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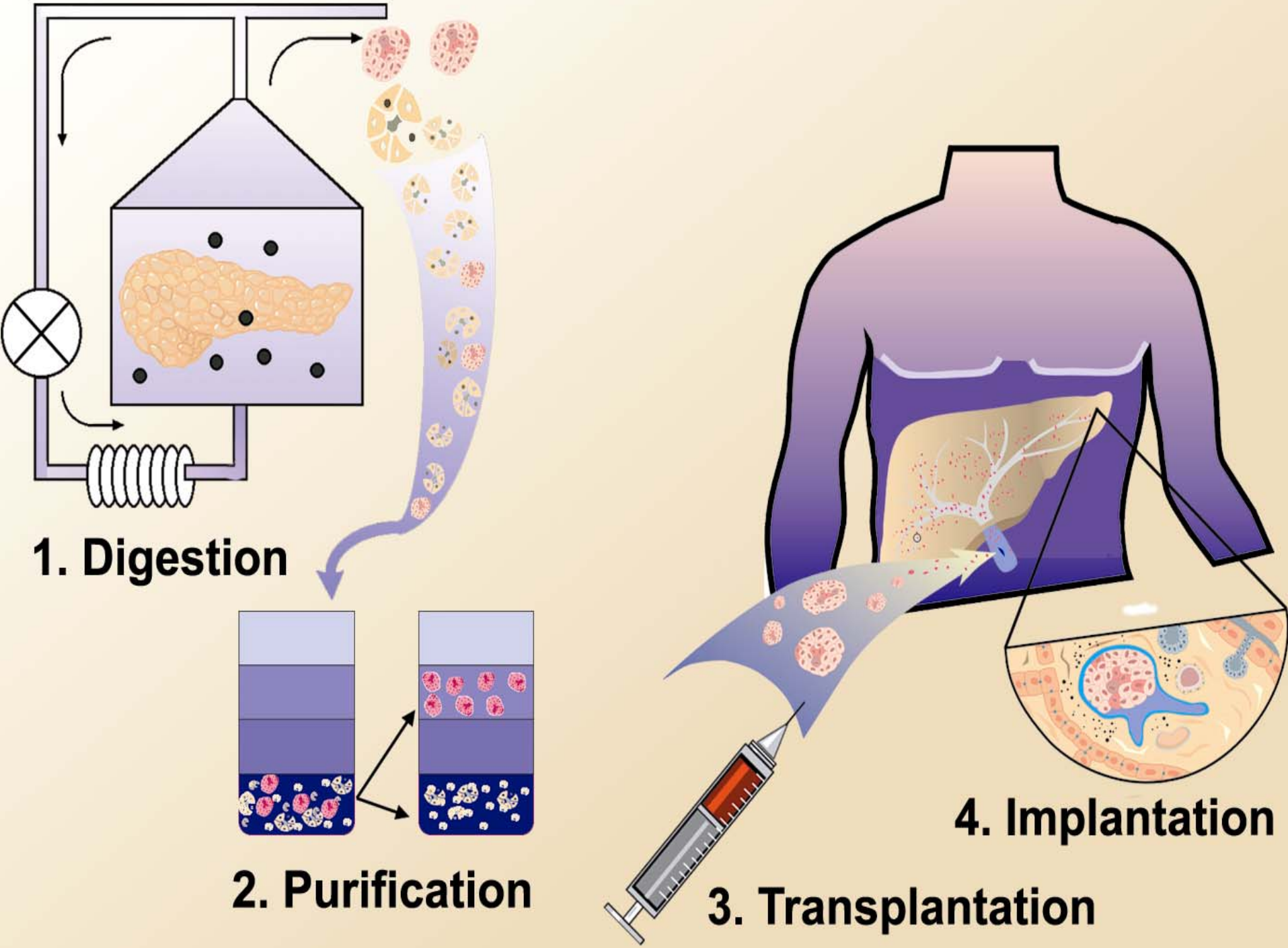
Clinical magnetic resonance imaging of islet grafts using nanoparticle labeling

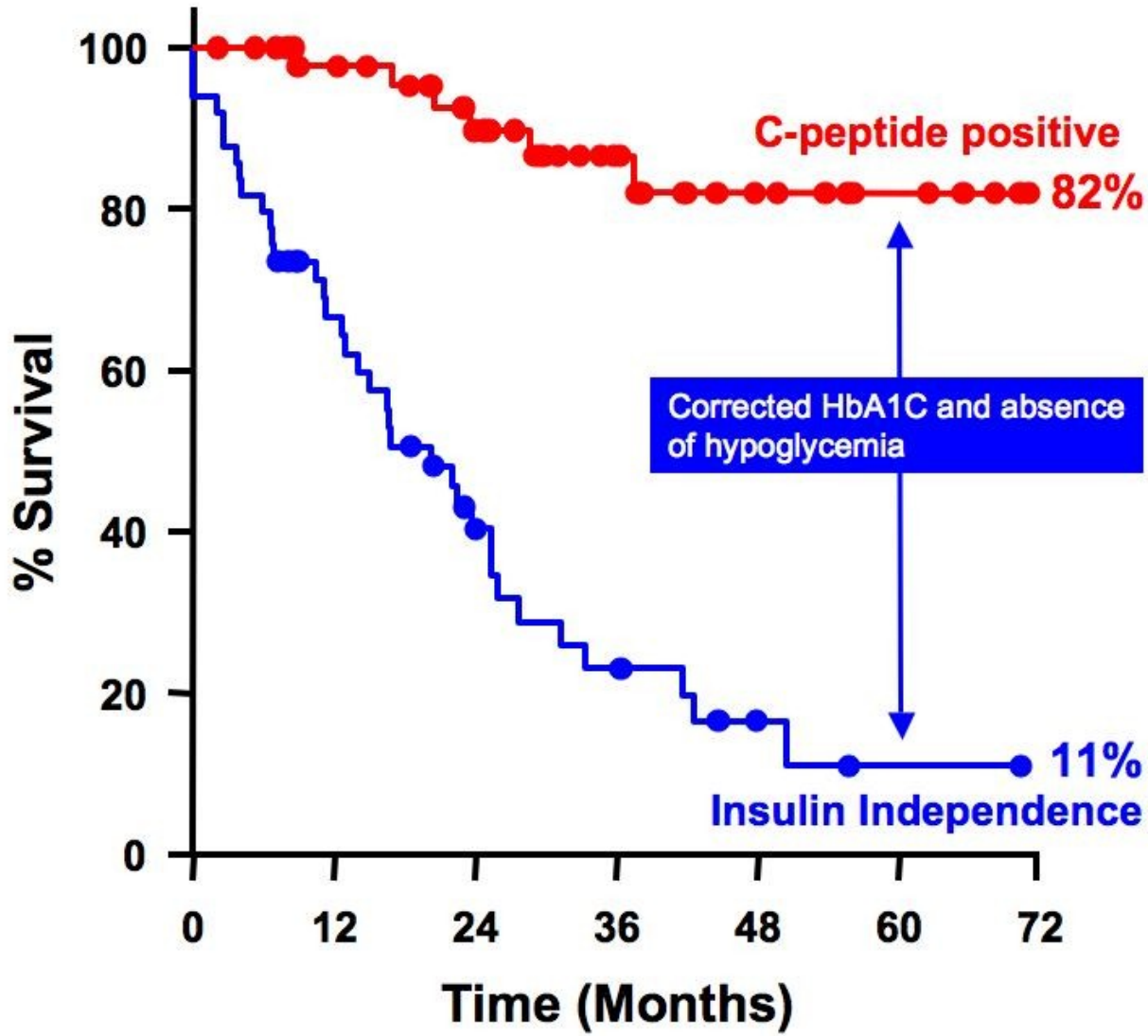
Christian Toso,MD

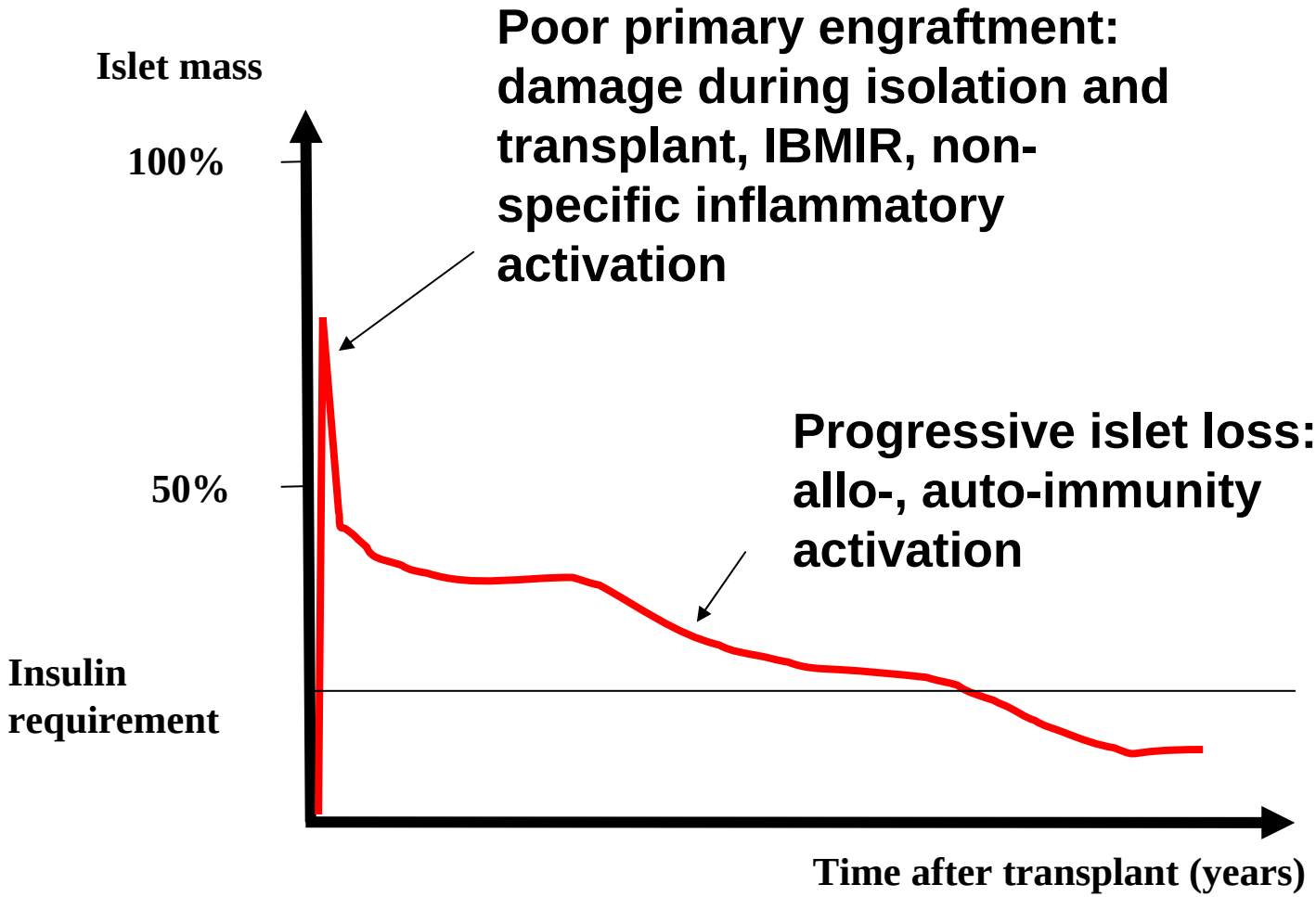
University of Alberta, Edmonton, Canada
Islet Transplant Center

Islet Cell Resource Center Consortium
4th Annual Islet Workshop


1. Digestion
2. Purification
3. Transplantation
4. Implantation

Five Year Islet Function - University of Alberta





Toso and Berney, Islet graft monitoring and imaging, In Shapiro and Shaw, eds. Islet transplantation and beta cell replacement therapy. New-York. 2007: 179-191

