-722

In-vivo bioluminescence imaging of transplanted human islets

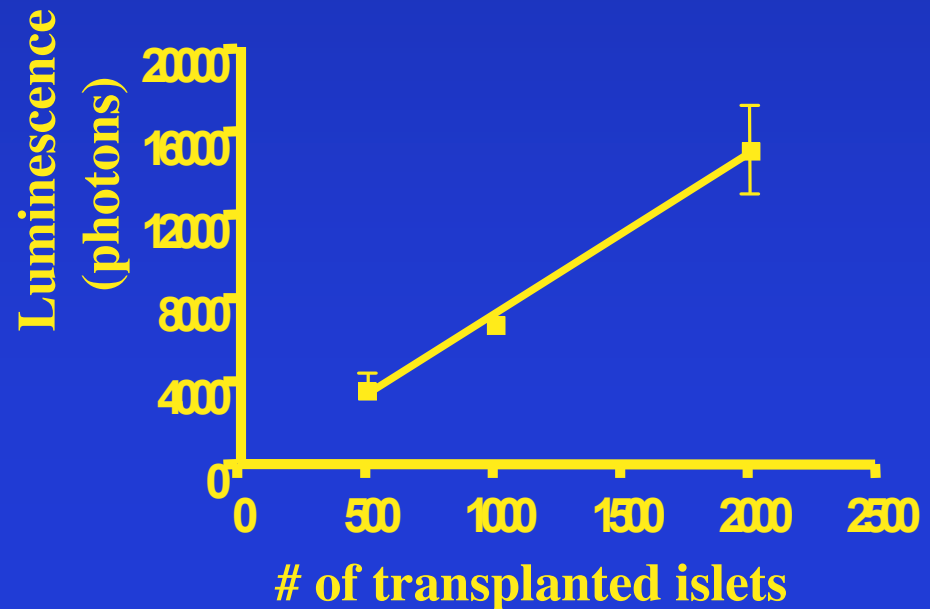
Light field photo



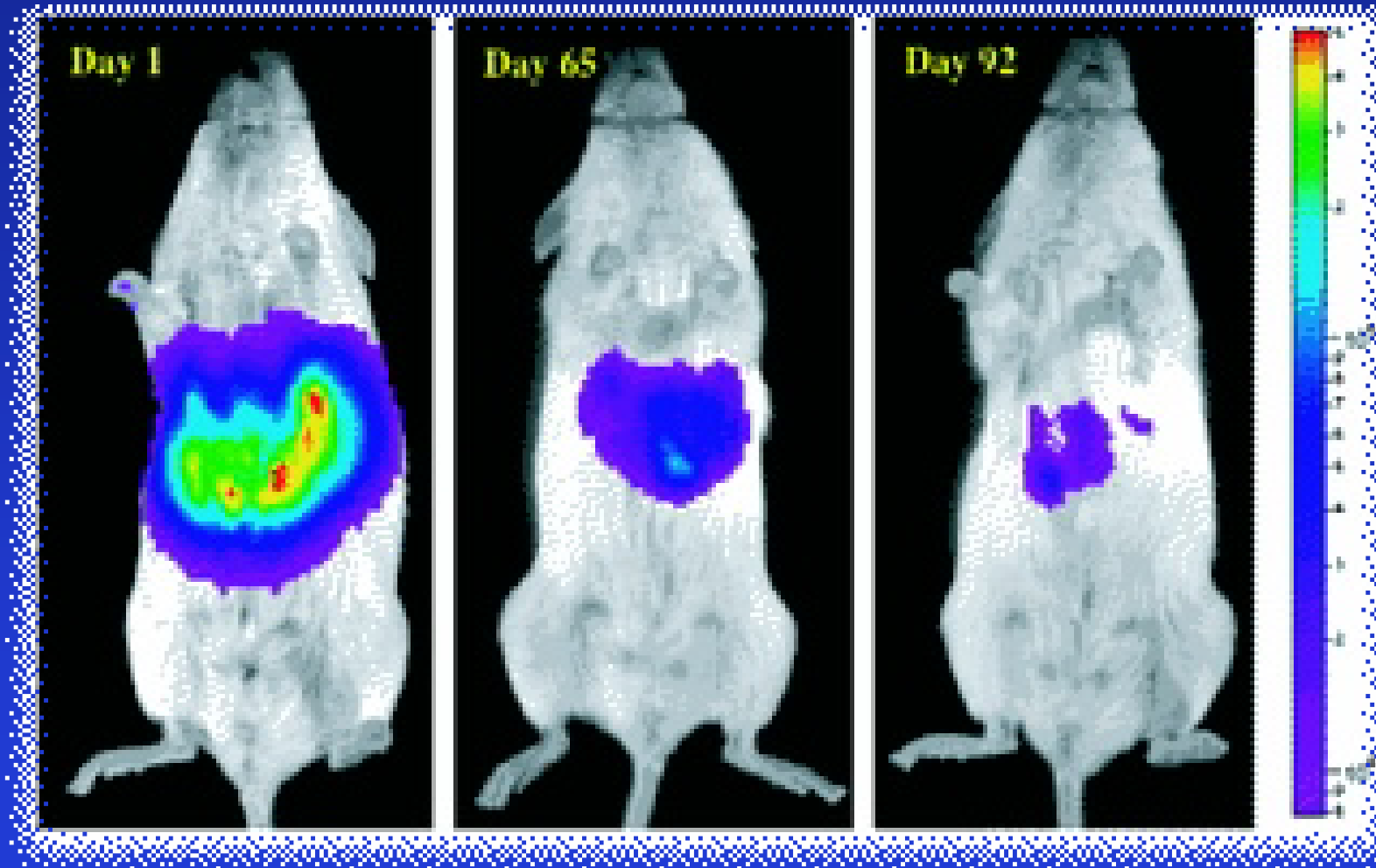
