Deutsche
Gesellschaft
für Nuklearmedizin
e.V.

SUMMER SCHOOL 2016

Translational Research
in Molecular Imaging and Radionuclid Therapy

August 25 – 27, 2016

SPECT/CT

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SPECT/CT

Overview:

•Why SPECT?

•The shortcomings of clinical SPECT are the power of preclincal SPECT

•Development of a radiotracer for SPECT imaging: from bench to bedside

•Quantitative imaging with SPECT: why not?

SPECT/CT – why SPECT ?

- We all know that PET is better, so why should anyone be interested in using SPECT???

SPECT/CT – why SPECT ?

- Availability
- Price
- Radiolabeling comparatively easy
- No cyclotrone needed
- Generator nuclides or nuclides with long half life available

SPECT/CT

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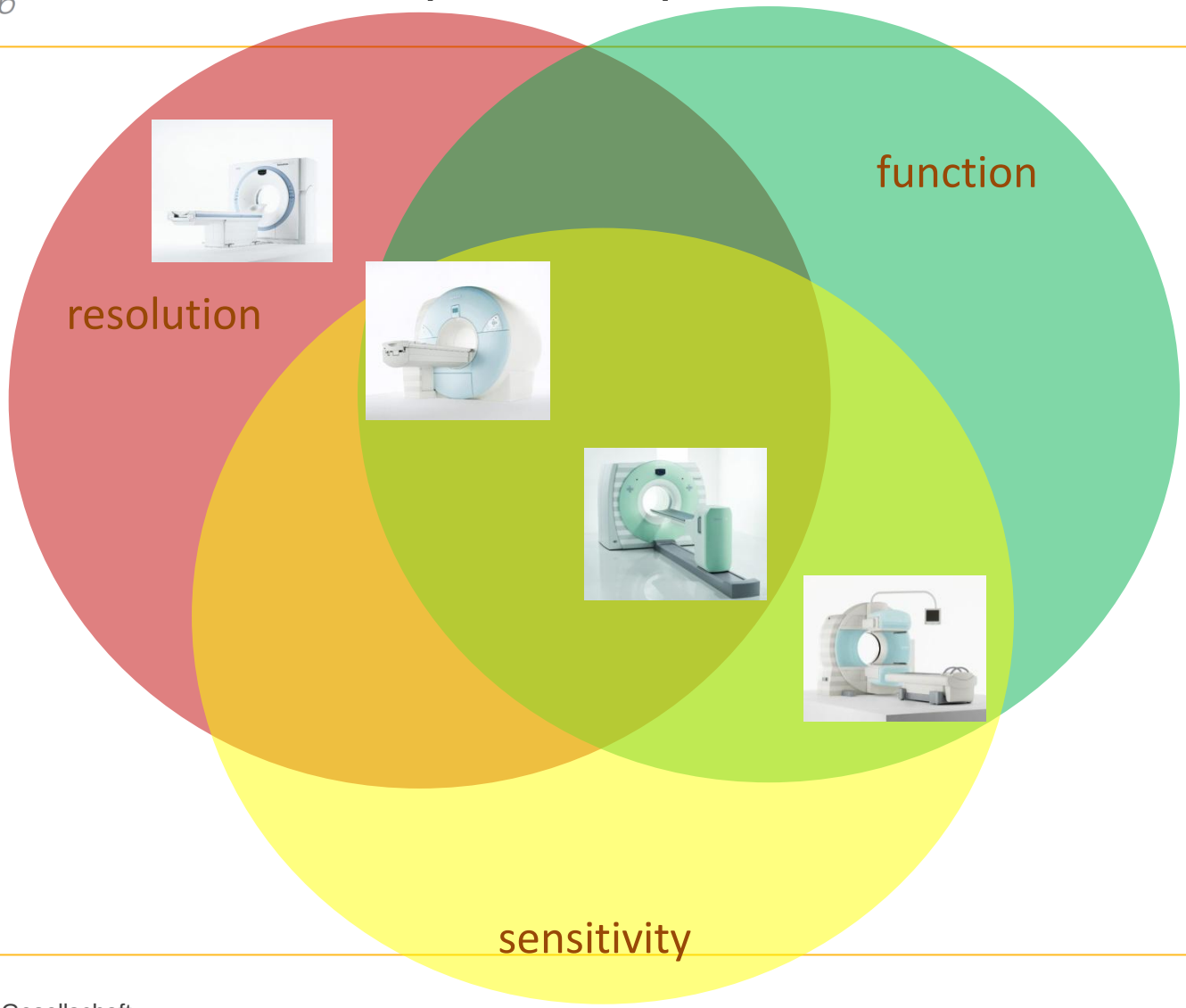
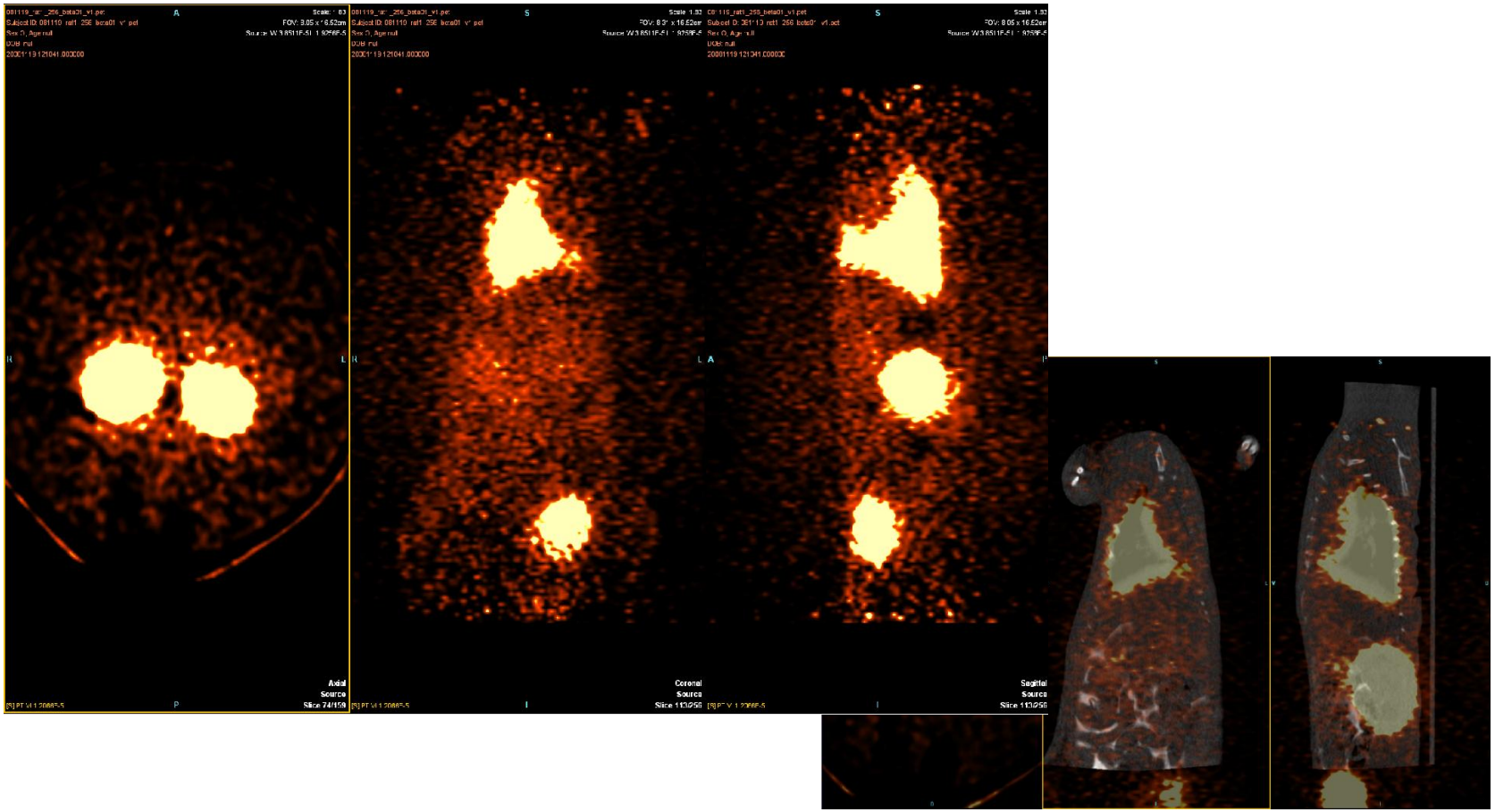