The ideal monitoring technique:

- Non invasive
- Non harmful to the graft
- Enable a repeated and accurate assessment
- Early detection of graft damages to allow treatment

Two types of monitoring:

- Monitoring of islet mass
- Monitoring of harmful events to the graft (rejection, autoimmunity)

Islet monitoring:

- Metabolic tests
  - IVGTT
  - Arginine test
  - Mixed meal...
- Blood tests
  - PCR for insulin or Granzyme B mRNA
  - Donor HLA DNA
  - Flow-cytometry
- Biopsy
- Imaging
  - PET (FDG, DTBZ labeling)
  - MRI (SPIO labeling)

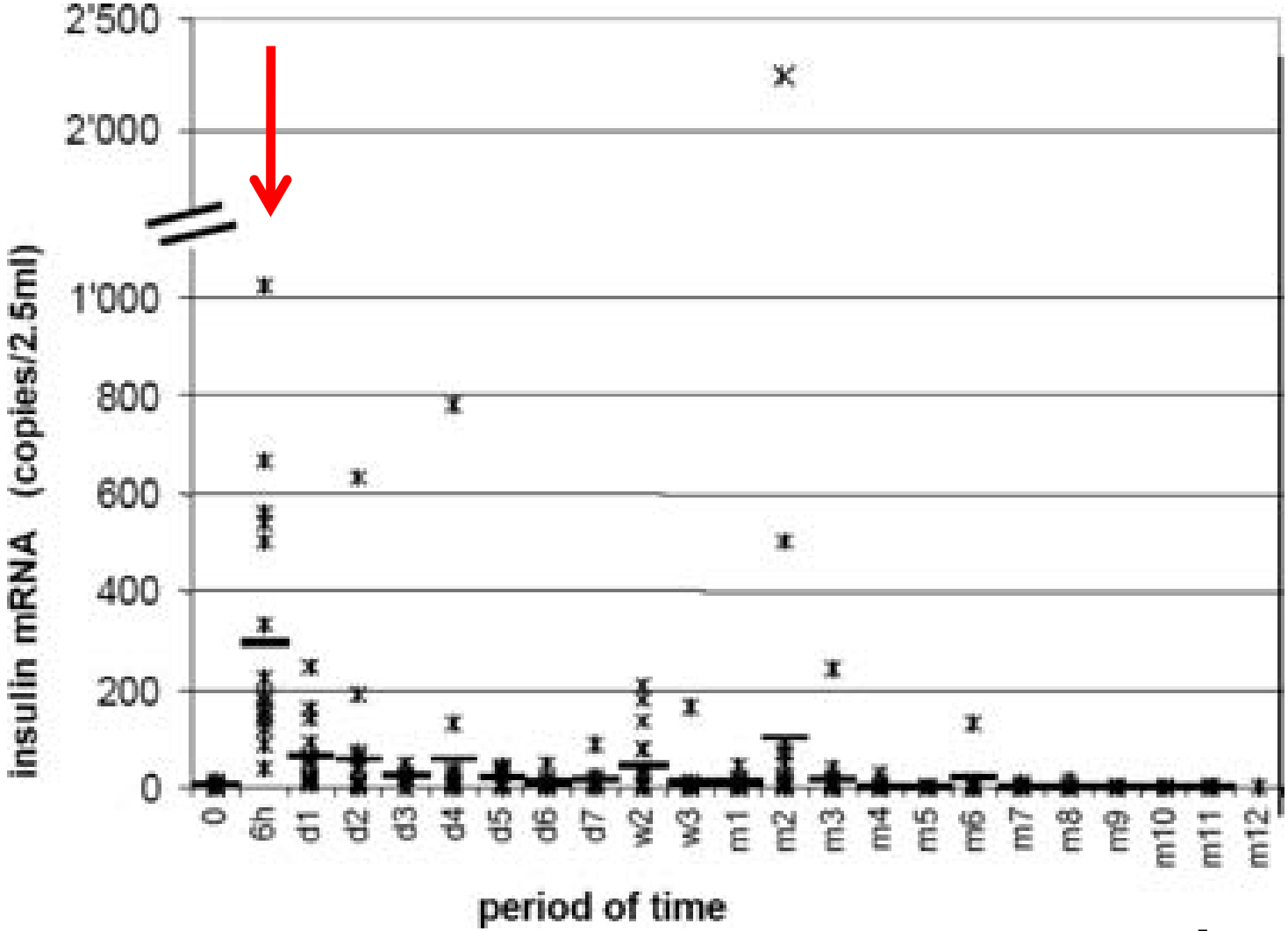
Table 1 Islet Graft Function Monitoring

Overall function	Serum glucose
	Serum insulin
	Serum C peptide
	HbA1c, fructosamine
	Insulin requirement (U/Kg)
	Number of hypoglycemias
	Secretory Unit of Islet Transplant Objects (SUITO)
	Beta score
Glucose stability	Mean Amplitude of Glycemic Excursions (MAGE)
	Lability index
	Continuous Glucose Monitoring Systems (CGMS)
Hypoglycemic events	HYPO score
	Continuous Glucose Monitoring Systems (CGMS)
Stimulation tests	Arginine stimulation test
	Glucagon test
	Mixed meal stimulation test
	Oral Glucose Tolerance Test (OGTT)
	IV Glucose Tolerance Test (IVGTT)

Toso and Berney, Islet graft monitoring and imaging, In Shapiro and Shaw, eds. Islet transplantation and beta cell replacement therapy. New-York. 2007: 179-191

Detection of circulating insulin mRNA in the blood after islet transplantation

Detection of Insulin mRNA in the Peripheral Blood after Human Islet Transplantion Predicts Deterioration of Metabolic Control



Berney et al, AJT, 2006

Sensitivity: 85%; Specificity: 73%

For negative metabolic events:

- Kidney rejection (simultaneous islet kidney transplant)
- Doubling of insulin requirements
- Start insulin
- Increase of HbA1c (over 0.7%)

Berney et al, AJT, 2006

Assessment of Cytotoxic Lymphocyte Gene Expression in the Peripheral Blood of Human Islet Allograft Recipients

Elevation Precedes Clinical Evidence of Rejection

Dongmei Han,[1] Xiumin Xu,[1] David Baidal,[1] Jenifer Leith,[1] Camillo Ricordi,[1,2,3] Rodolfo Alejandro,[1,2] and Norma S. Kenyon[1,2,3]

RT-PCR for

- Granzyme B
- Perforine
- Fas ligand

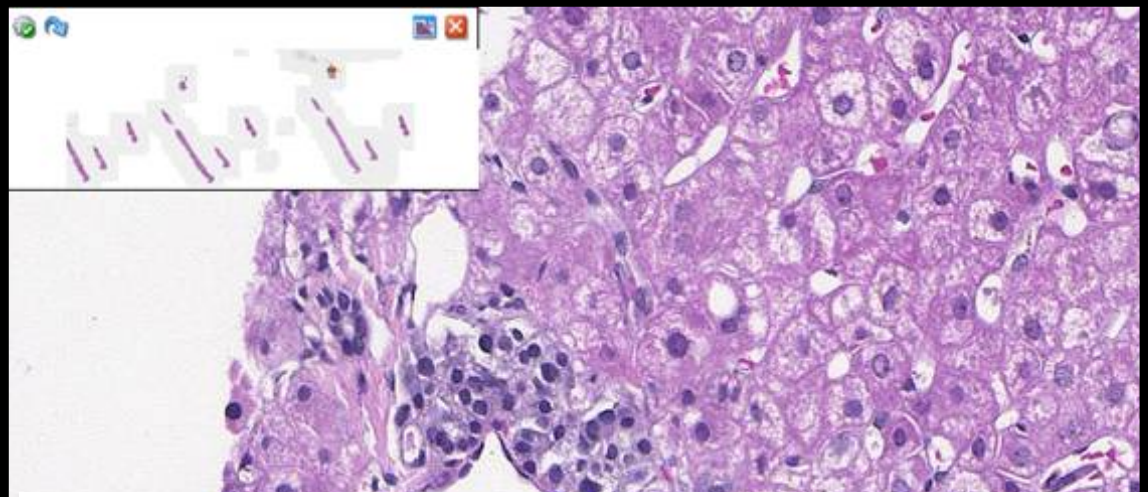
Han et al, Diabetes, 2004

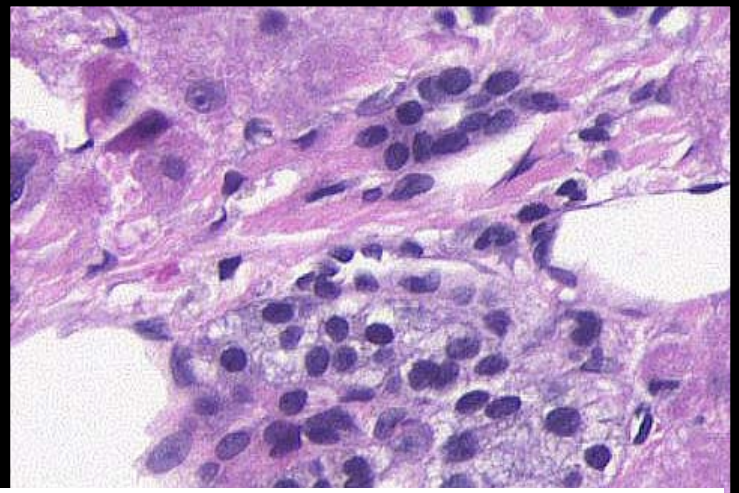
Biopsy


SIEMENS
MULTISKOP

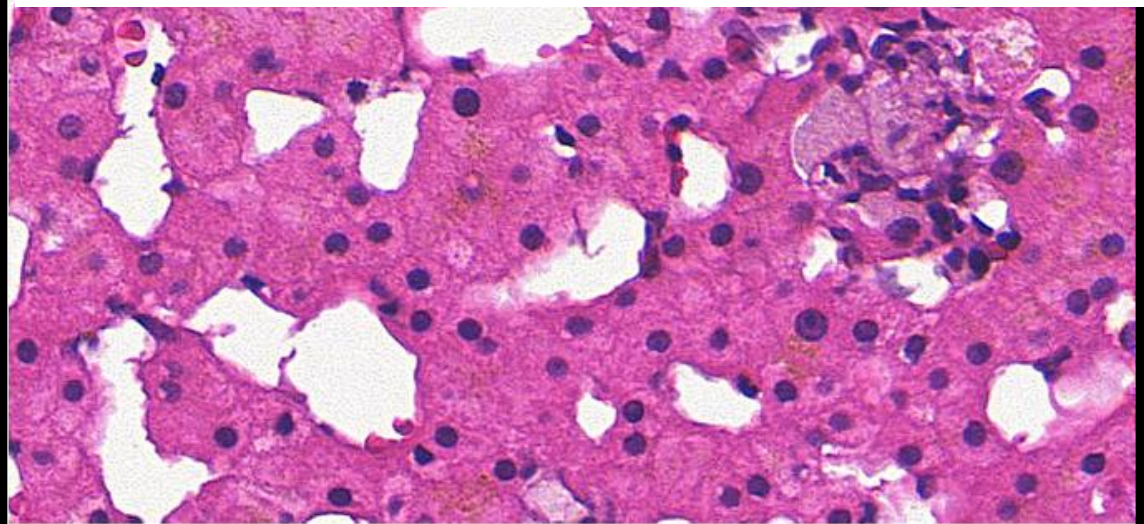
Islet graft monitoring

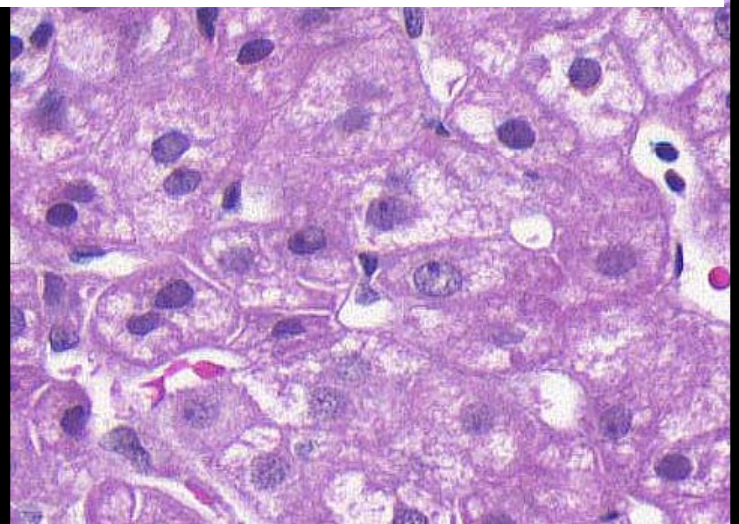

Liver
Islets





Islets in 7/16 needle biopsies (44%)