Superimposed images



CCD imaging



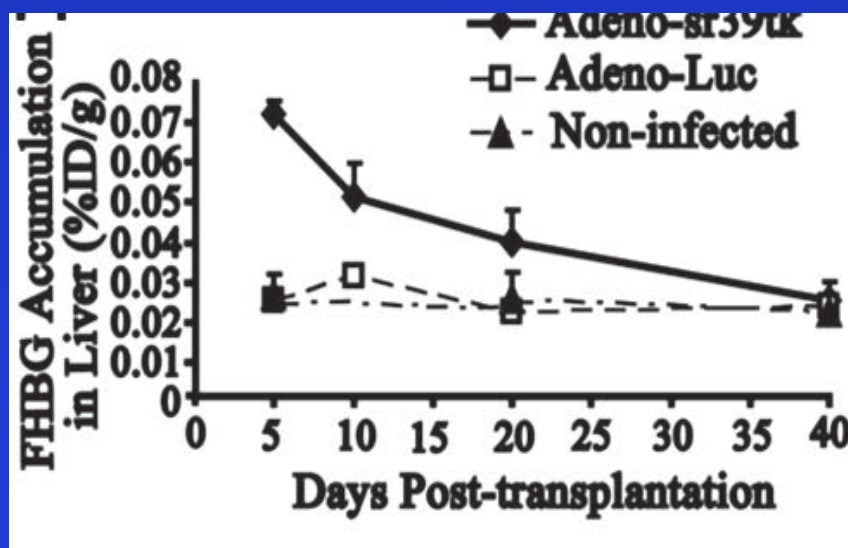
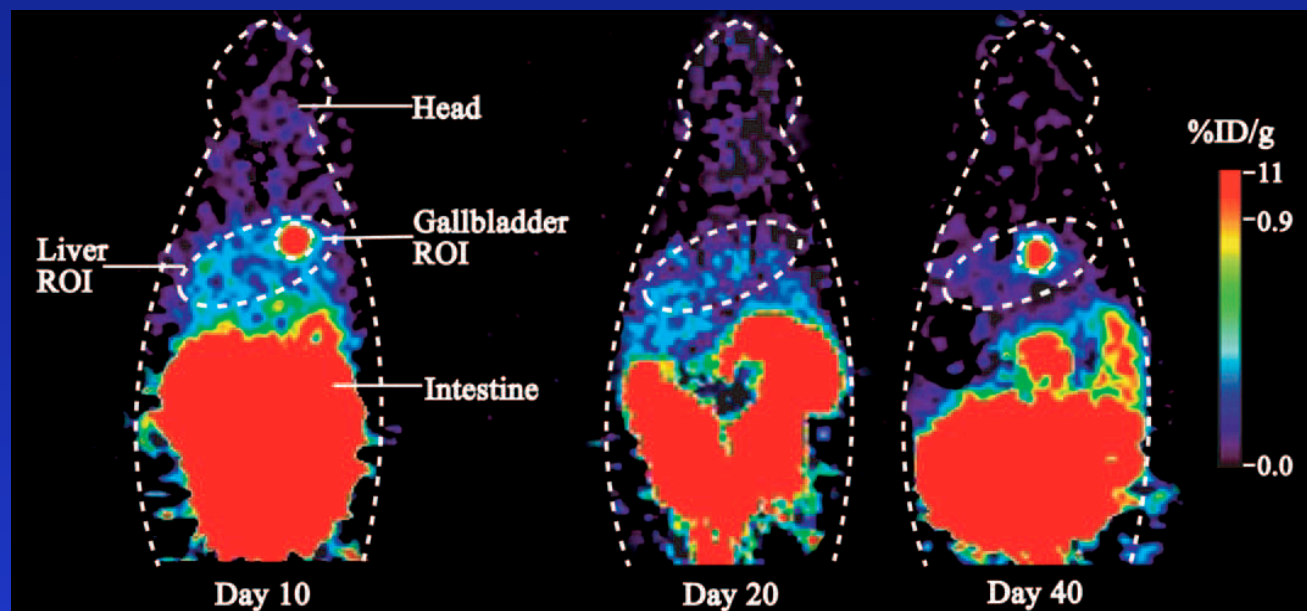
Longitudinal BLI of transplanted islets