The shortcomings of clinical SPECT are the power of preclinical SPECT



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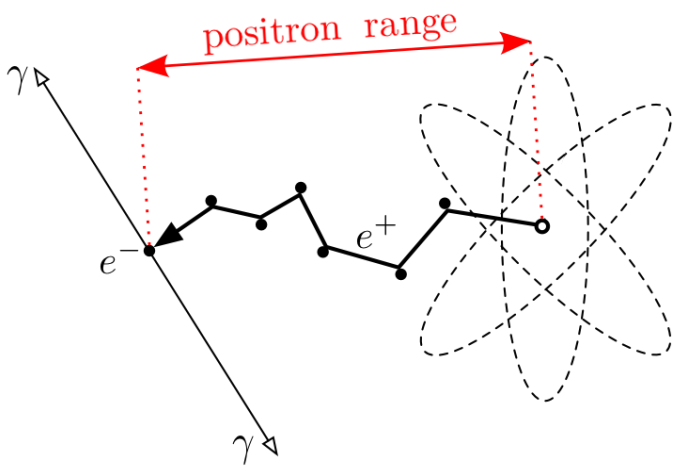
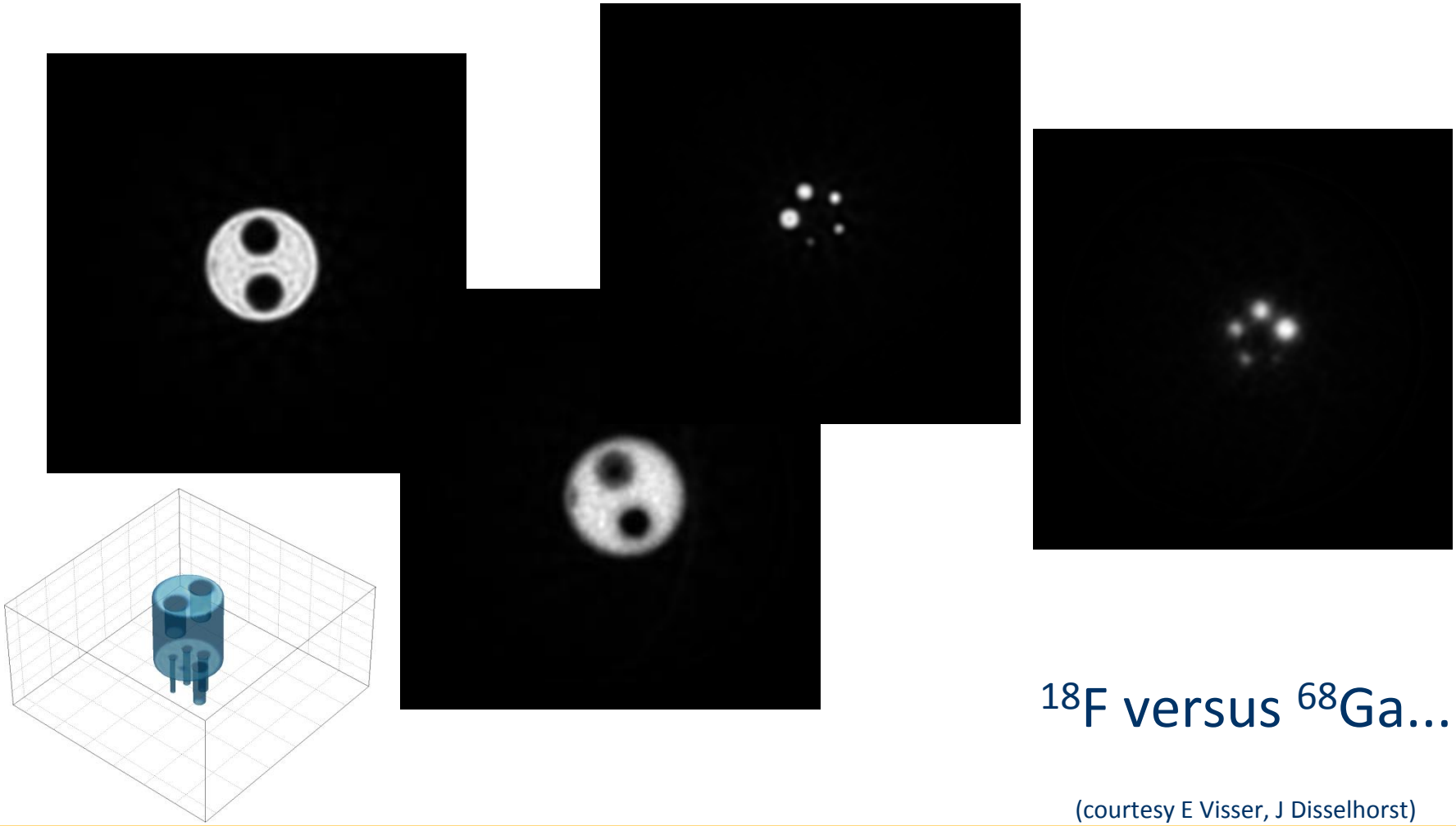


e^+ positron
e^- electron
γ gamma (511keV)

Isotope	Mean Energy (MeV)	FWHM (mm)	FWTM (mm)
^{18}F	**0.250**	**1.67**	**3.11**
^{64}Cu	0.278	1.71	3.21
^{52}Fe	0.340	1.81	3.50
^{11}Cu	0.386	1.88	3.77
^{89}Zr	0.396	1.91	3.80
^{13}N	0.492	2.06	4.43
^{61}Cu	0.500	2.08	4.47
^{73}Se	0.564	2.22	4.94
^{55}Co	0.570	2.18	4.91
^{86}Y	0.661	2.27	5.38
^{15}O	0.735	2.50	6.30
^{124}I	**0.820**	**2.70**	**6.86**
^{68}Ga	**0.830**	**2.74**	**7.11**
^{19}Ne	0.963	2.96	8.27
^{52}Mn	1.172	3.50	10.20
^{76}Br	1.180	2.52	8.92
^{134}La	1.203	3.74	10.58
^{38}K	1.214	3.56	10.56
^{62}Cu	1.314	3.89	11.55
^{82}Rb	1.479	4.29	13.05
^{120}I	1.700	4.38	14.66

The shortcomings of clinical SPECT are the power of preclinical SPECT



^{18}F versus ^{68}Ga...

(courtesy E Visser, J Disselhorst)

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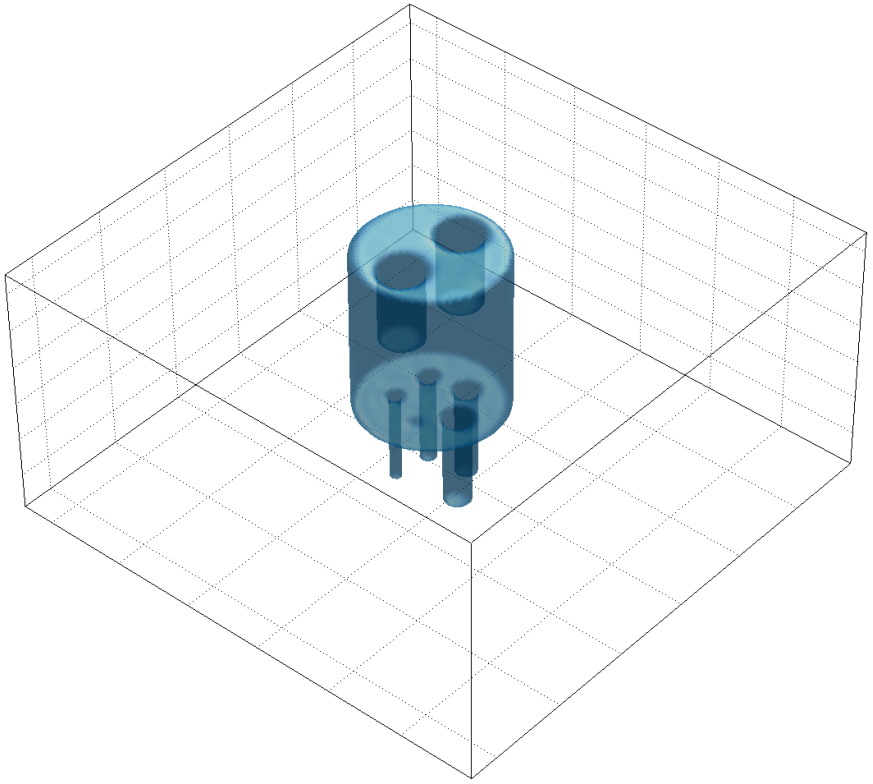
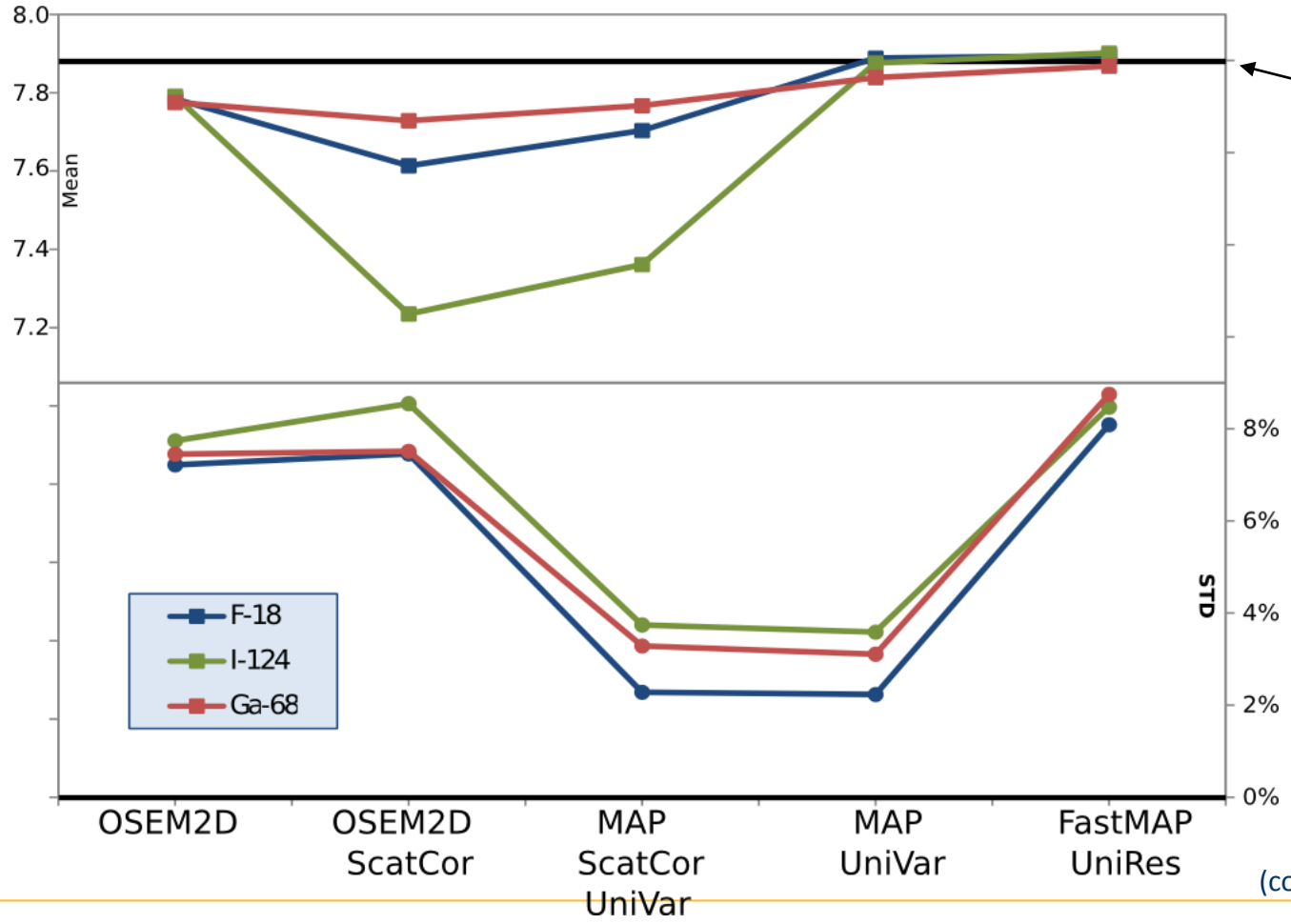


Uniform Area
Cylinder with uniform activity

(courtesy E Visser, J Disselhorst)