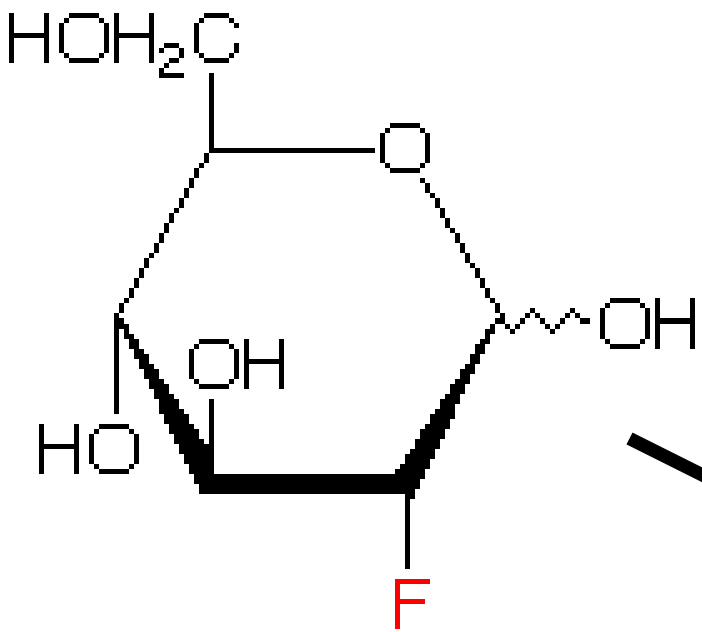


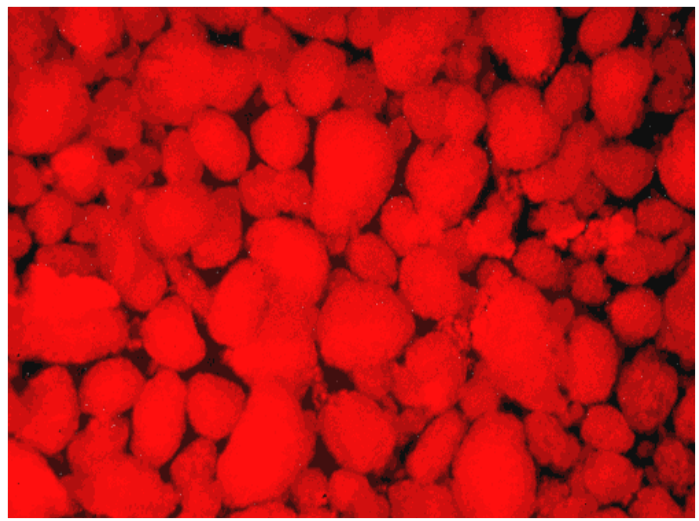


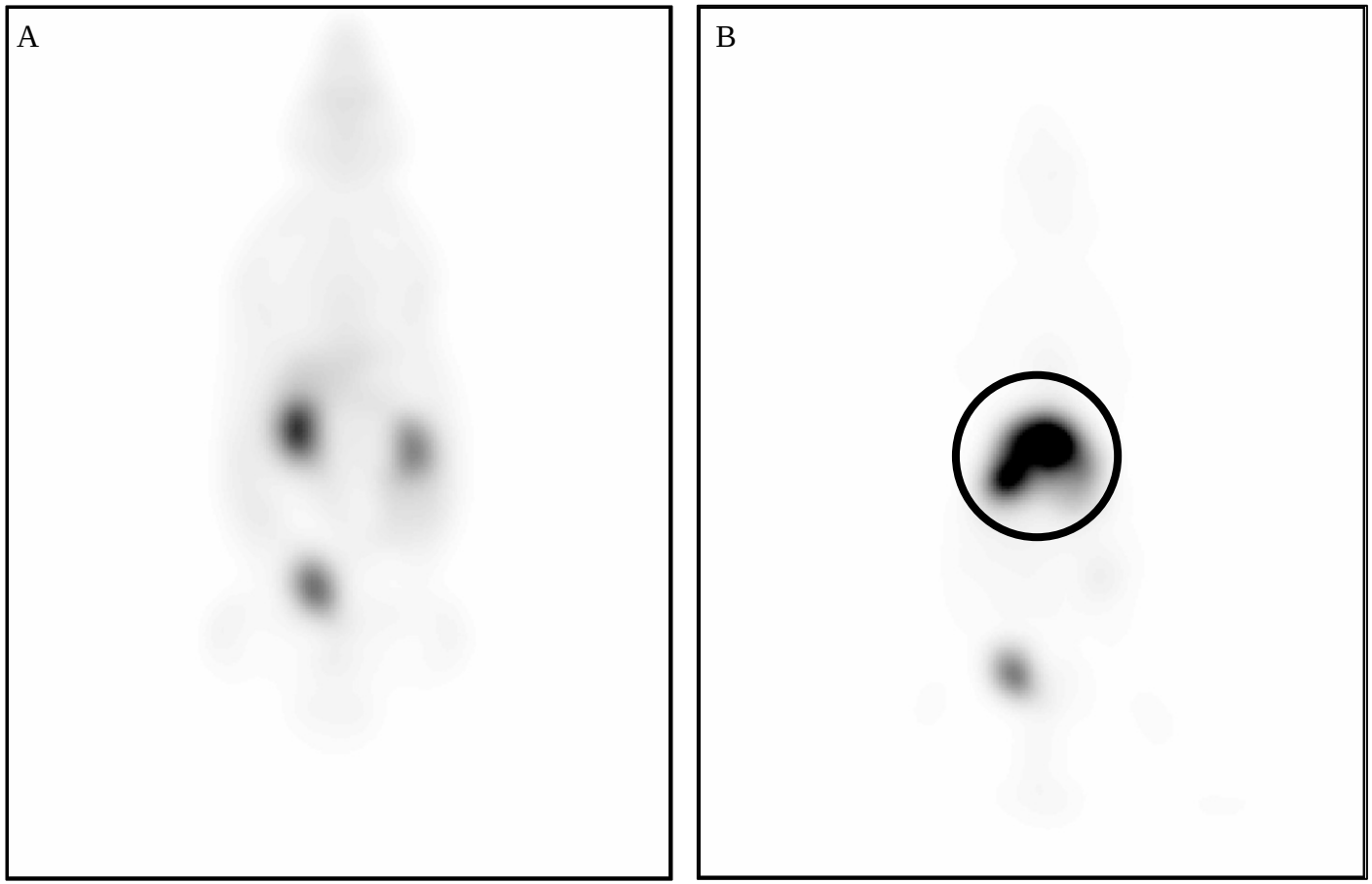
Islet imaging:

- Positron-Emission Tomography (PET)
    - Ex vivo labelling: FDG
    - In situ labelling: DTBZ
- Magnetic Resonance Imaging (MRI)

[^{18}F] Fluoro-deoxyglucose (FDG) :

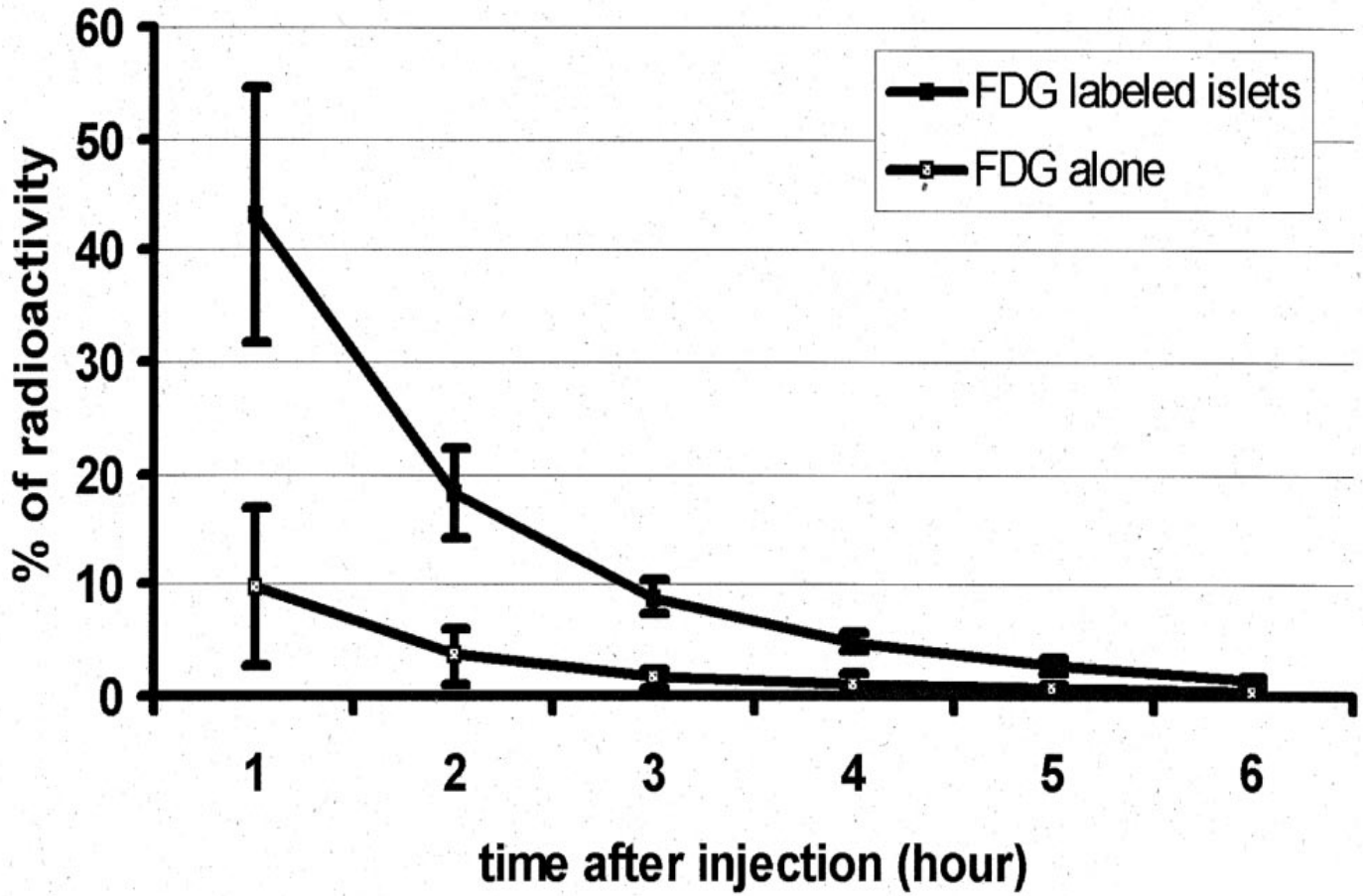






Fluoro-deoxy-glucose (FDG)