Cao YA et al, *Transplantation*, 2005, 80:134

PET imaging of islet grafts

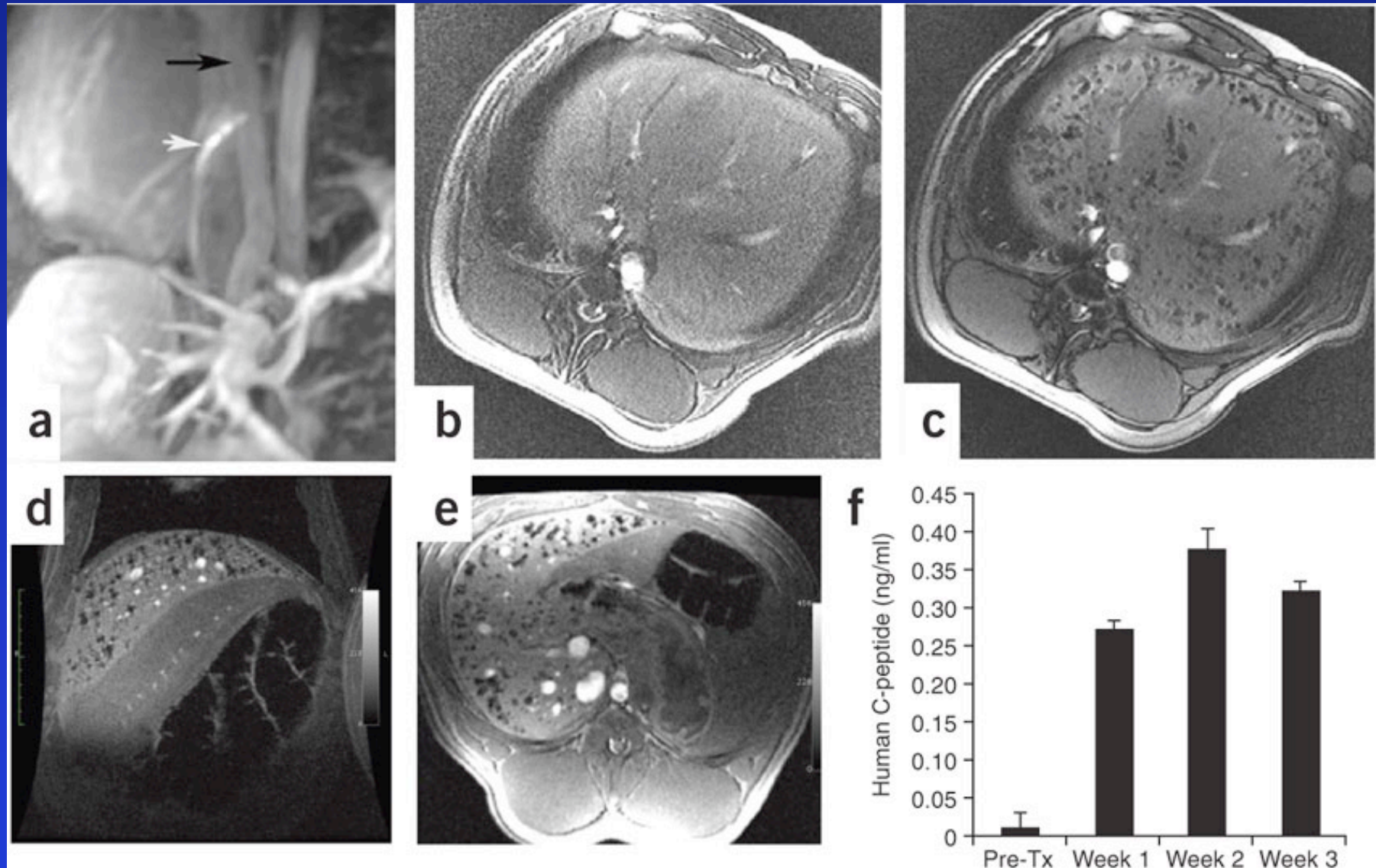
Islets express *Adeno-sr39tk* and probed with [^{18}F]FHBG



Problems???