The shortcomings of clinical SPECT are the power of preclinical SPECT

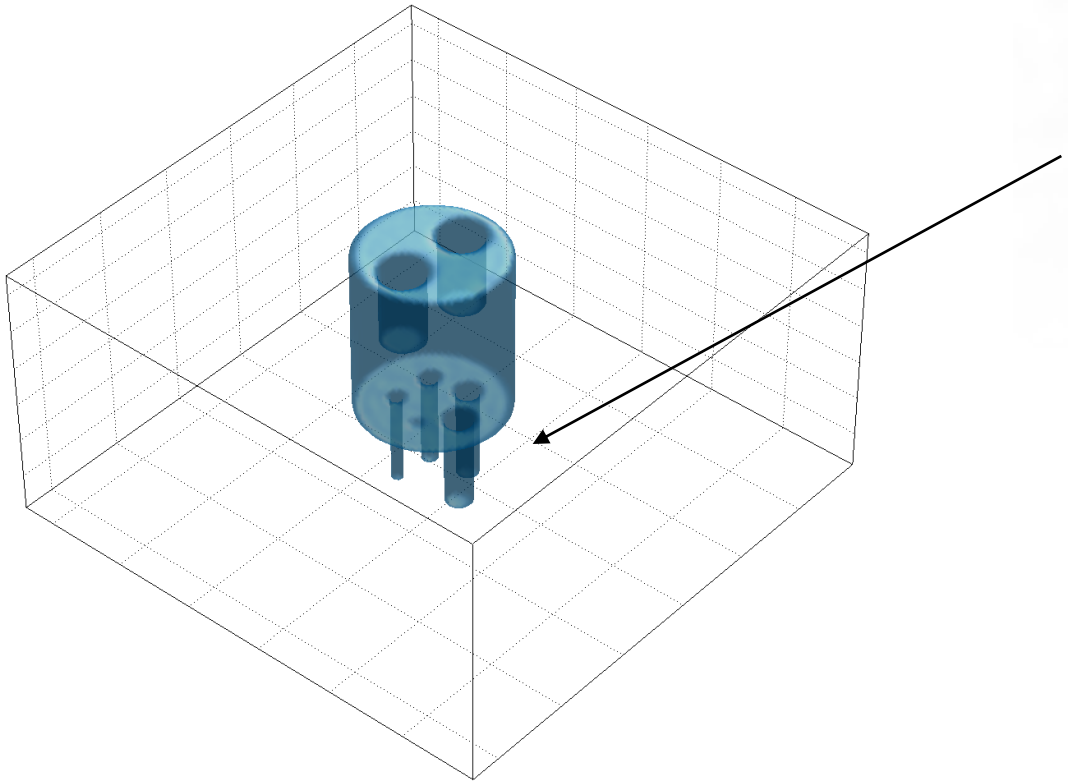


Closer to
=
Better

Lower = Better

(courtesy E Visser, J Disselhorst)

The shortcomings of clinical SPECT are the power of preclinical SPECT



Recovery
5 Rods (1-5 mm diameter)
in cold background

(courtesy E Visser, J Disselhorst)

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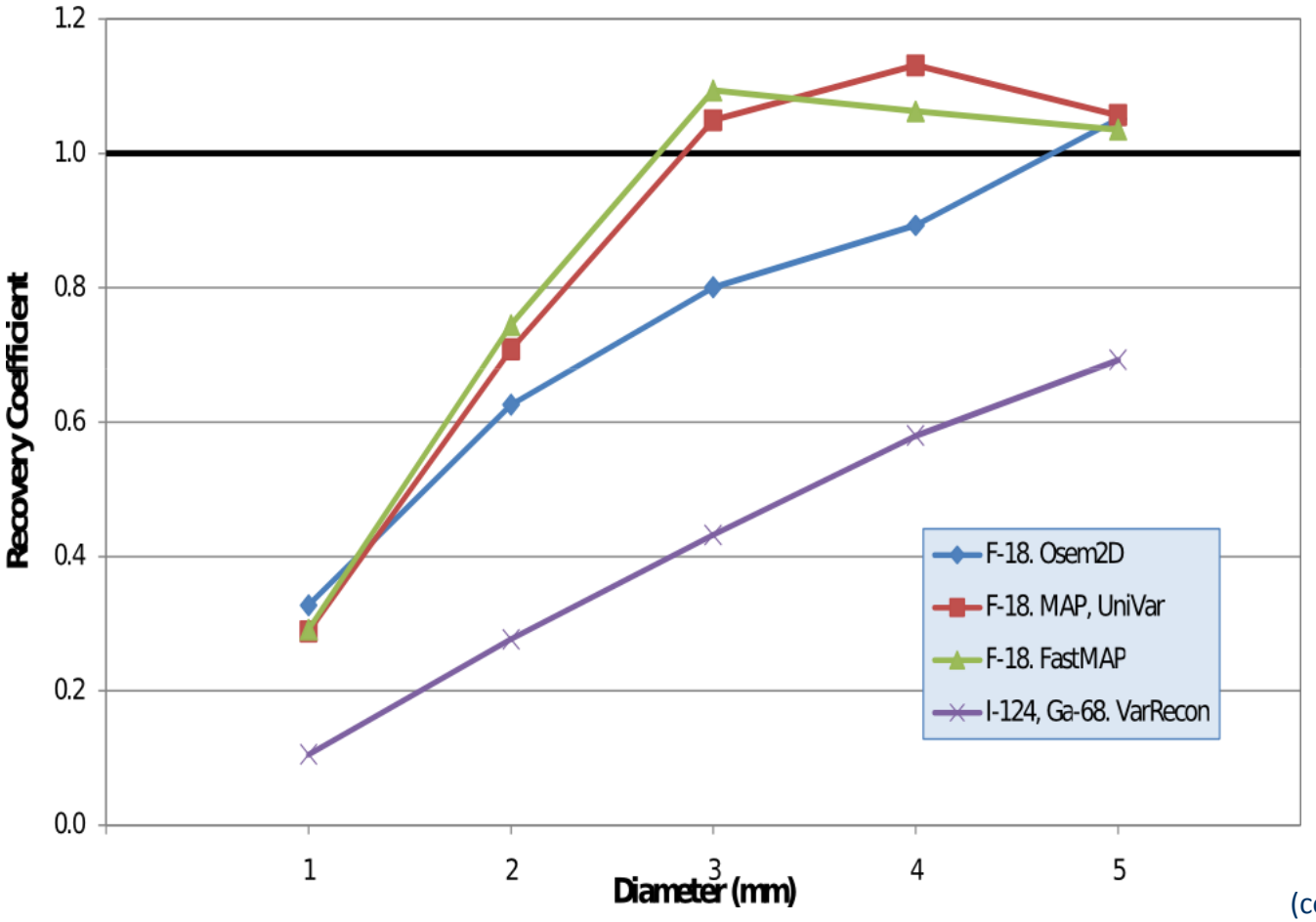

Close to 1
=
Better

(courtesy E Visser, J Disselhorst)

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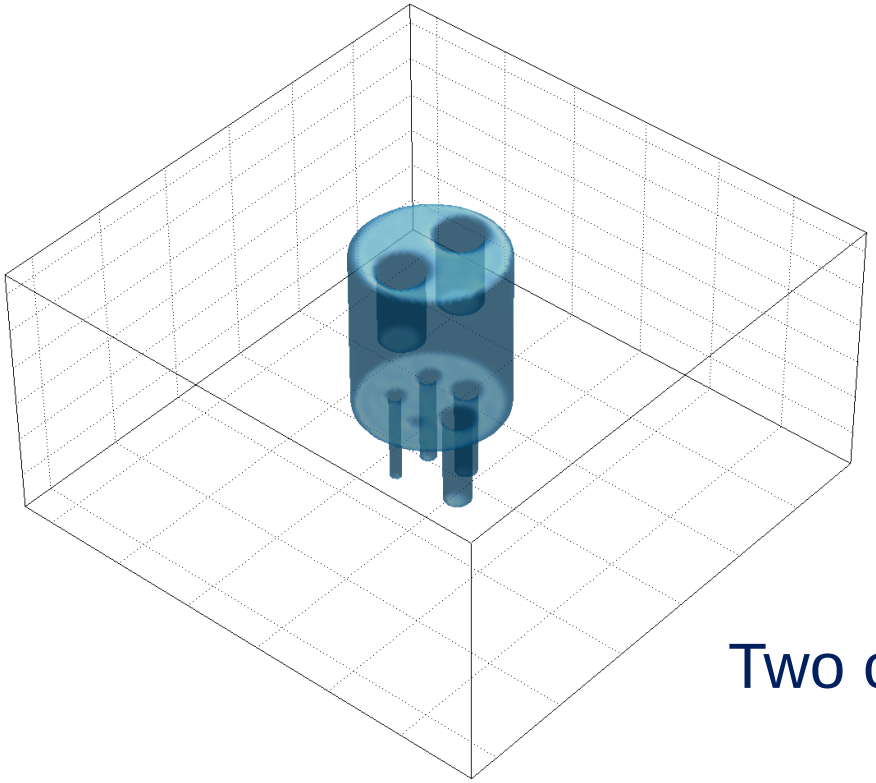

Spill Over Ratio

Two cold cylinders (one water, one air), uniform background

(courtesy E Visser, J Disselhorst)

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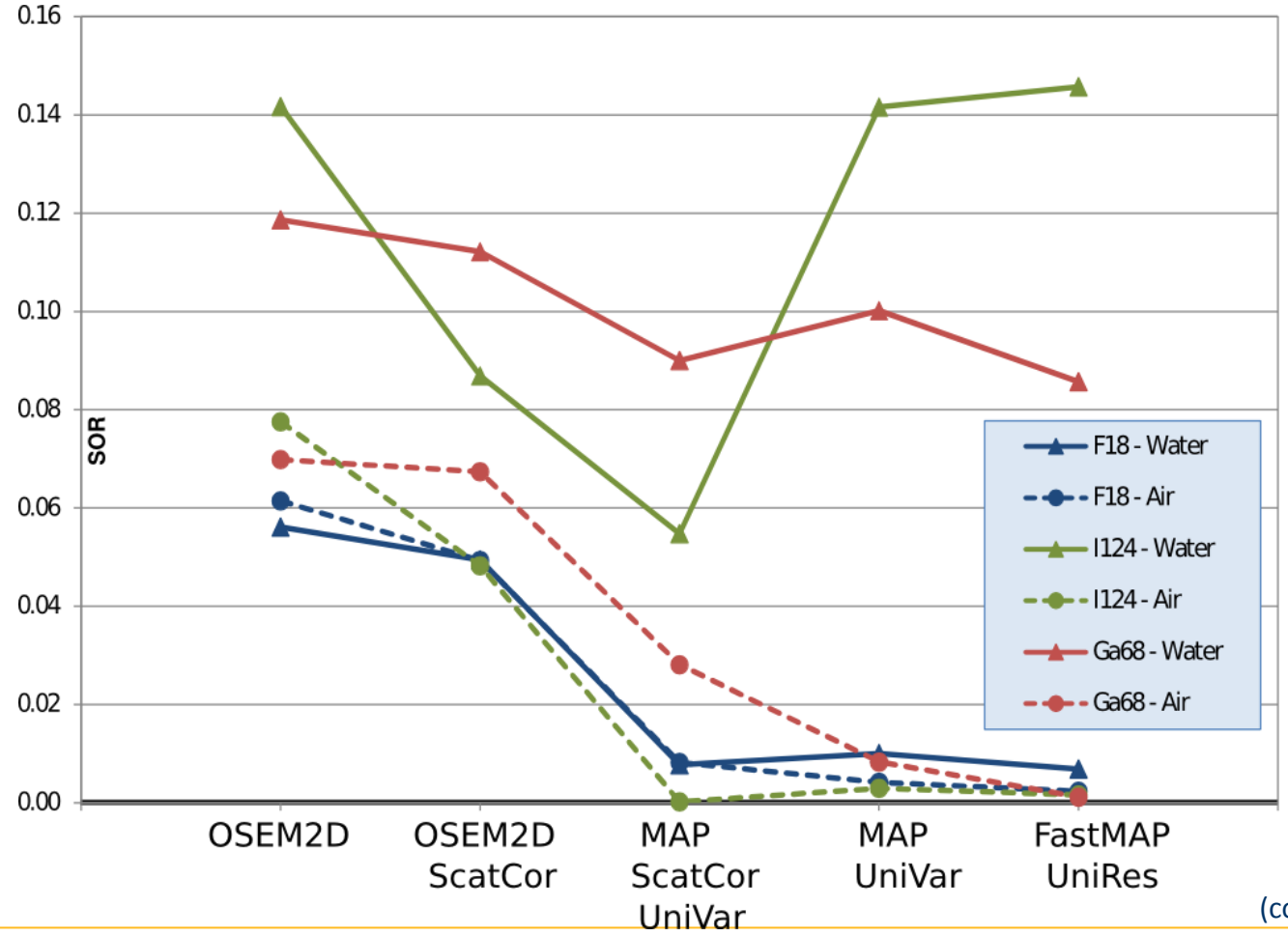

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(courtesy E Visser, J Disselhorst)

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•Quantitative imaging with SPECT: why not?