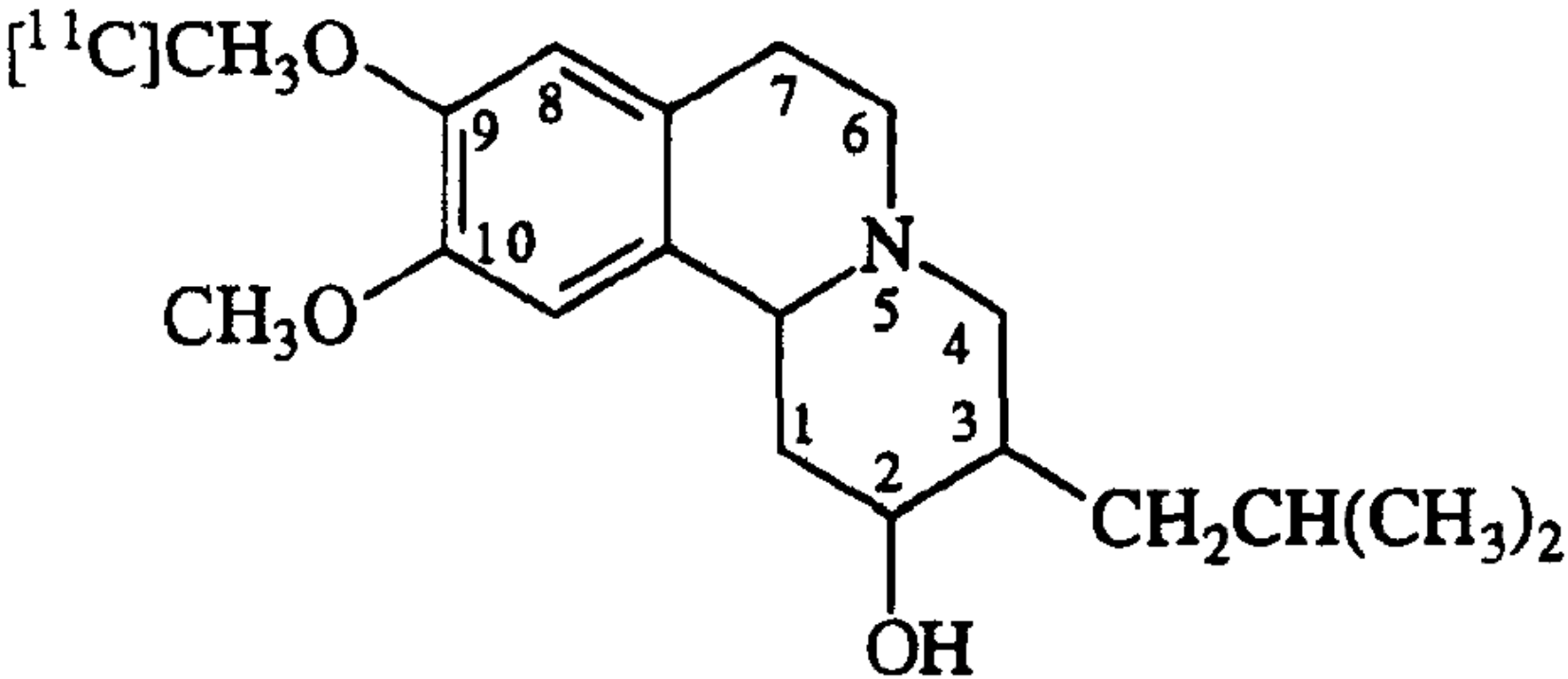
Toso et al, Transplantation, 2005



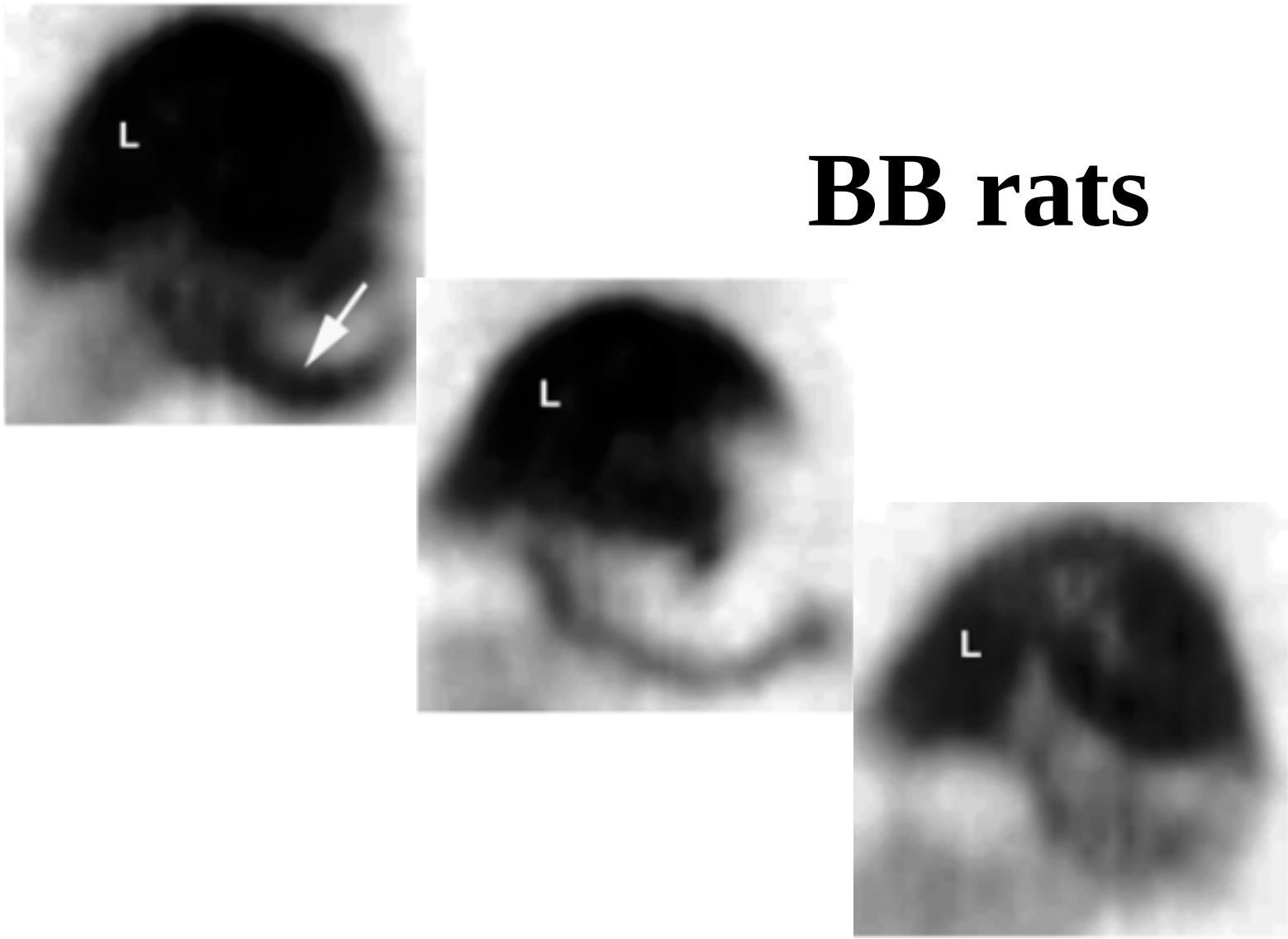
- short half-life of the tracer (FDG: 110min)
- rapid release of the tracer from the cells

Toso et al, Transplantation, 2005

[^{11}C]Dihydrotetrabenazine (DTBZ) :