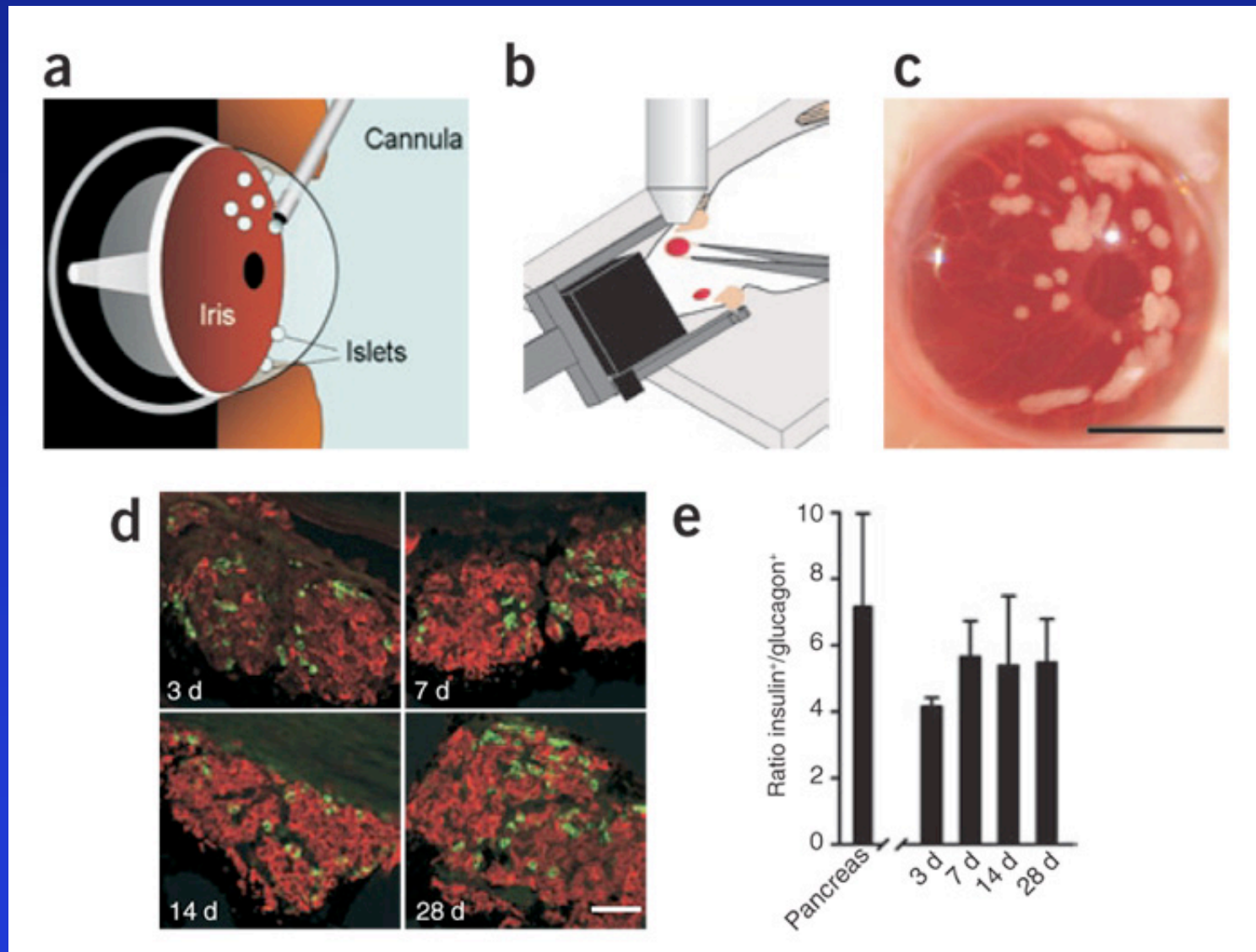
Lu Y et al, *PNAS*, 2006, 103:11294

MRI of encapsulated transplanted islets



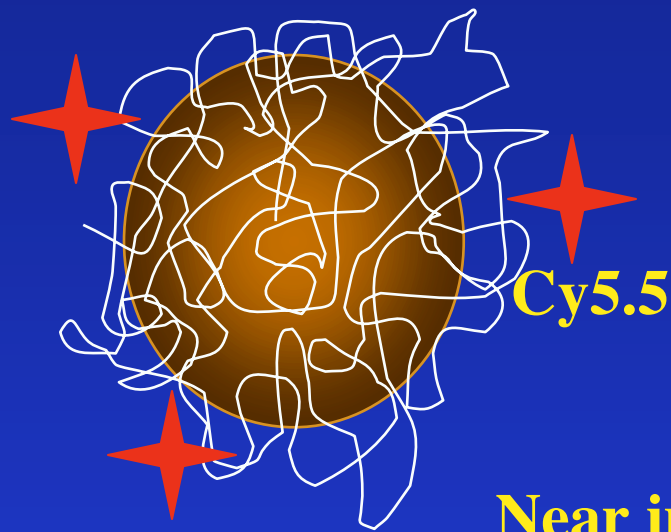
Barnett B et al, *Nat Med*, 2007, 13:986-991

Imaging of islets transplanted into the anterior chamber of the eye.



Speier et al, *Nat Med*, 2008, 14:574

Magnetic nanoparticles-Cy5.5 for islets labeling (MN-Cy5.5)



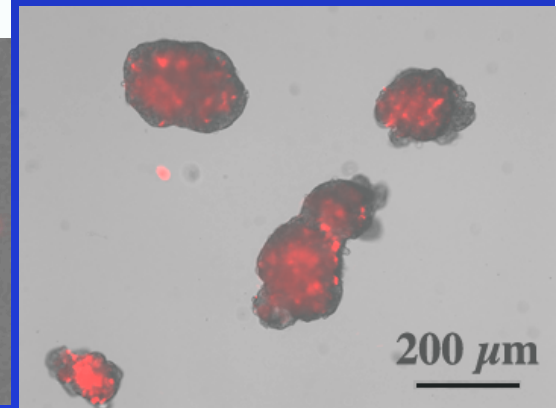
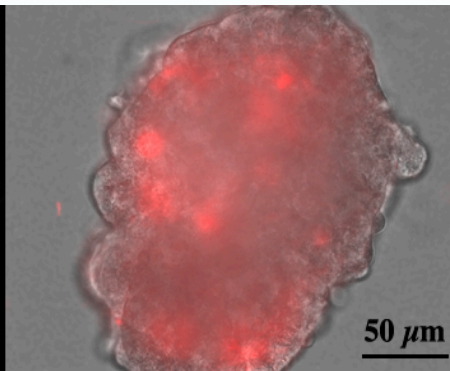
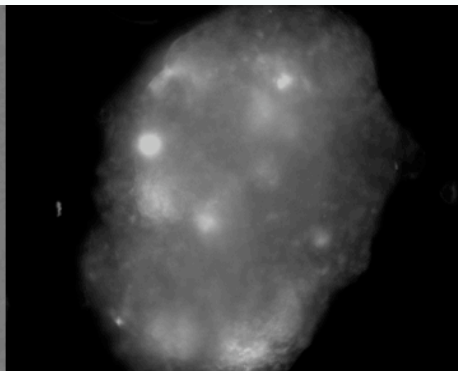
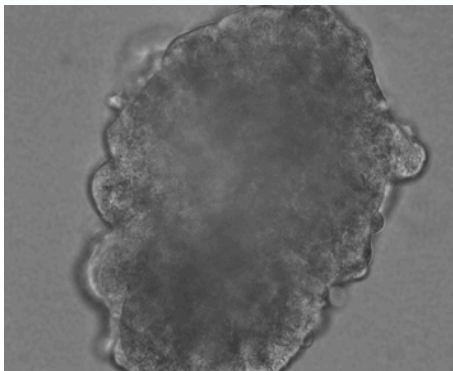
MR imaging

Near infrared fluorescence imaging (NIRF)