Development of a radiotracer for SPECT imaging: from bench to bedside

- Synthesis of the ligand
- Radiolabeling
  - Procedure, yield, pitfalls
- In vitro characterization
  - Stability, affinity, specificity, internalization
- In vivo characterization
  - Biodistribution, specificity of target uptake, physiologic uptake, dose effects, preclinical imaging
- Phase I studies
  - Safety, Radiation dose estimation, physiologic uptake, preliminary diagnostic evaluation

Development of a radiotracer for SPECT imaging: from bench to bedside

Exendin-4 (1-39) for imaging of beta cells in diabetes

His- Ser- Asp- Gly- Thr- Phe- Thr- Ser- Asp- Leu- Ser- Lys- Gln-Met- Glu- Glu- Glu- Ala- Val- Arg- Leu- Phe- Ile- Glu- Trp- Leu-Lys- Asn- Gly- Gly- Pro- Ser- Ser- Gly- Ala- Pro- Pro- Pro- Ser-NH_2

(homologies to GLP-1 in red)

Radiometal labeling:

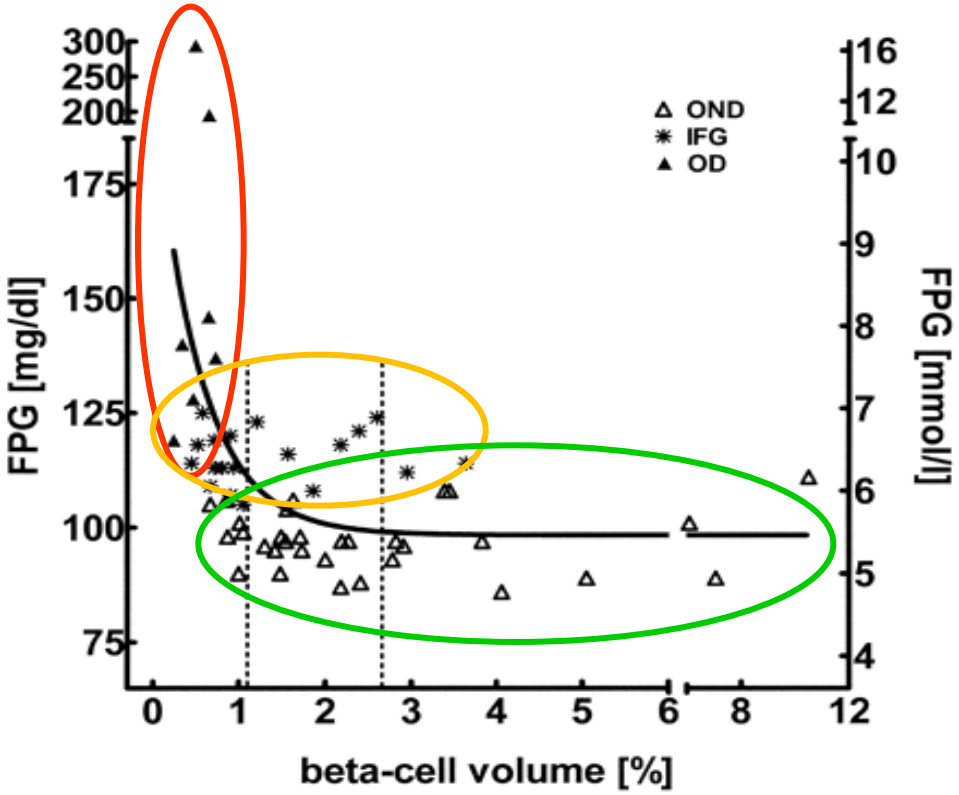
Exendin-4-Lys_{40}-[e-AHX-DTPA]

But first of all

Why, oh why…?

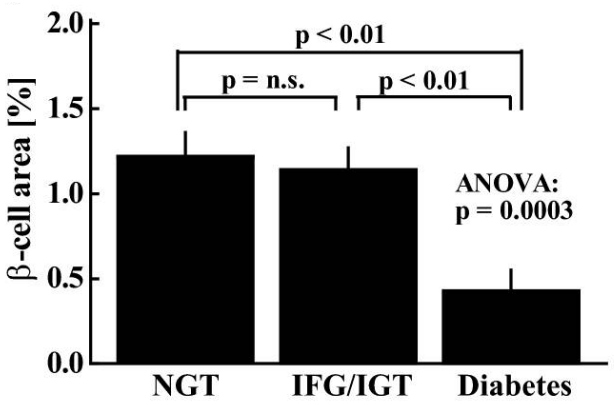
Diabetes is a clinical diagnosis in the end!

Development of a radiotracer for SPECT imaging: from bench to bedside



Ritzel RA et al., Diabetes Care. 2006 Mar;29(3):717-8.

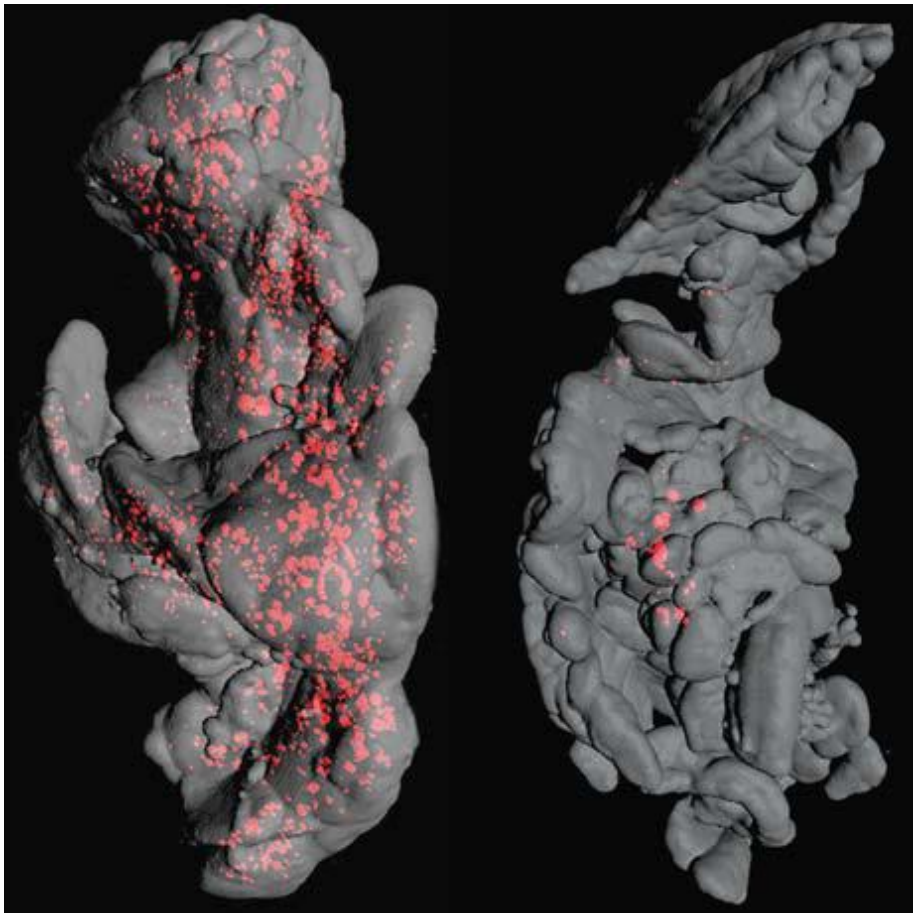
OGTT prior to pancreatectomy
8 NGT, 14 IGT/IFG, 11 DM