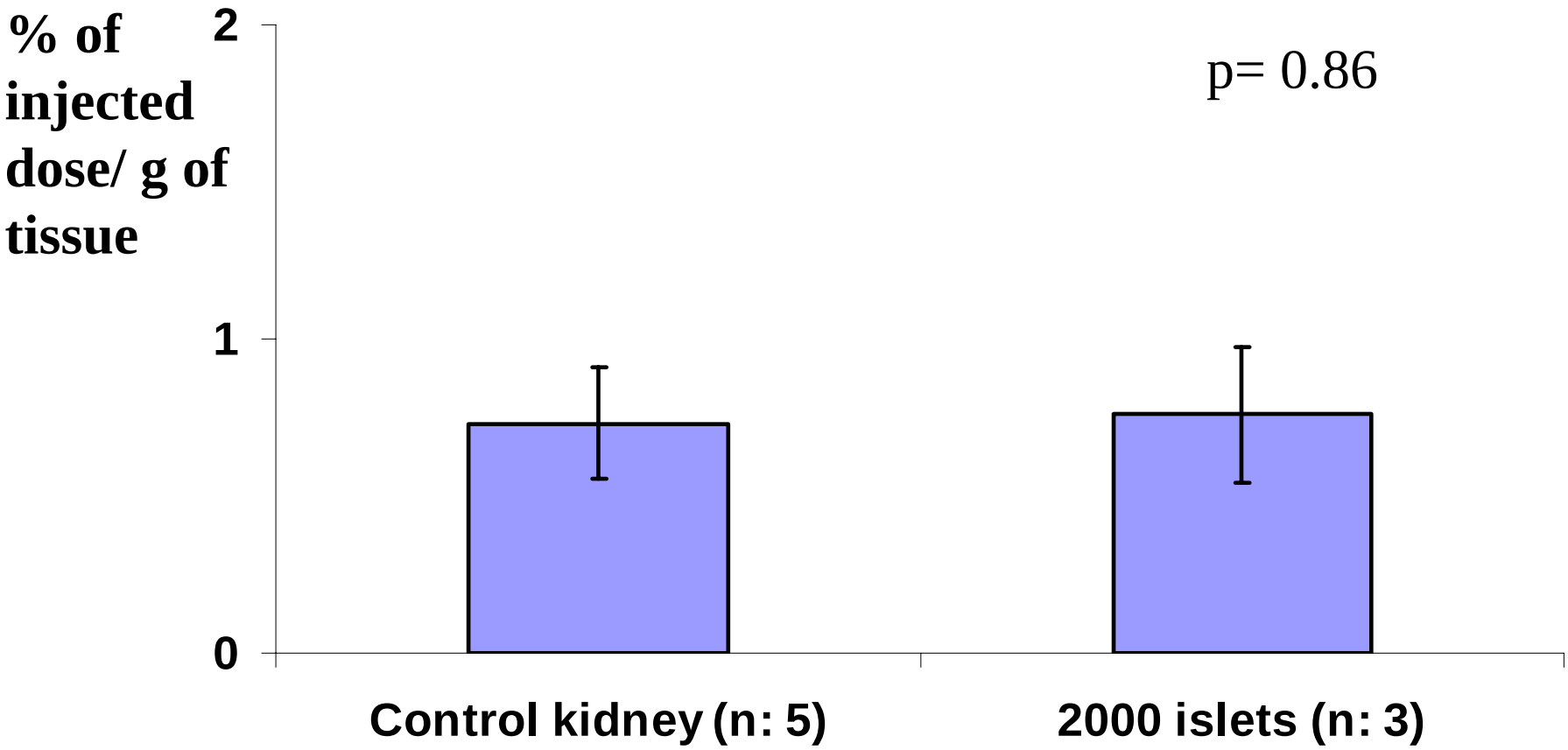
Souza et al, JCI, 2005



BB rats

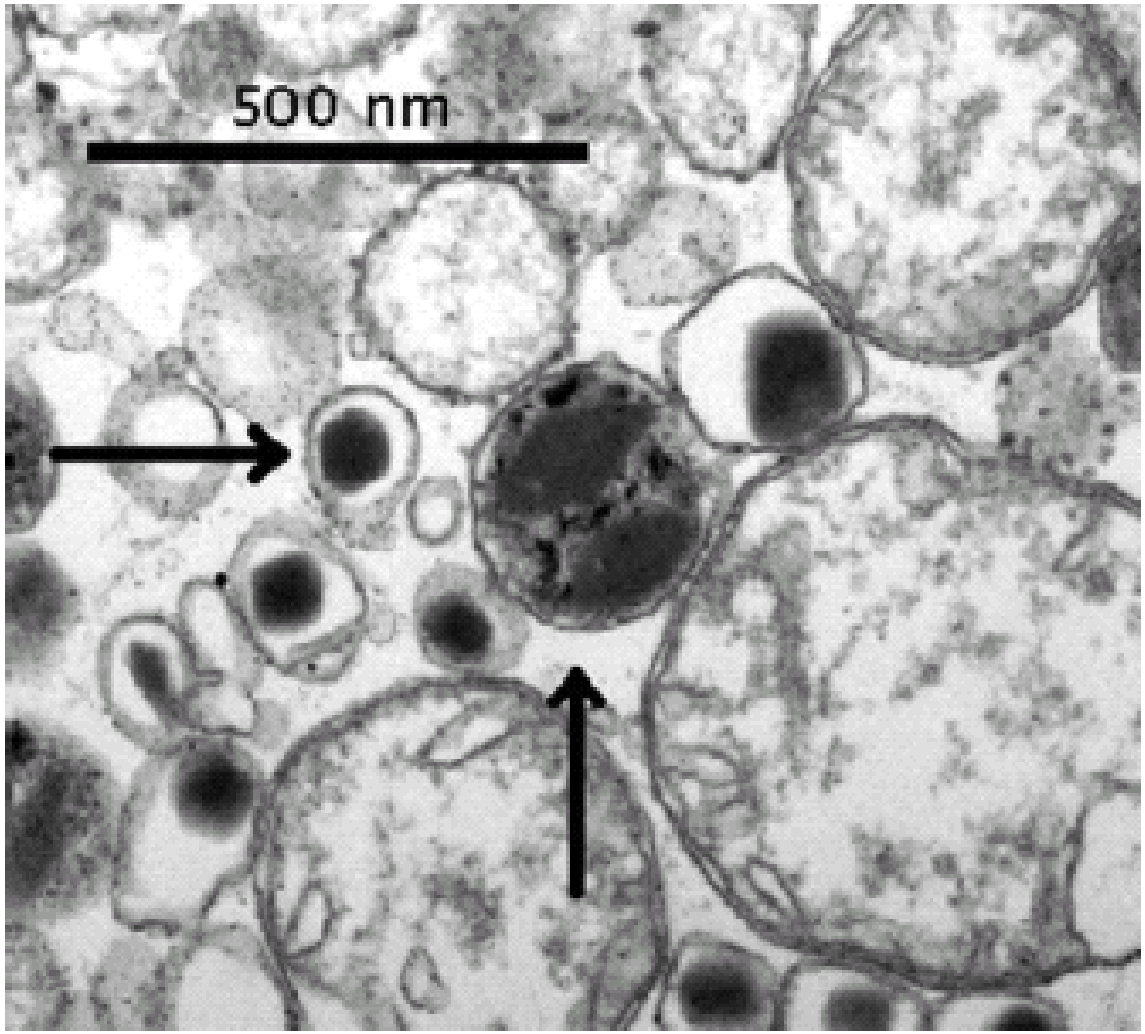
Souza et al, JCI, 2006

DTBZ-PET scans in rats



Islet imaging:

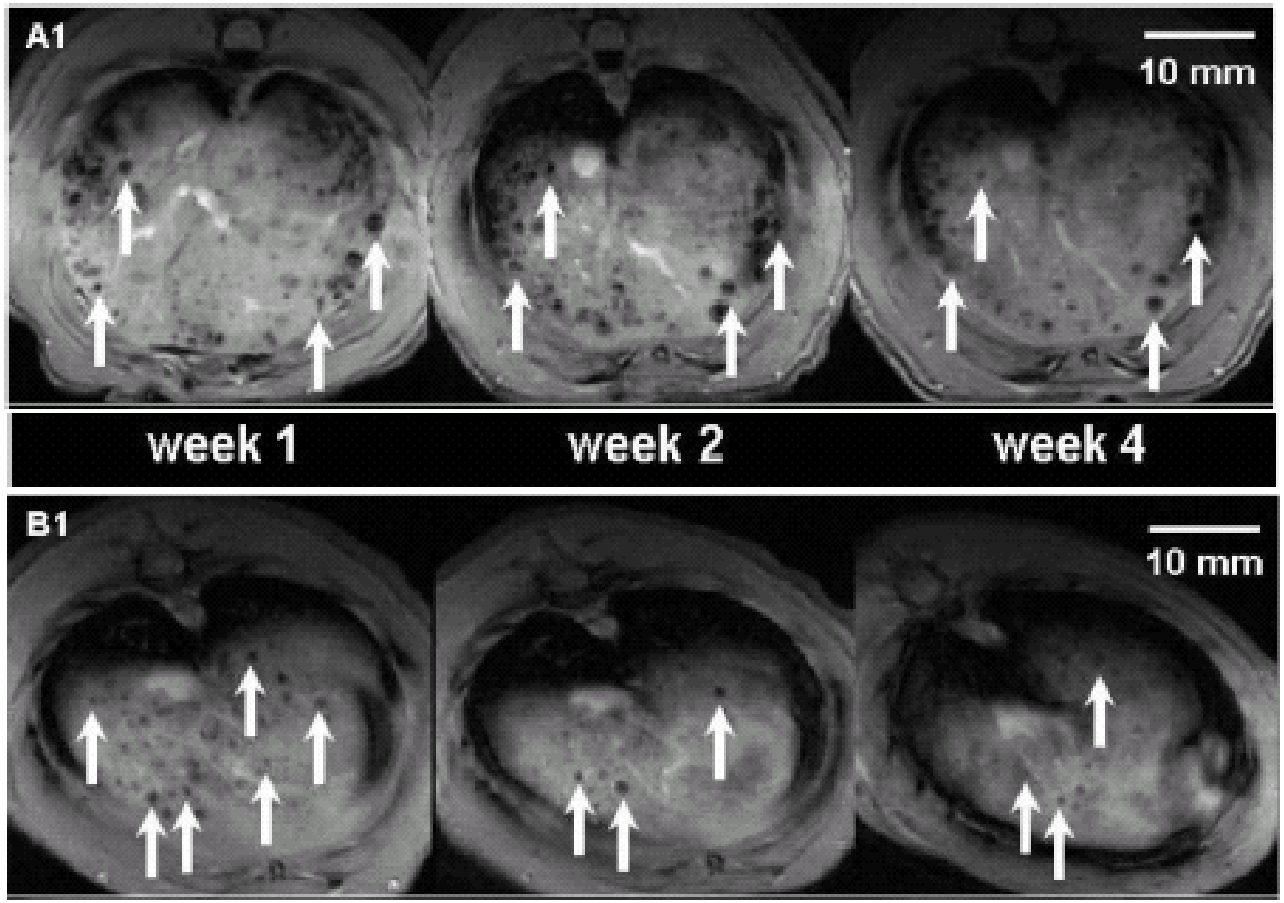
- Positron-Emission Tomography (PET)
    - Ex vivo labelling: FDG
    - In situ labelling: DTBZ
- Magnetic Resonance Imaging (MRI)


500 nm

Rat islet transplantation:

Syngeneic

Allogeneic

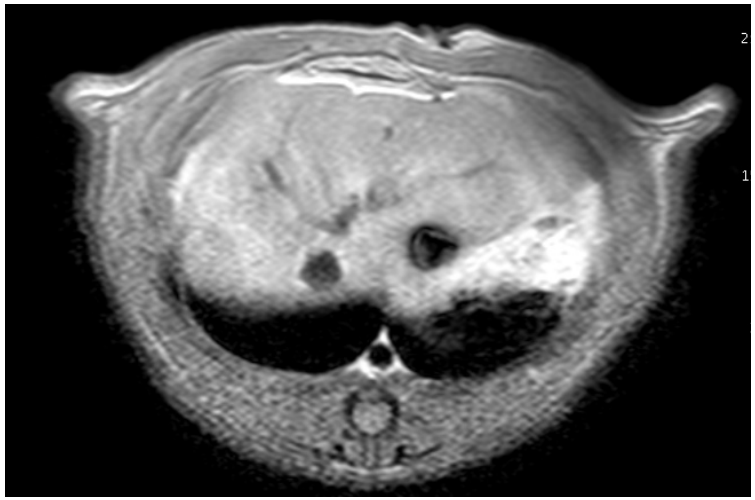


Jirak et al Magn Reson Med 2004
Berkova et al Transplant Proc 2005
Kriz et al Transplantation 2005
Evgenov et al Nat Med 2006

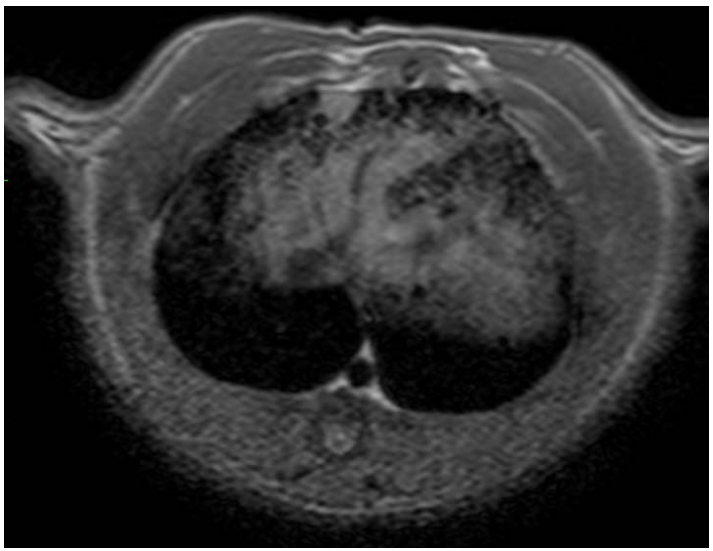
Feasibility and safety in human?