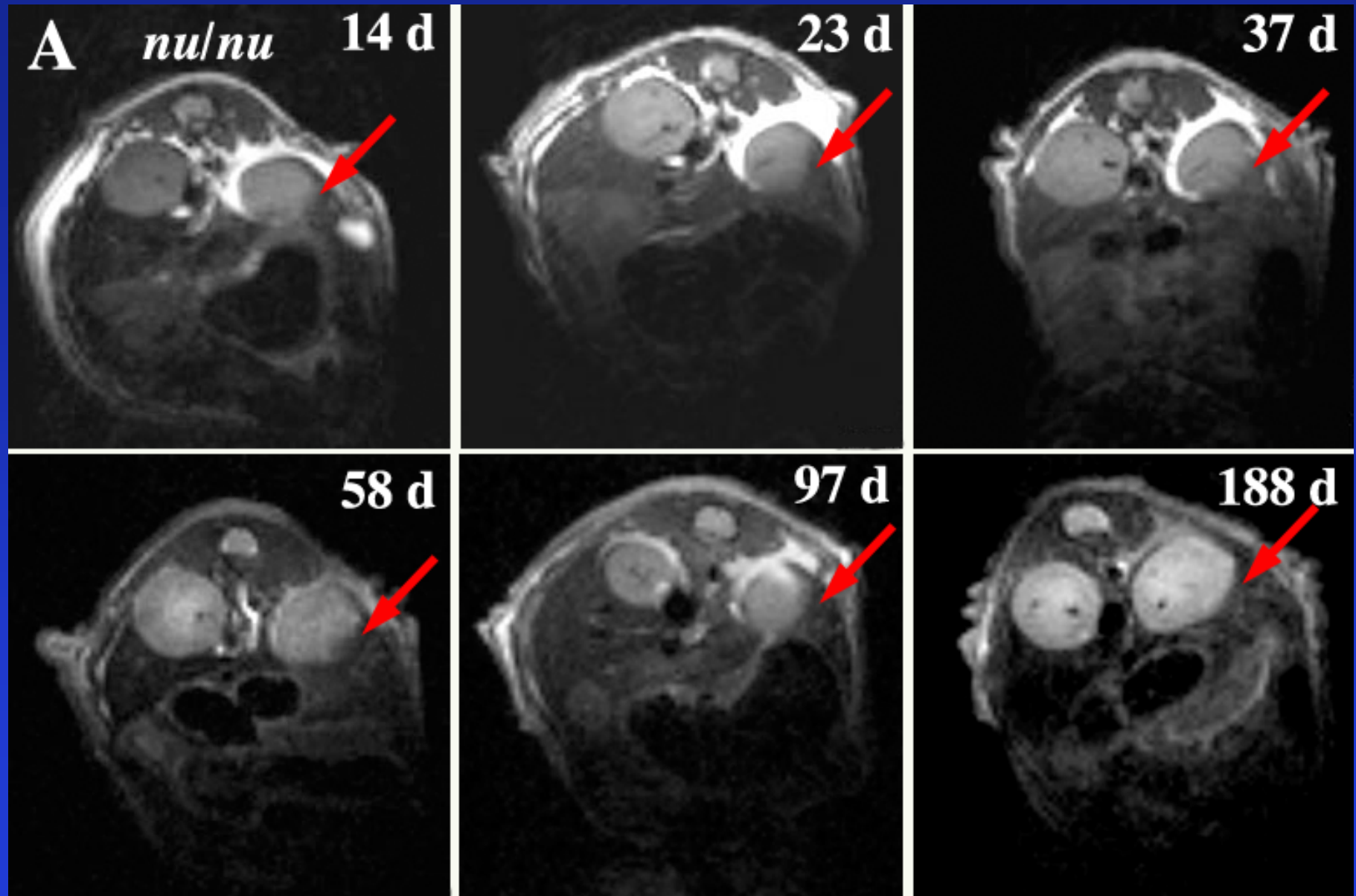
bright light

NIRF

overlay NIRF+bright

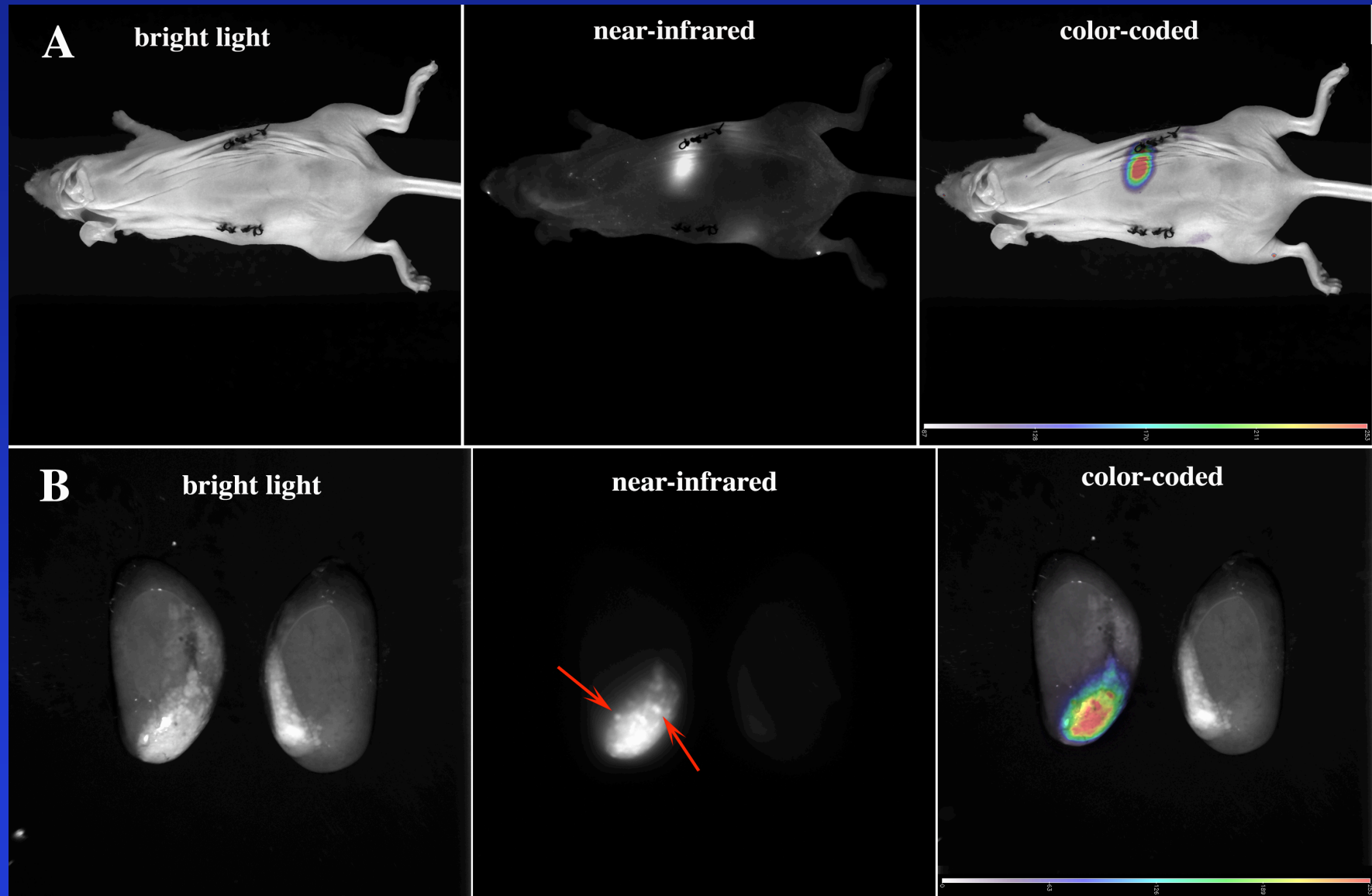


Feasibility MR imaging (4.7T)



Evgenov N., et al. In vivo imaging of islet transplantation. *Nature Medicine*, 2006, 12:144-148

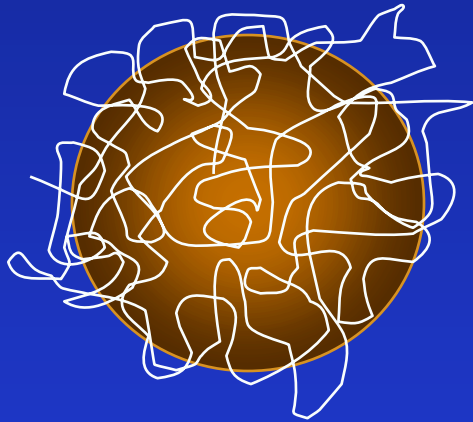