Juris J. Meier et al., Diabetes (2009) 58:1595-1603

Development of a radiotracer for SPECT imaging: from bench to bedside

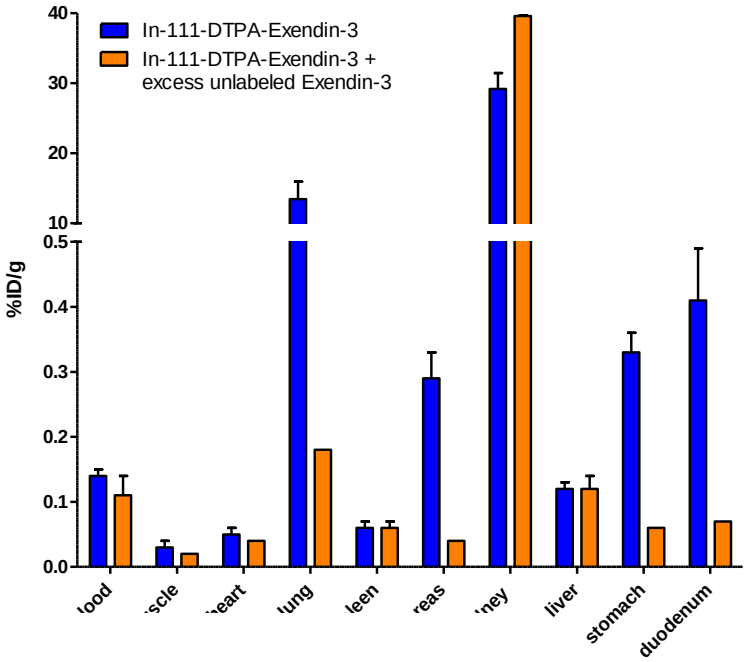
THE CHALLENGE

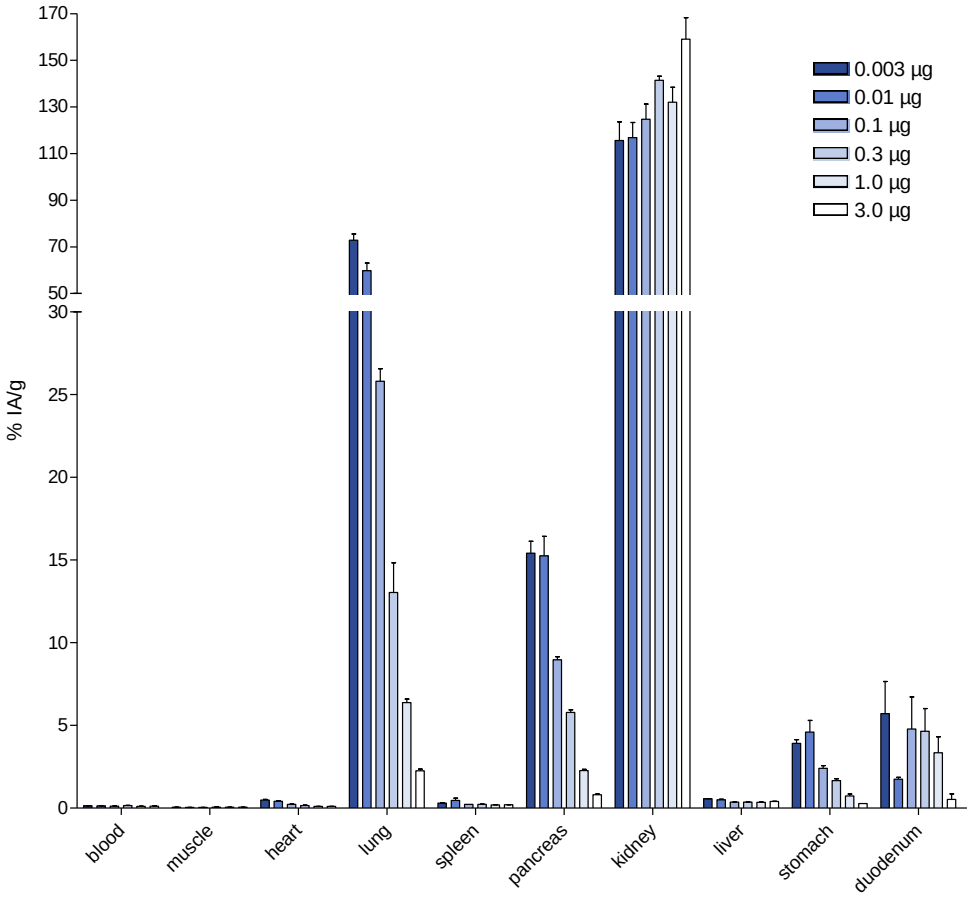


Ahlgren U, Gotthardt M. Approaches for imaging islets: recent advances and future prospects. Adv Exp Med Biol 2010;654:39-57

Image by T. Alanentalo and U. Ahlgren

Development of a radiotracer for SPECT imaging: from bench to bedside





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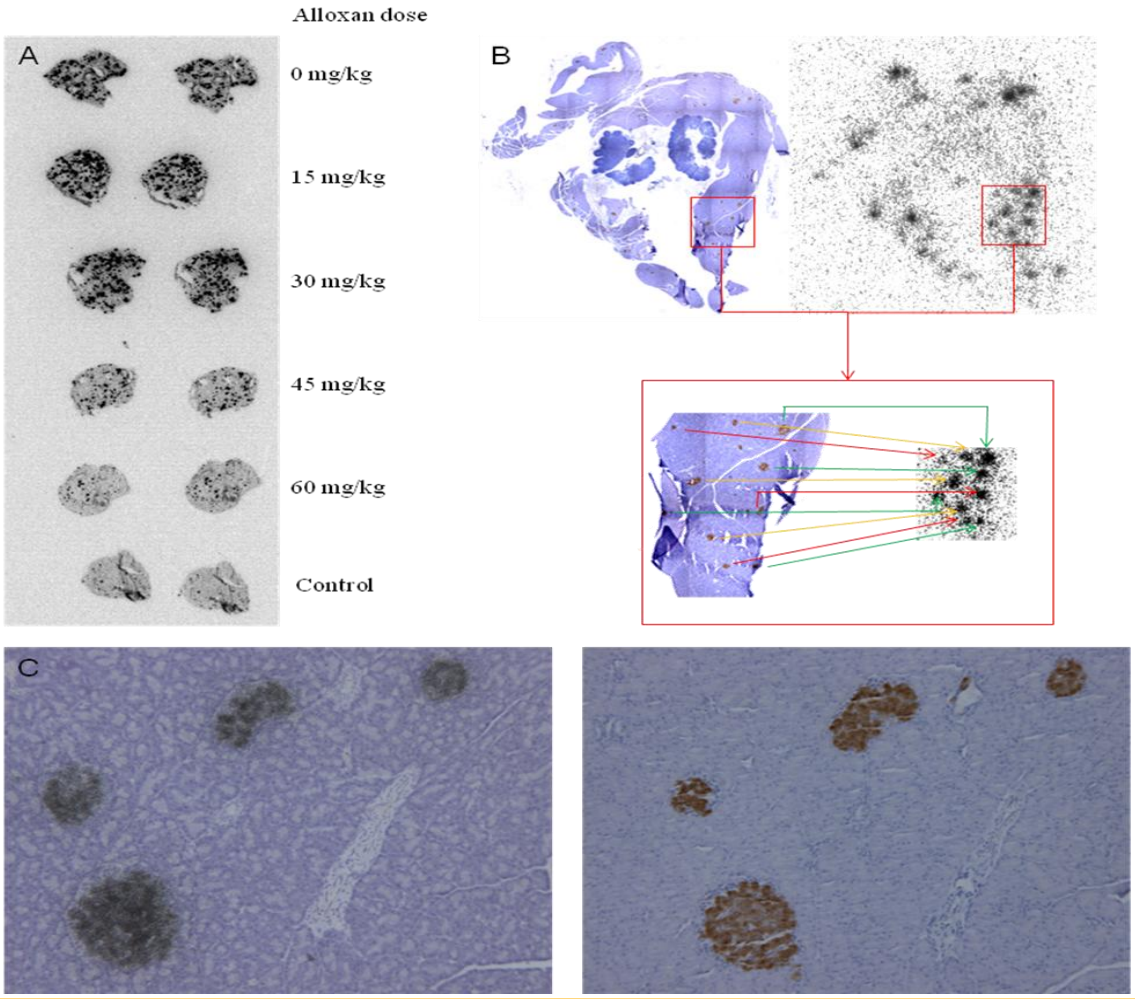

Brom et al., Diabetologia 57, 950-959 (2014);

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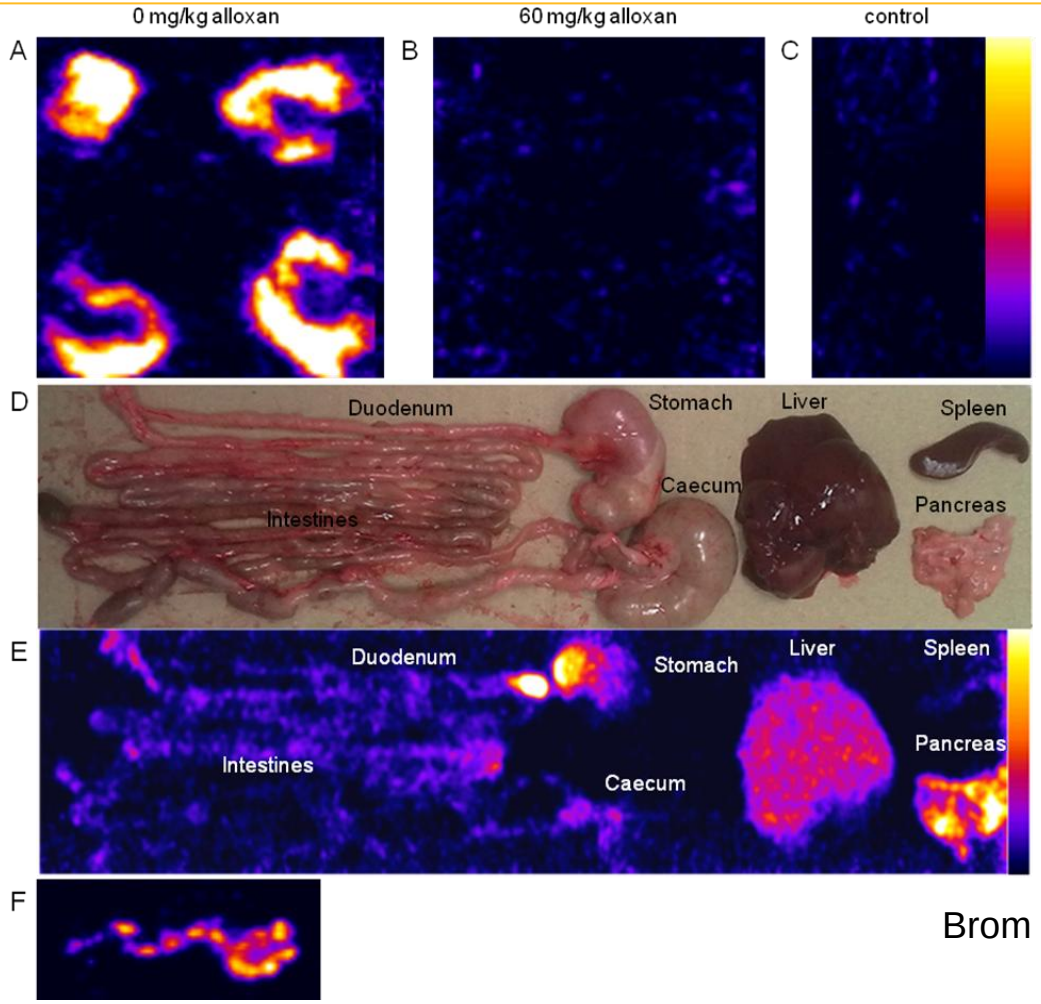