Transplantation of 10,000IEQ/Kg in rats

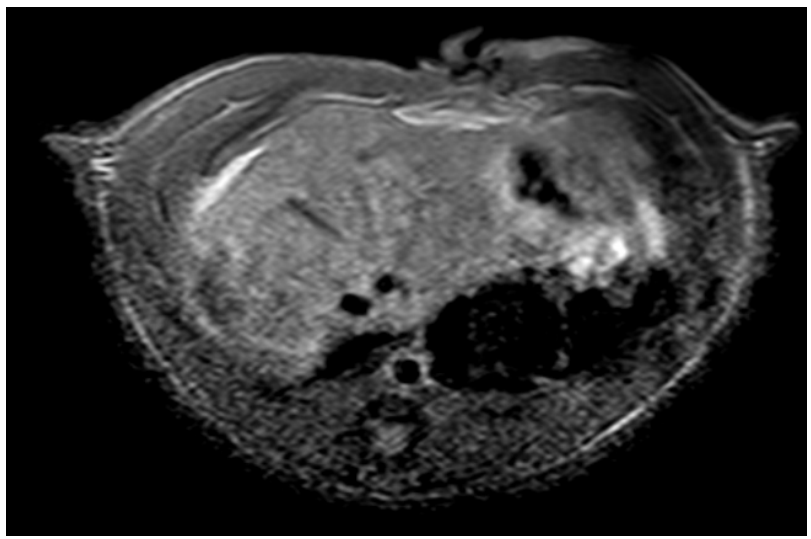
Pre-transplantation



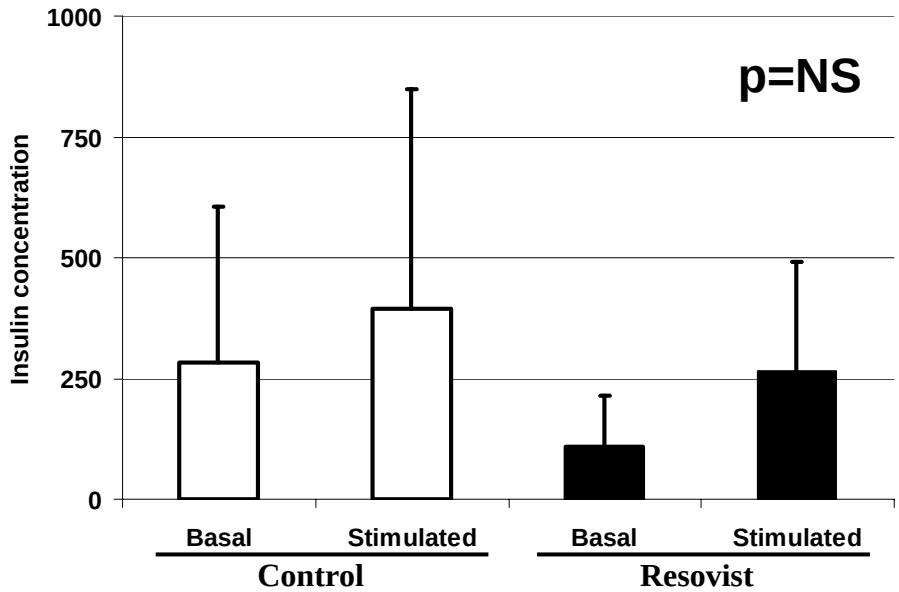
Resovist loaded Islets

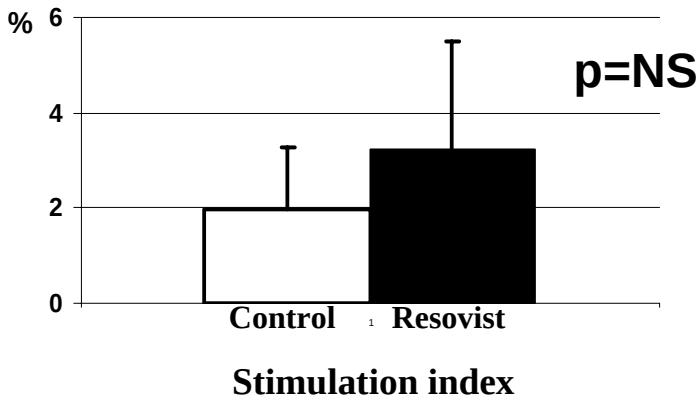


Endorem loaded Islets

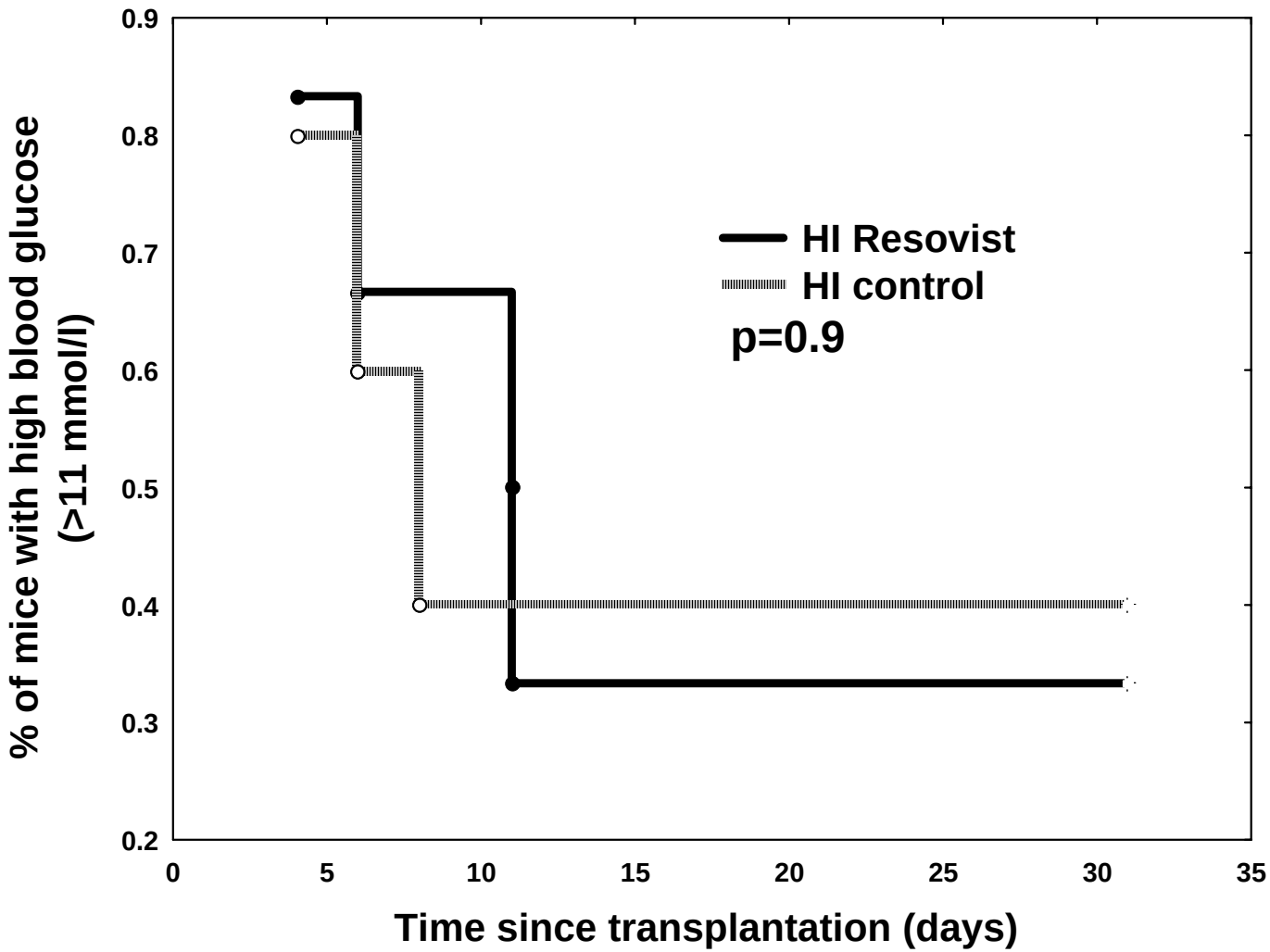


Static incubations (from 7 human islet isolations):





Transplantation in NUDE mice:



Case reports:

-7 labeled islet infusions in 4 patients with type I diabetes

-female/male: 1/3

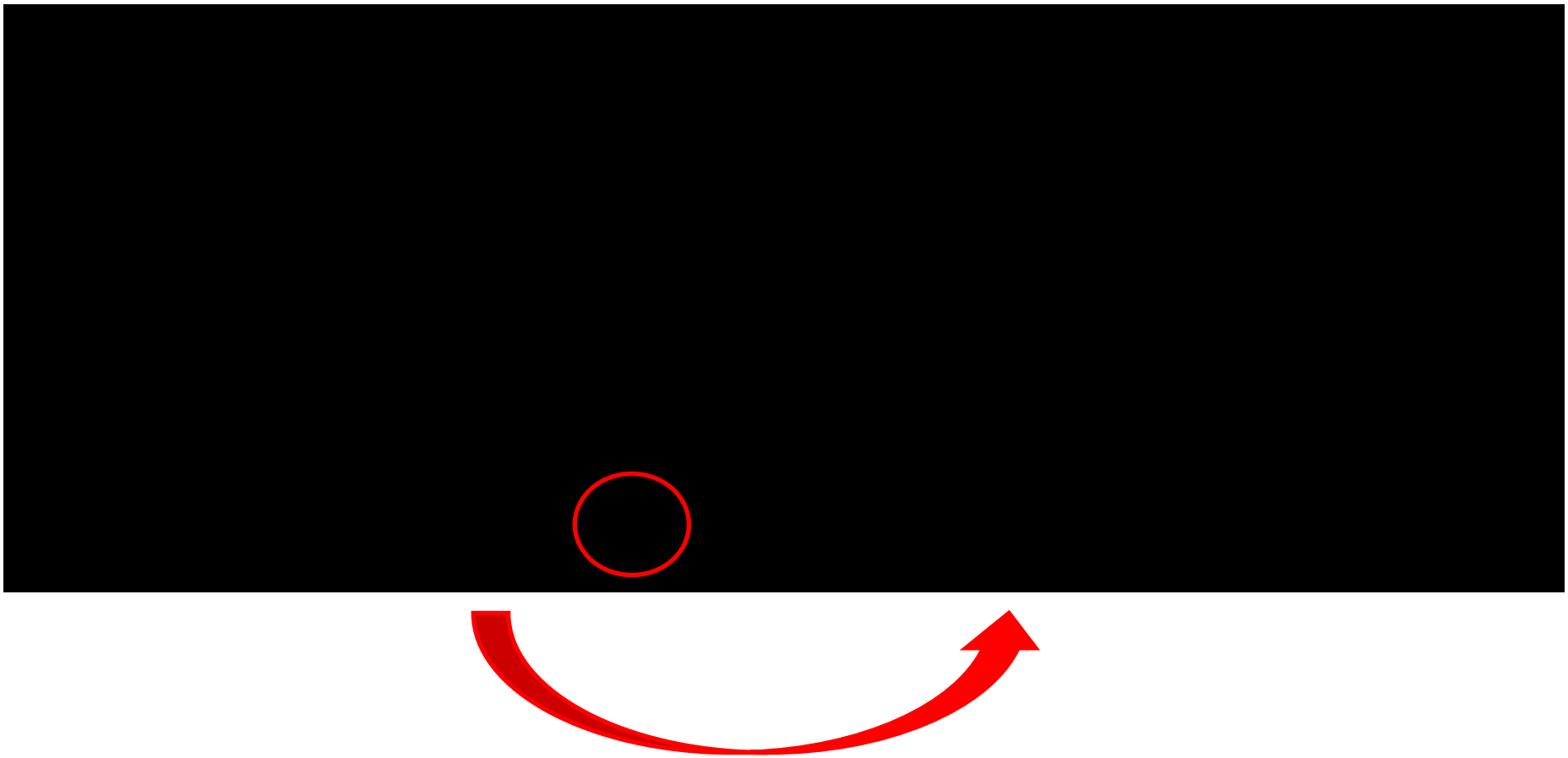
-47 to 56 year-old

-incubations with iron nanoparticles (Resovist) for 24 to 48 hours

-MRI pre- and at various time points post transplant

Toso et al, AJT, 2008

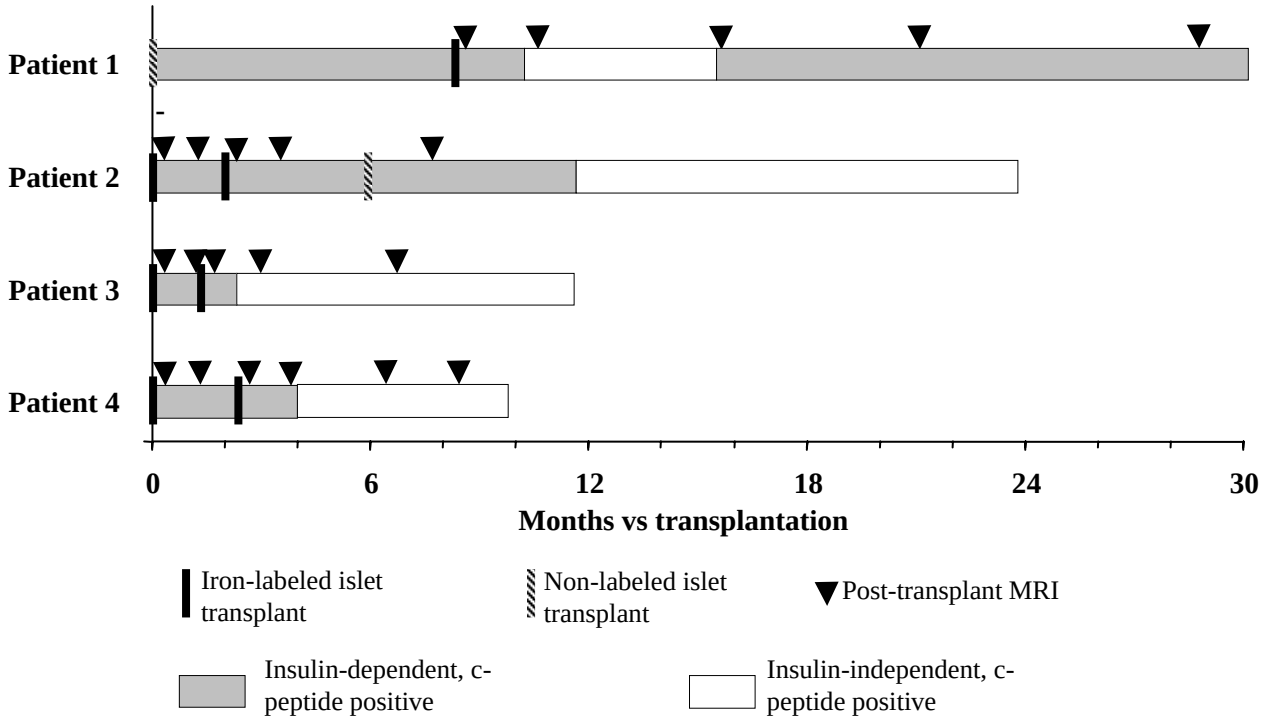
Islet graft monitoring



39 ±26 %

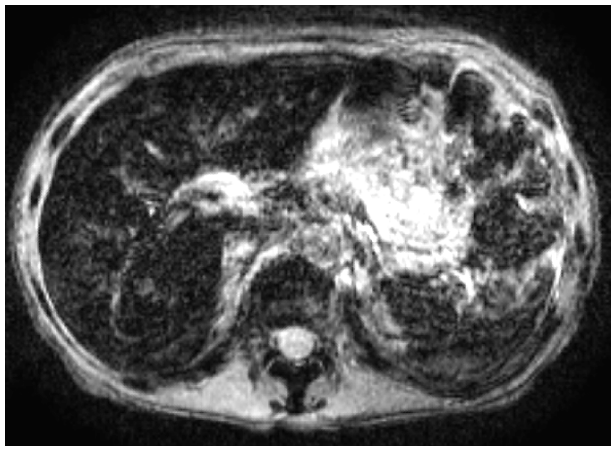
Toso et al, AJT, 2008

Islet graft monitoring

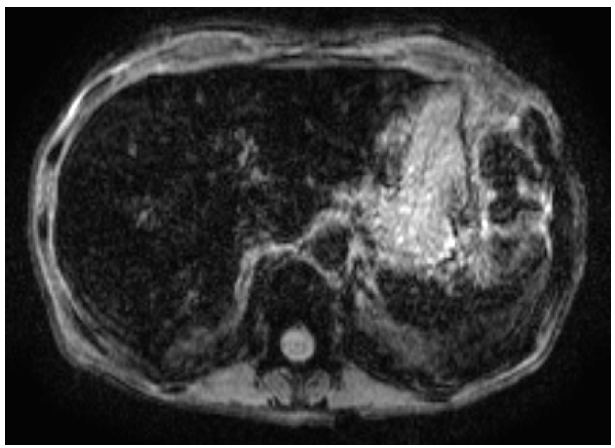


Toso et al, AJT, 2008

Patient 2



Pre-transplant



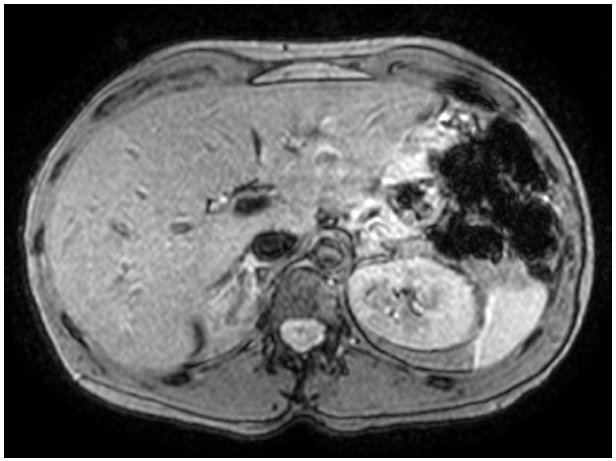
5 days

Toso et al, AJT, 2008

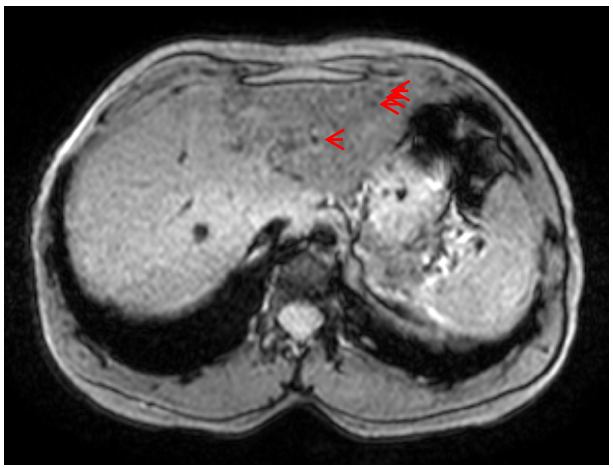
Iron overload (hemosiderosis) is a contraindication to MR imaging of islets grafts

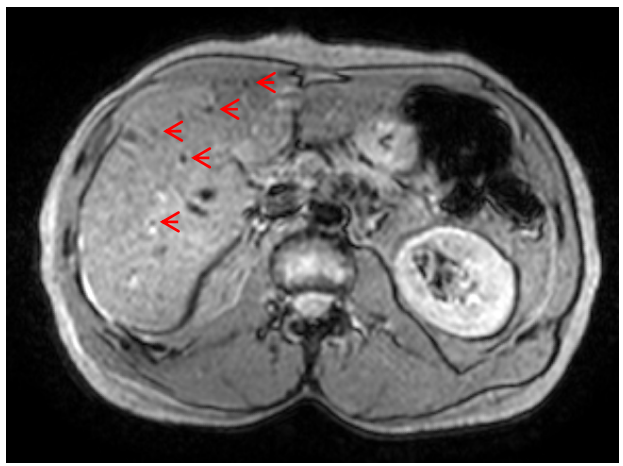
Toso et al, AJT, 2008

Patient 3



Pre-transplant

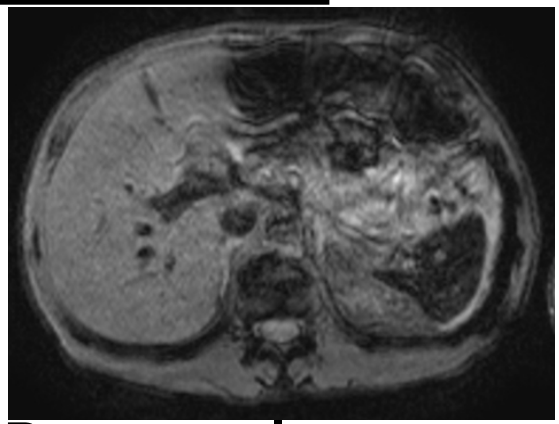




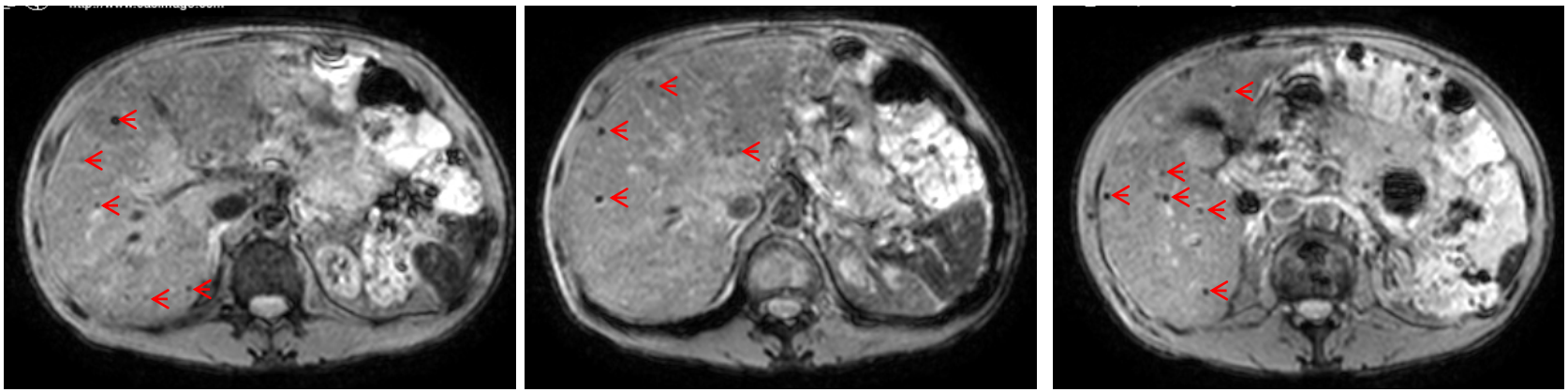
5 weeks after first infusion,
6 days after second infusion