Optical imaging of transplanted islets



Evgenov N., et al. In vivo imaging of islet transplantation. *Nature Medicine*, 2006, 12:144-148

In order to go to clinical trials:

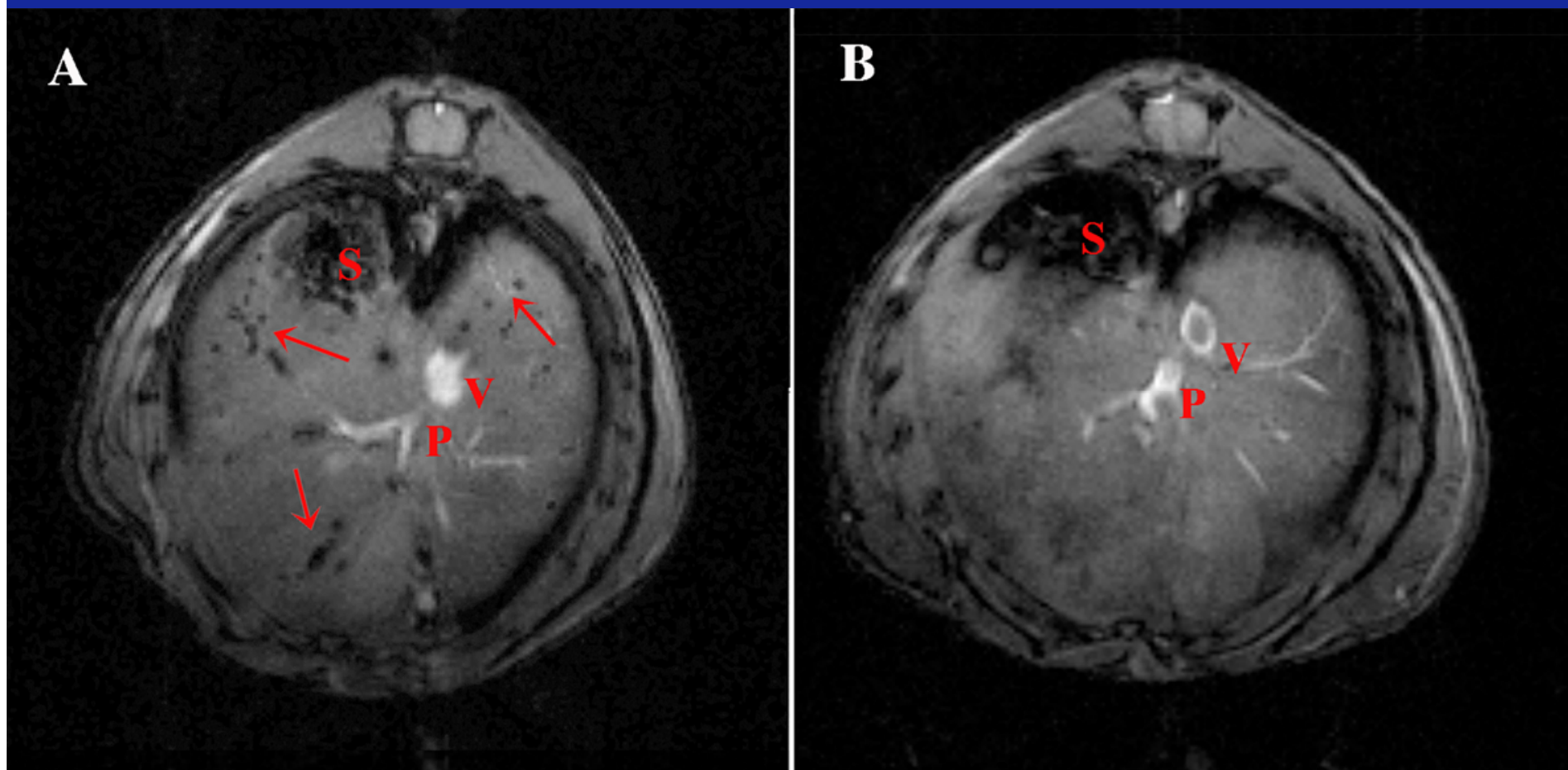
**1. Apply commercially available,
FDA-approved contrast agent**