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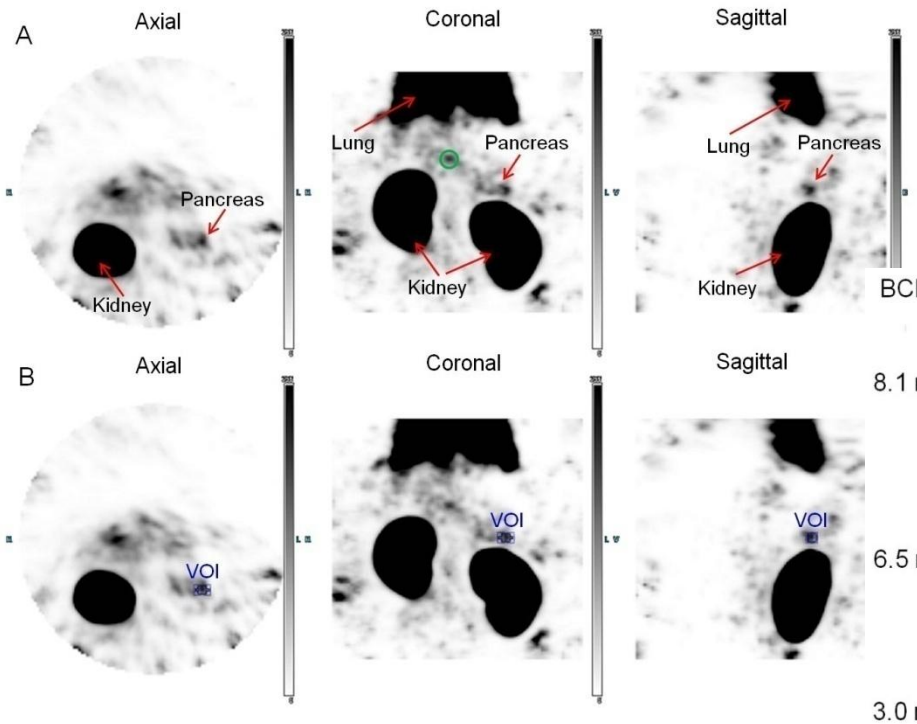

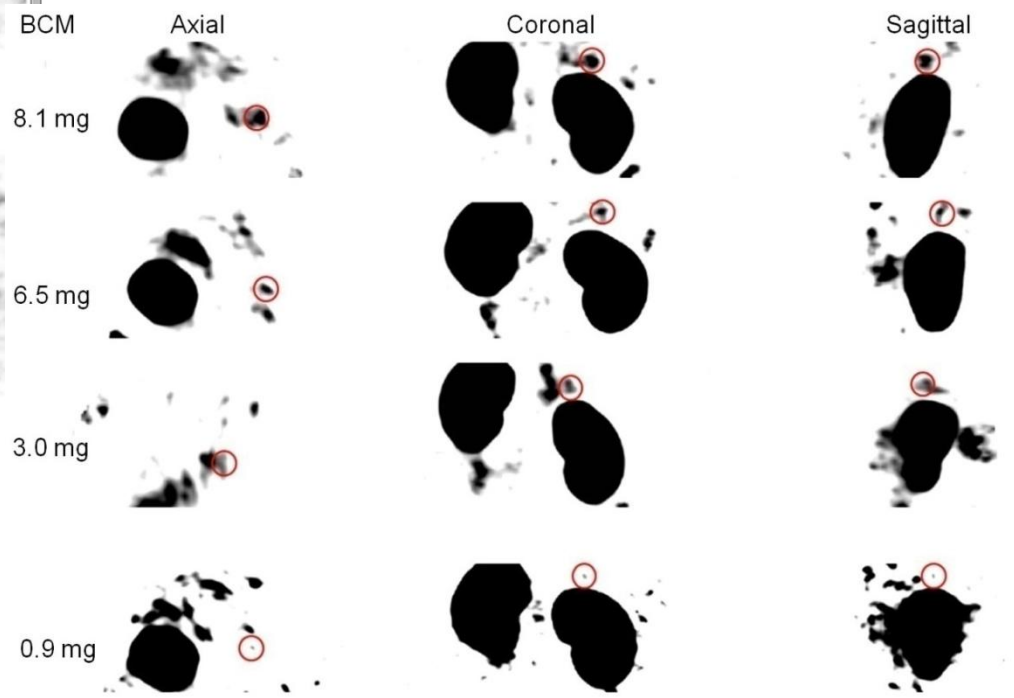

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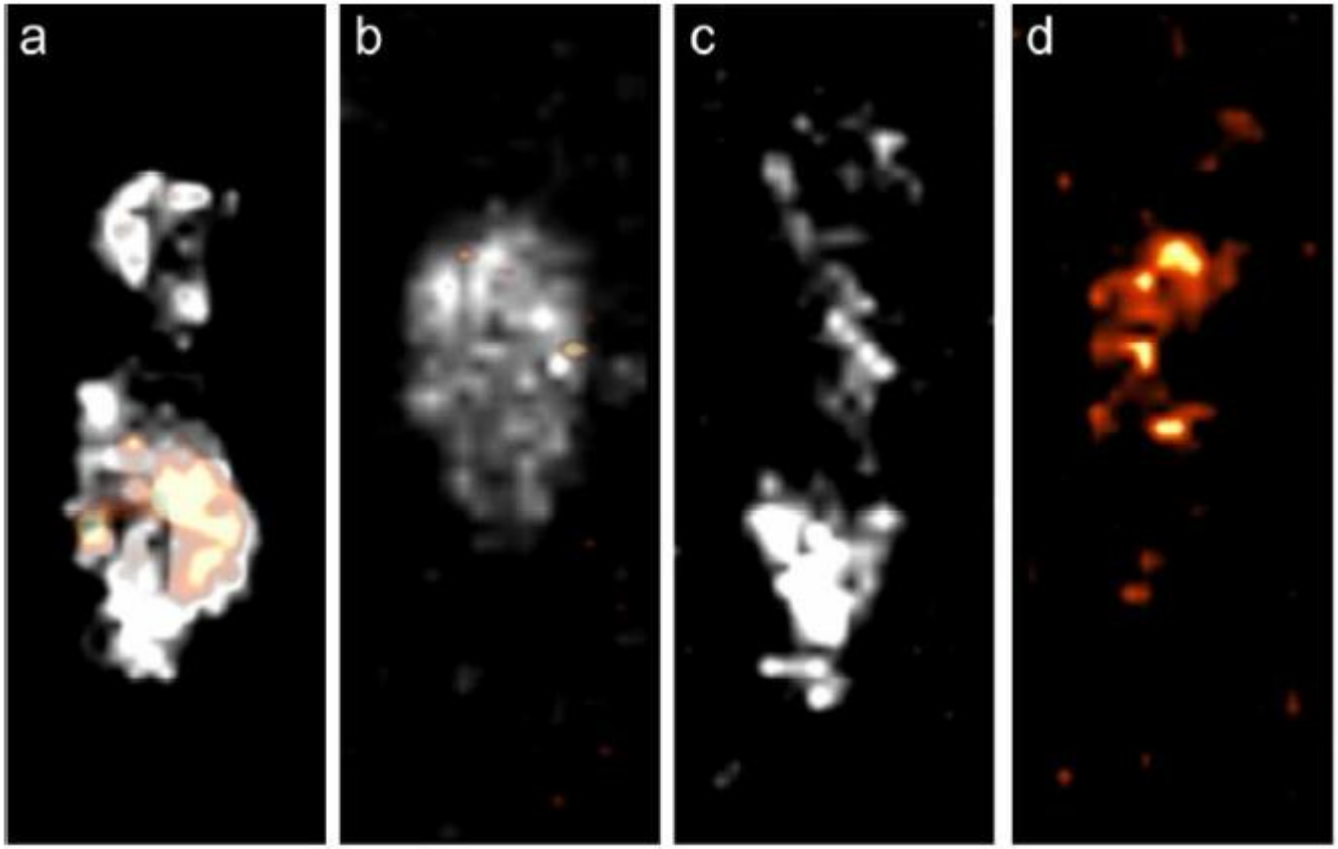

Kroon et al., Mol. Pharmaceutics, DOI: 10.1021/acs.molpharmaceut.6b00495 • Publication Date (Web): 18 Aug 2016

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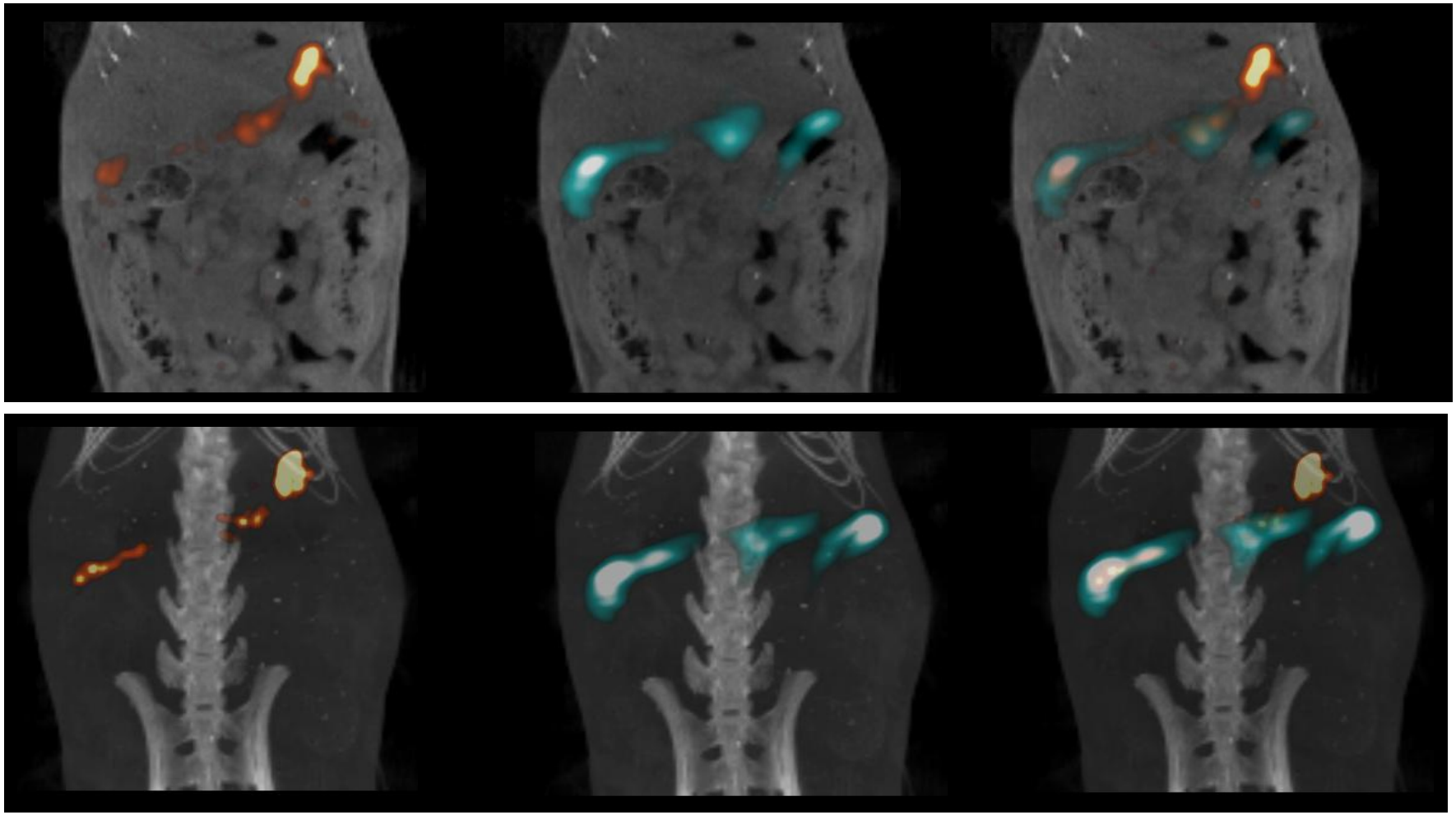