Toso et al, AJT, 2008

Patient 1



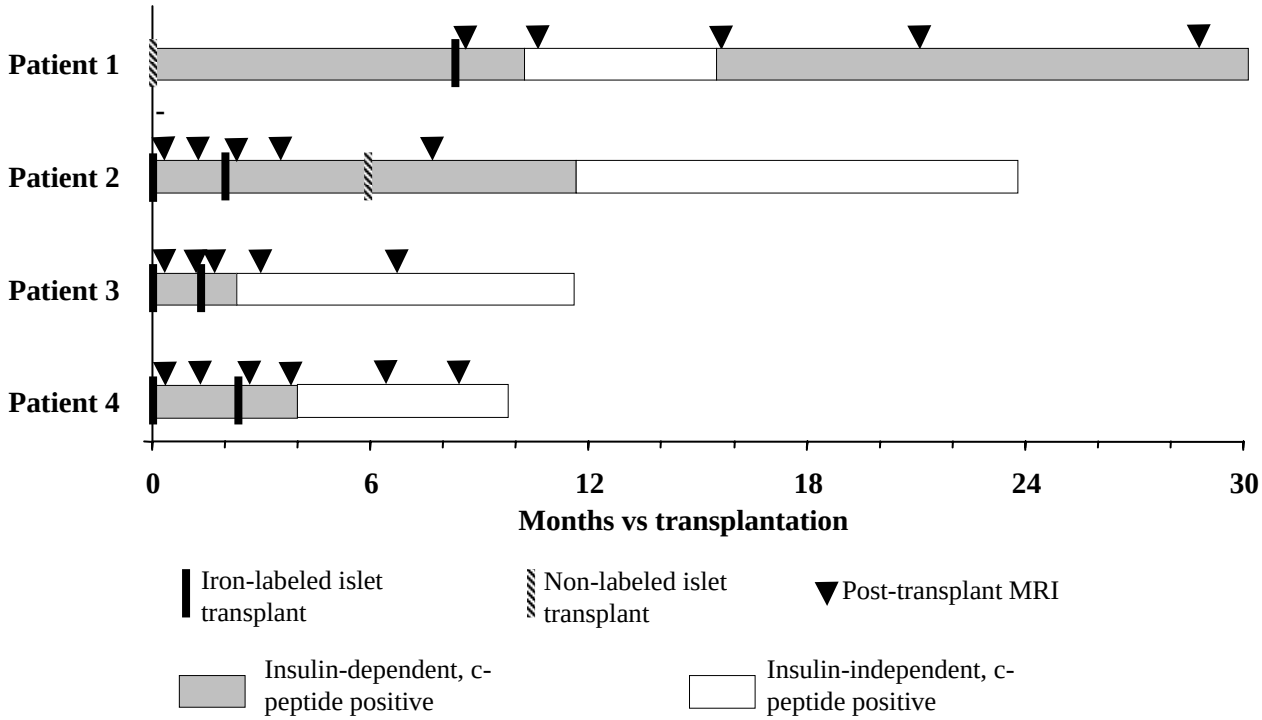
Pre-transplant



6 weeks

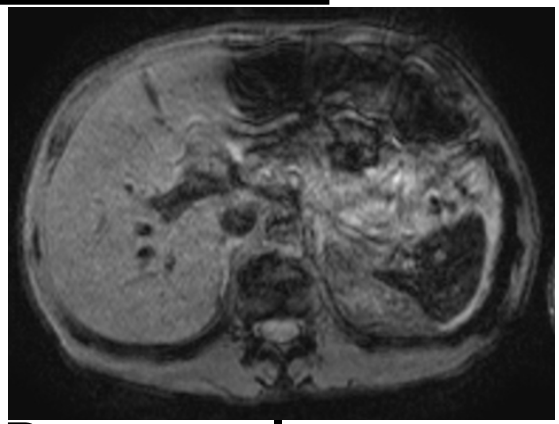
Toso et al, AJT, 2008

Islet graft monitoring

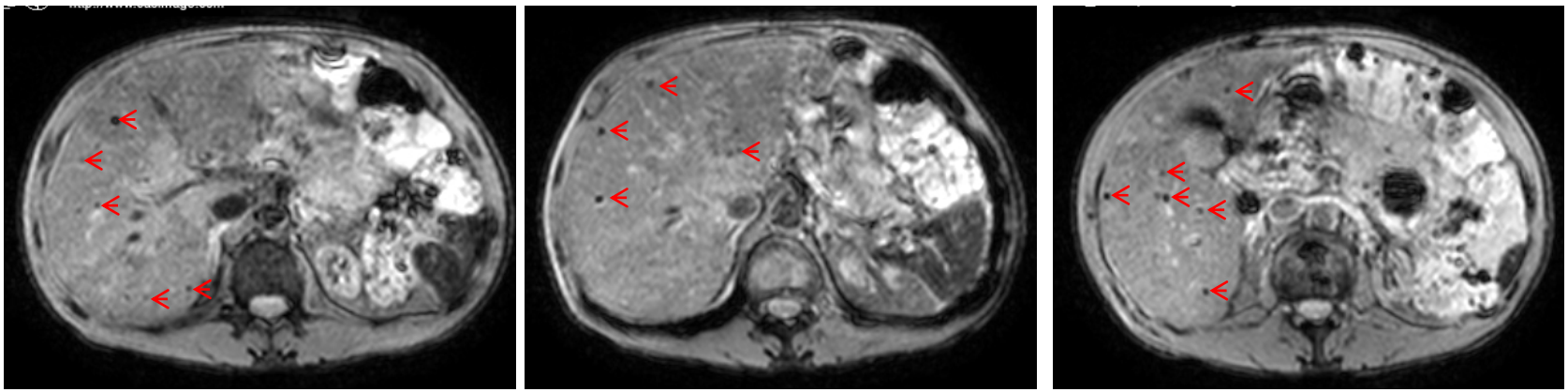


Toso et al, AJT, 2008

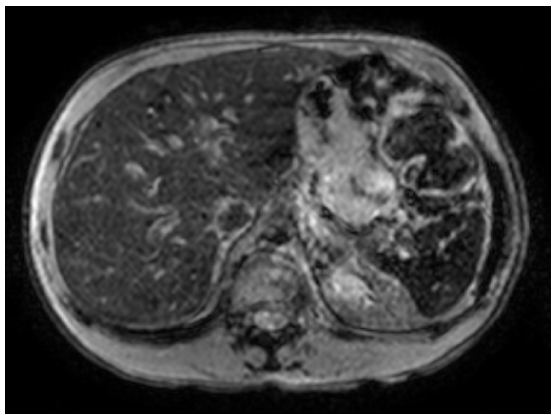
Patient 1



Pre-transplant



6 weeks



8 months

Toso et al, AJT, 2008

This study demonstrates the feasibility and safety of MRI-based islet graft monitoring in clinical practice.

Iron overload (spontaneous or induced) represents the major obstacle to the technique.

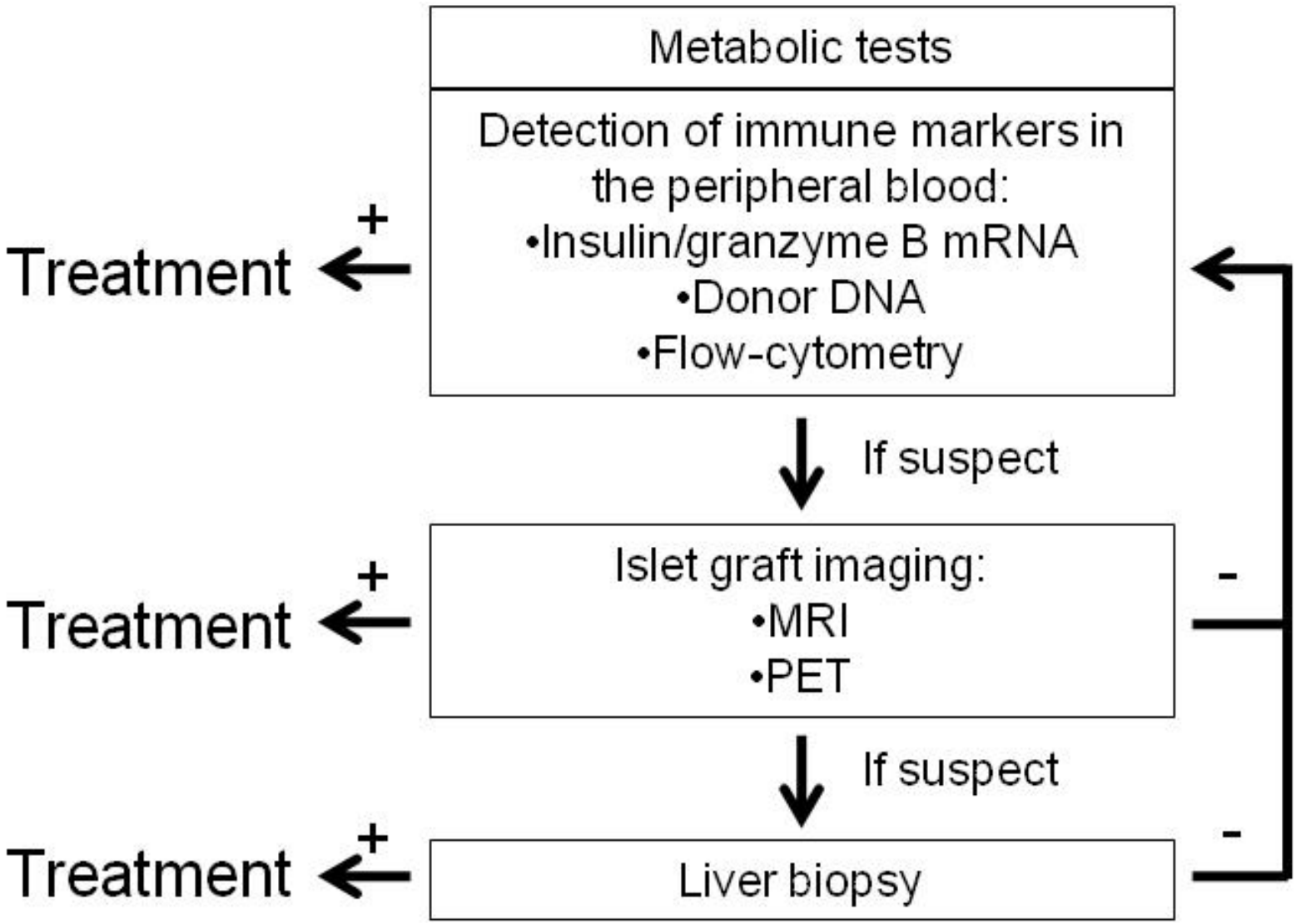
Toso et al, AJT, 2008

Future developments:

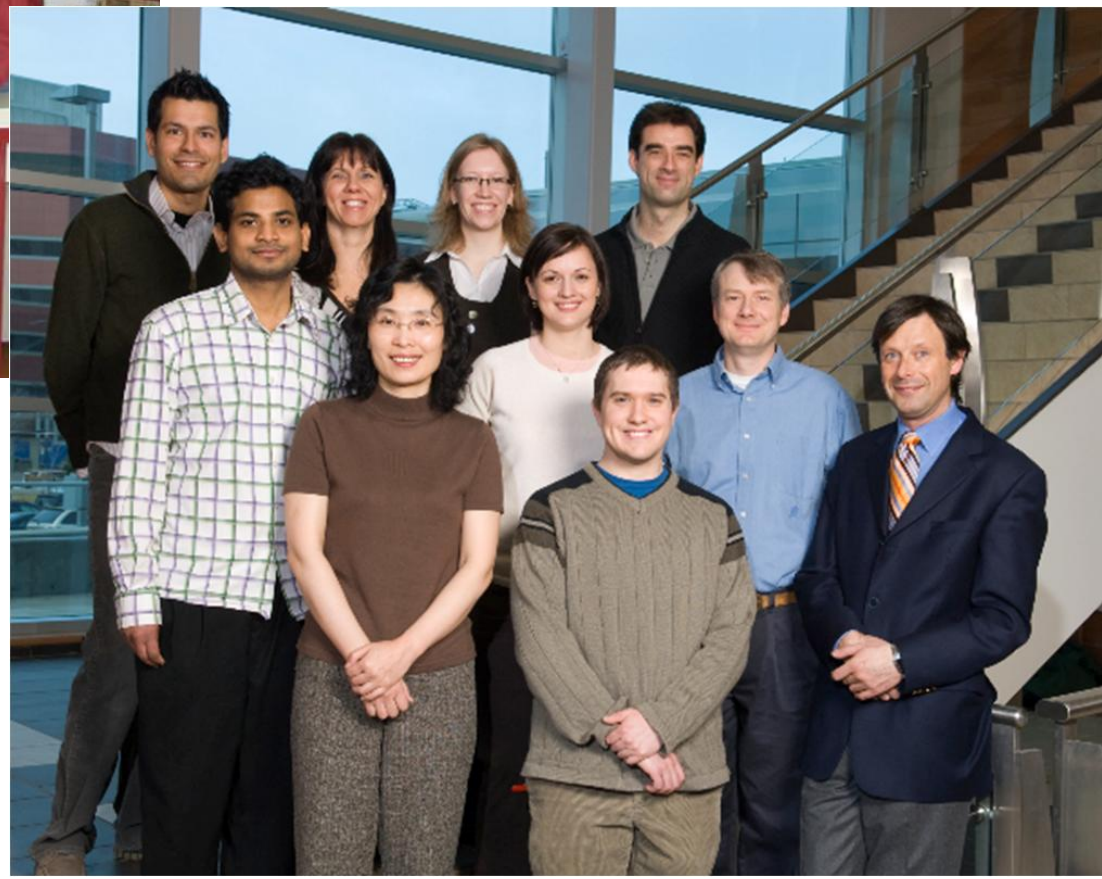
- Quantifying the spots within the liver

- Increase the number of patients to assess whether rejection can be detected in a timely fashion

Islet monitoring of tomorrow



University of Geneva, Switzerland



University of Alberta, Edmonton, Canada

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Thank you!