Feridex®

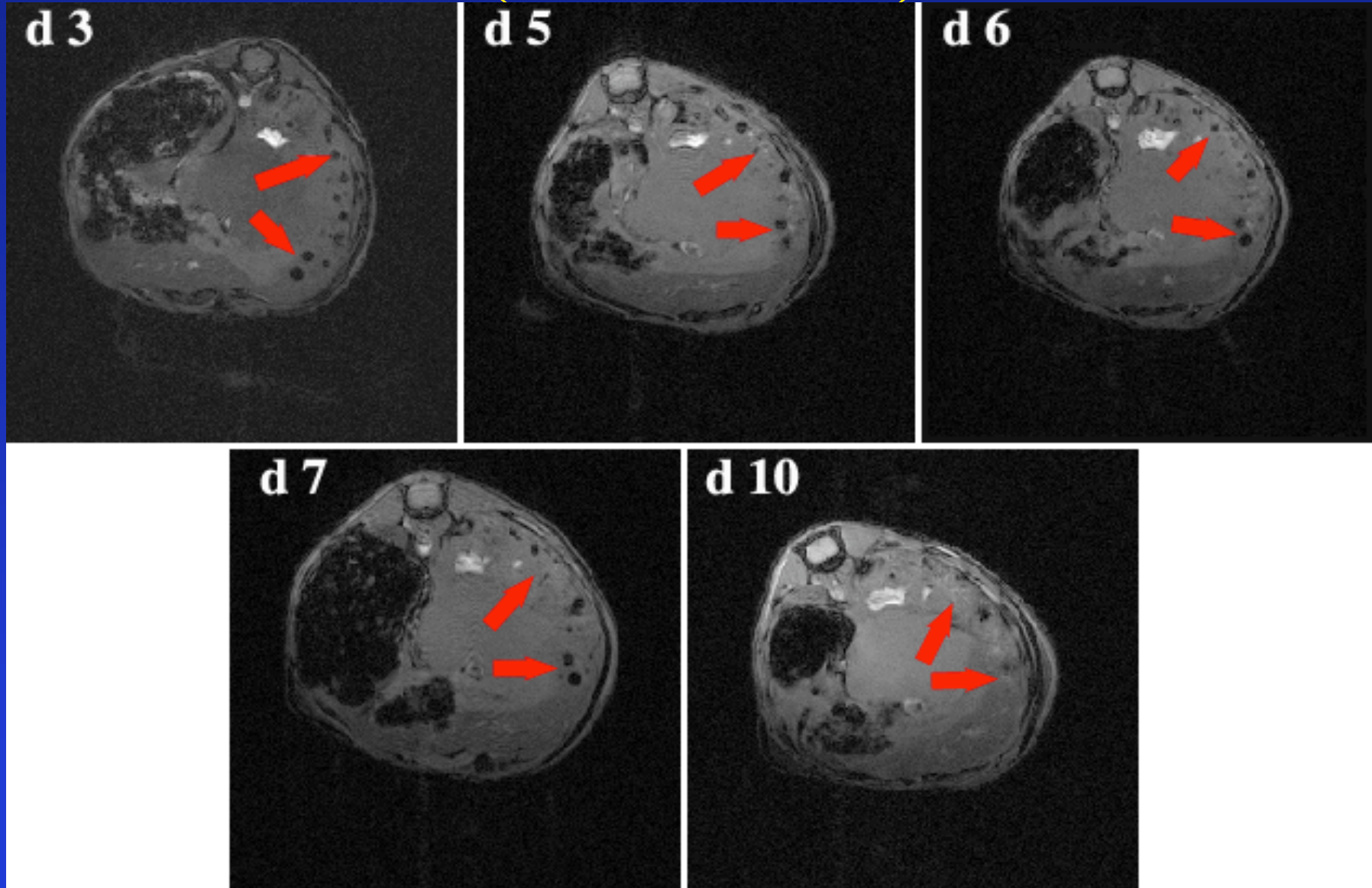
**2. Apply clinically-relevant intrahepatic model
of islet transplantation**