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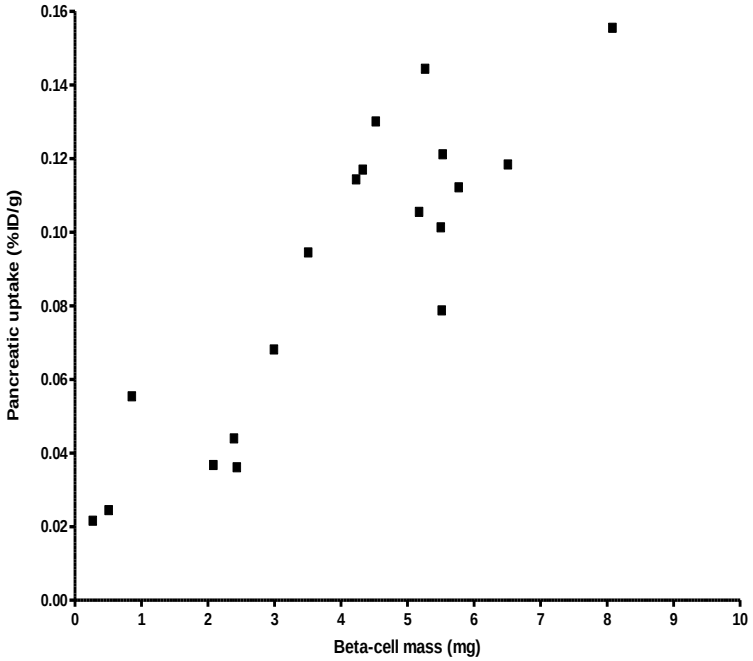
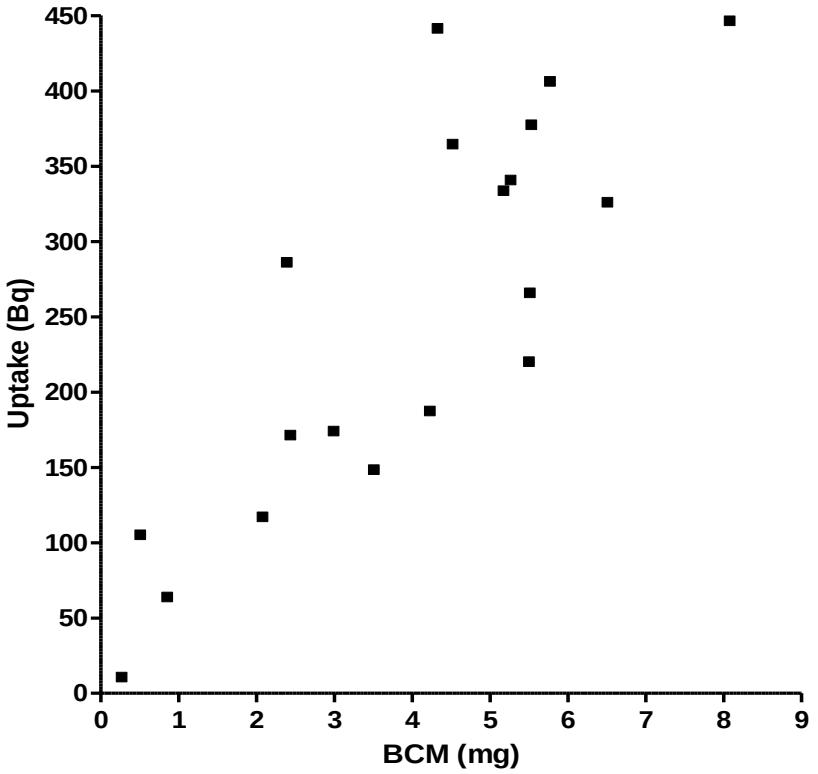


- Linear correlation of uptake and BCM, r=0.89 (left)
- Linear correlation of in vivo SPECT quantification and BCM, r=0.83 (right)



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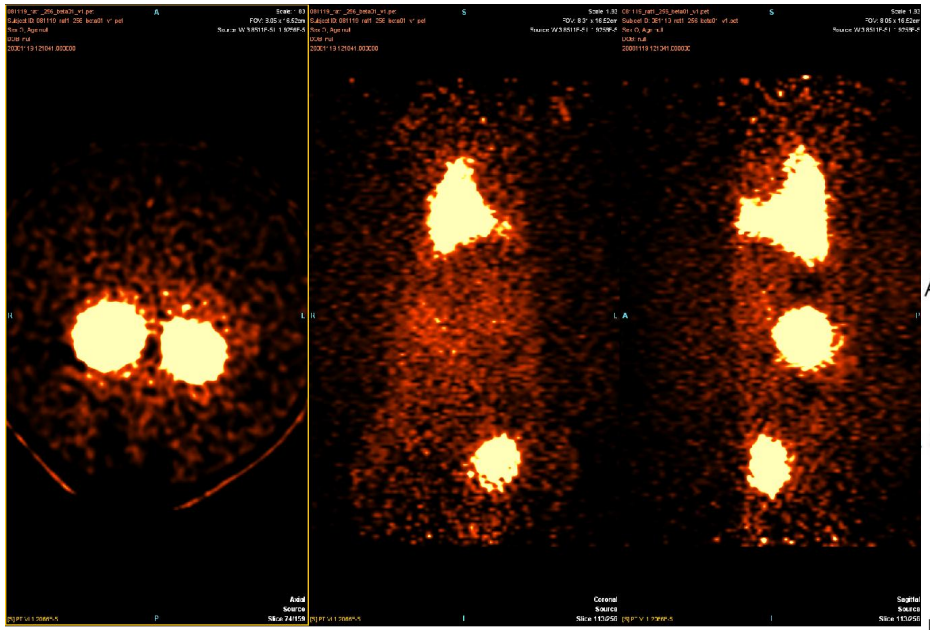