MRI of intrahepatic transplantation of islets labeled with FERIDEX®



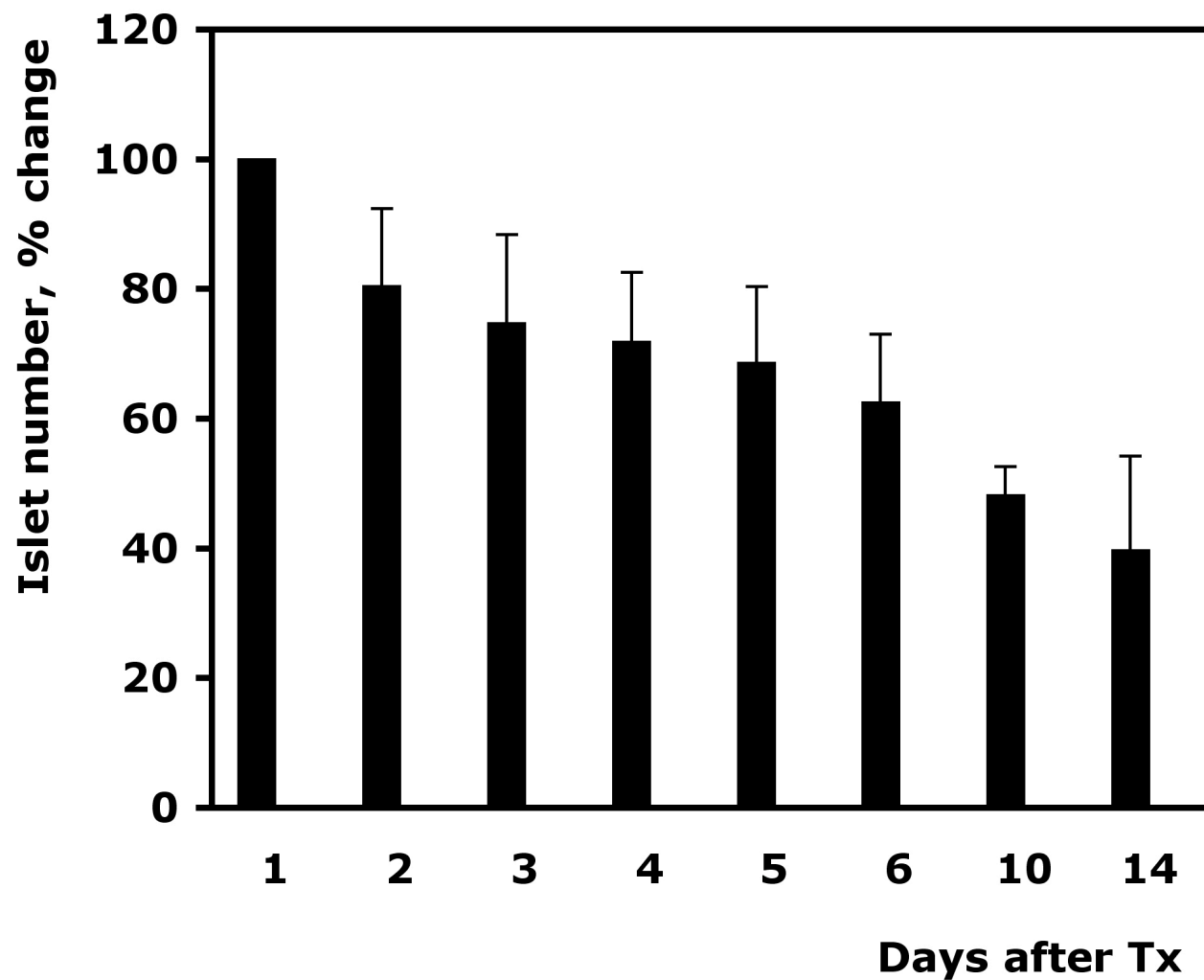
Evgenov N et al, *Diabetes*, 2006, 55:2419-2418.

MRI of intrahepatic transplantation (FERIDEX®)



Evgenov N et al, *Diabetes*, 2006, 55:2419-2418.

Quantitation of islet loss



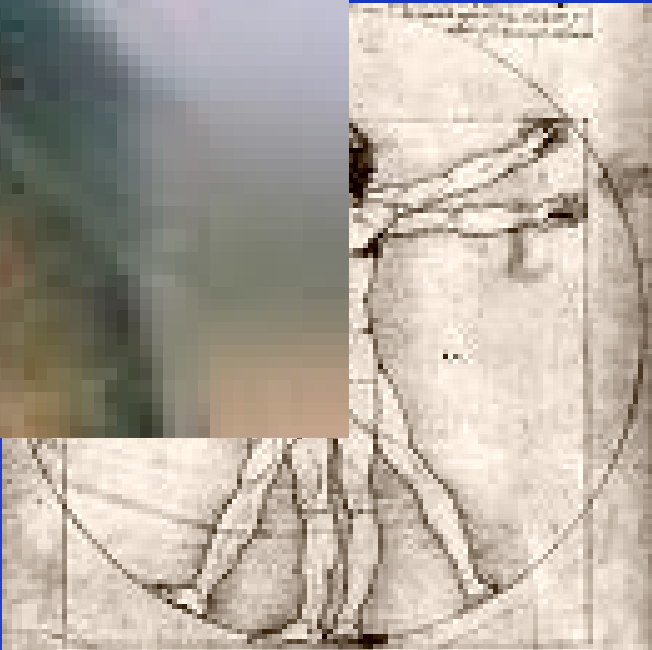
Evgenov N et al, *Diabetes*, 2006, 55:2419-2418.

Challenges for translation: from mice to man (from 4.7T to 1.5T)



PROBLEMS:

- Signal-to-noise ratio (SNR)
- Magnetic susceptibility
- Resolution (50x50x50 μm vs. 1x1x1 mm)
- Field of view
- Clinical grade coils
- Data analysis



Summary

- **Safe and effective way of islet labeling with superparamagnetic iron oxide nanoparticles**
- **Long-term monitoring by in vivo imaging**
- **Validation in non-human primate model**
- **Future: Clinical trials**

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