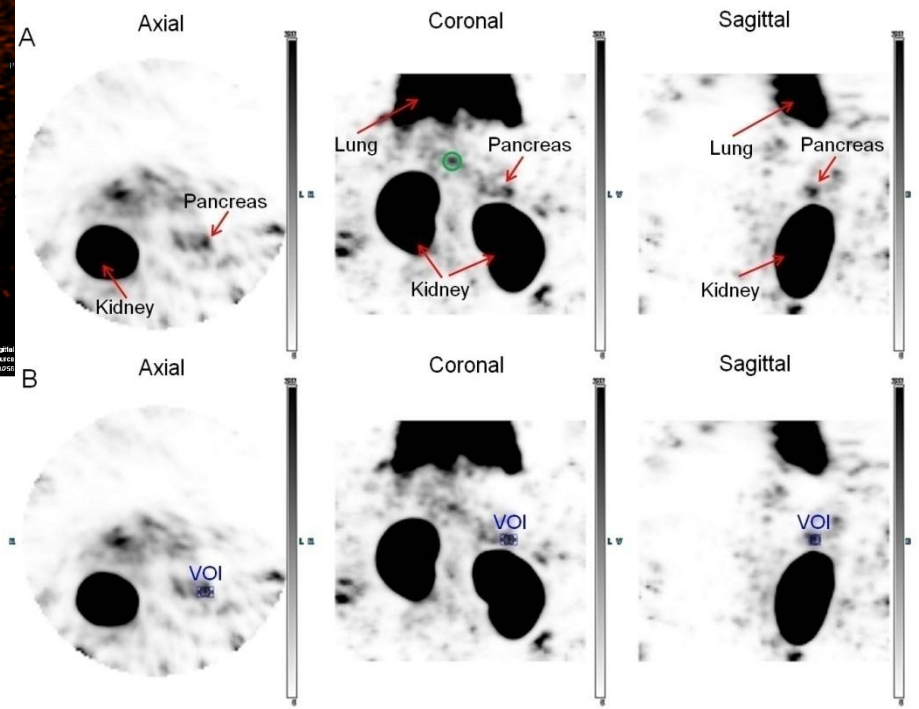

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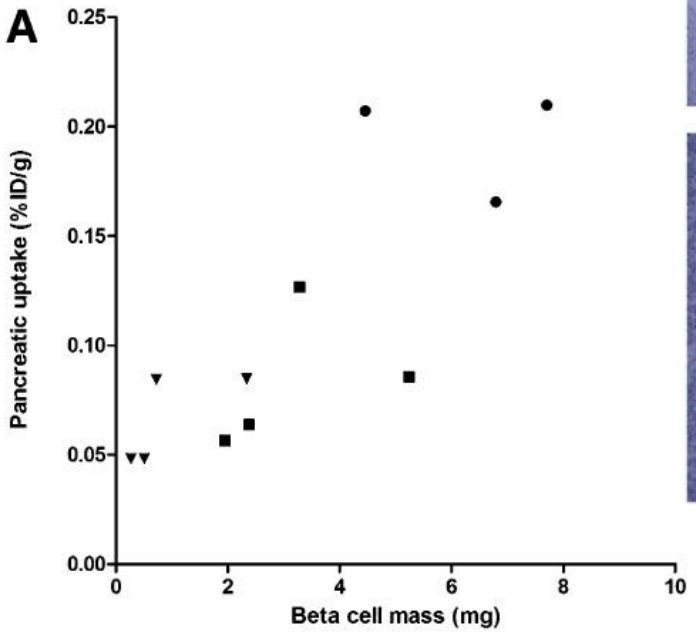
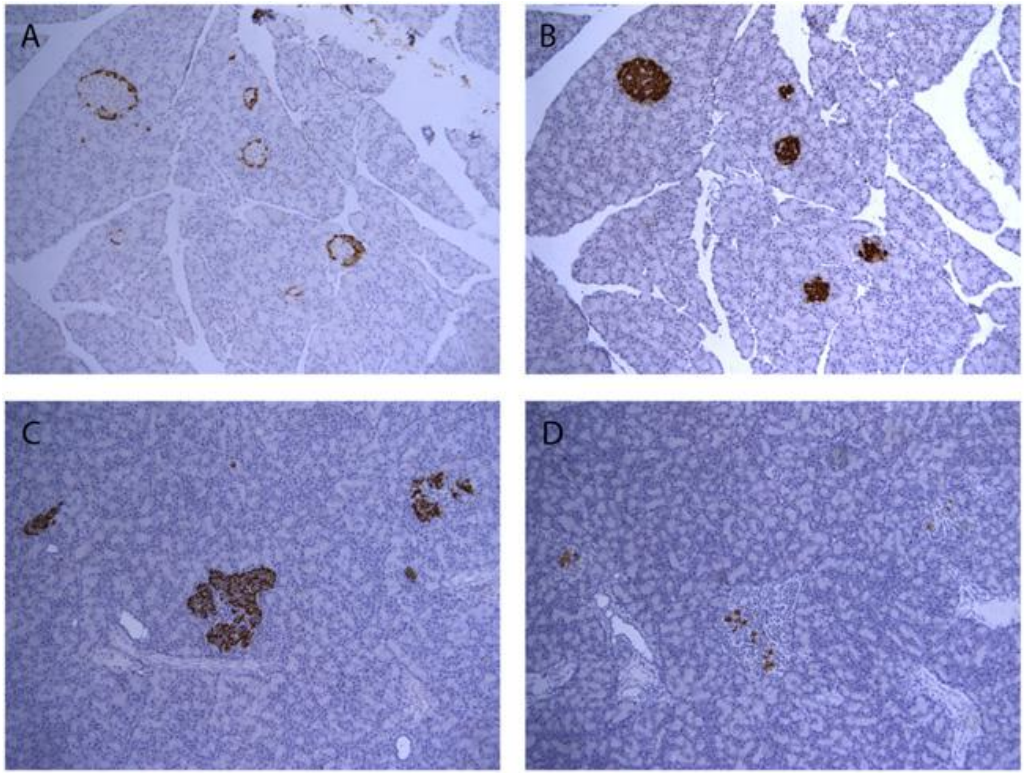
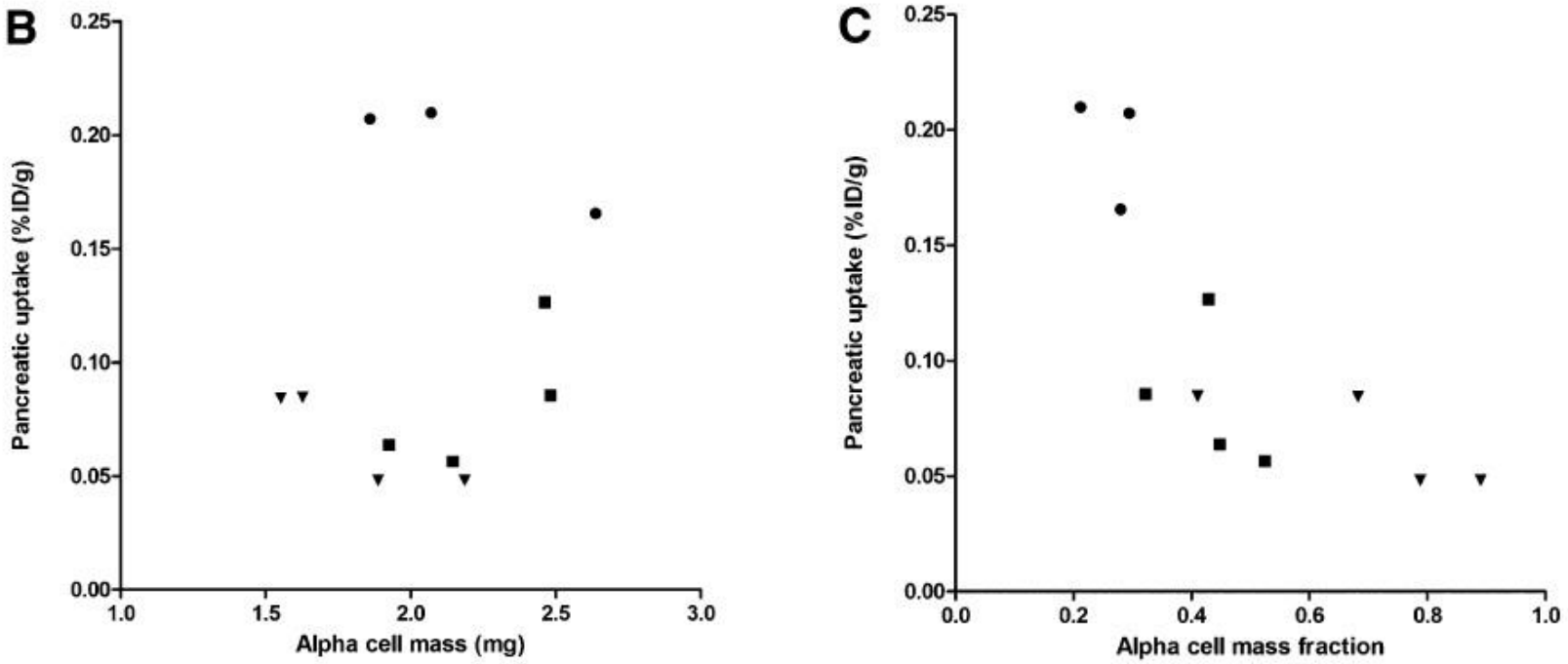




Brom et al, Diabetes 2015;64:1324–1328

Development of a radiotracer for SPECT imaging: from bench to bedside



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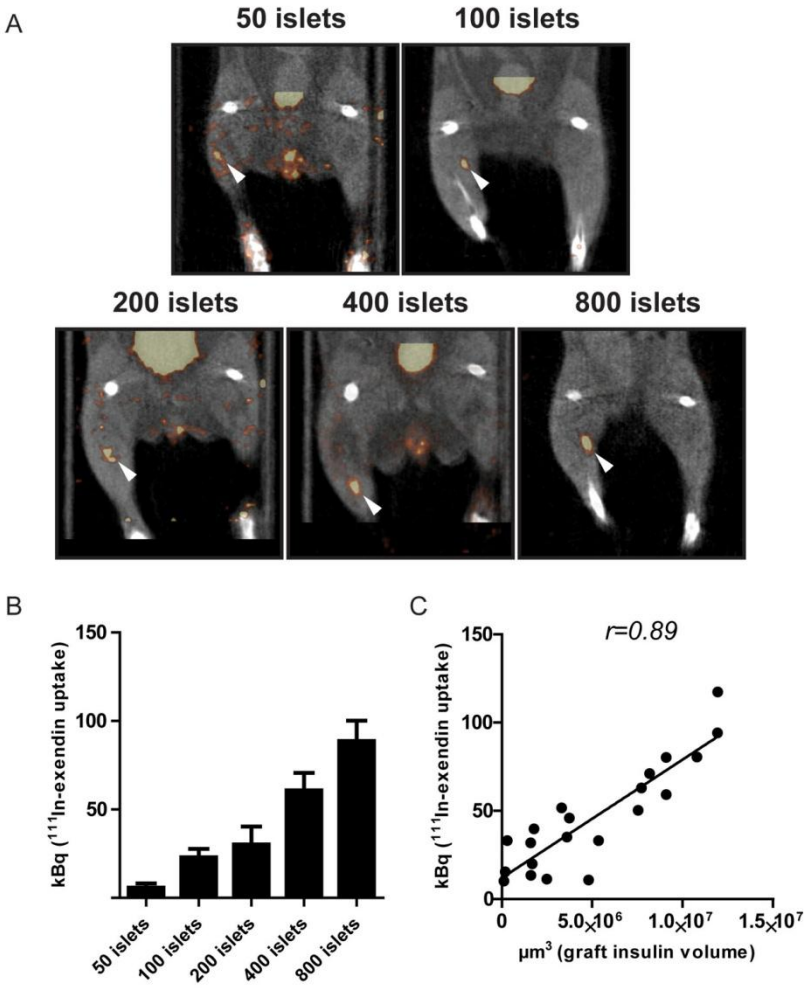

Kroon et al., J Nucl Med 2016; 57:799–804

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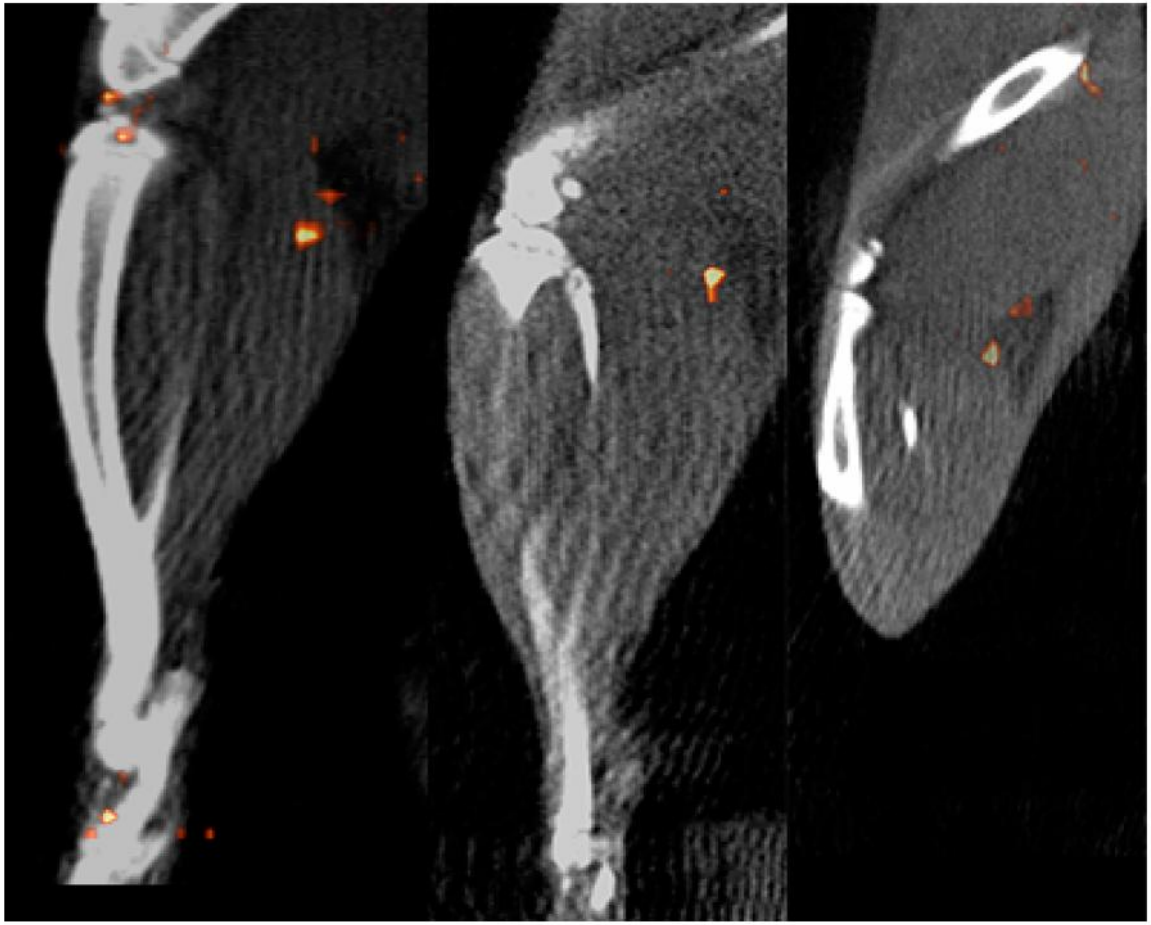

Willekens et al., Molecular pharmaceutics 13, 85-91 (2016)

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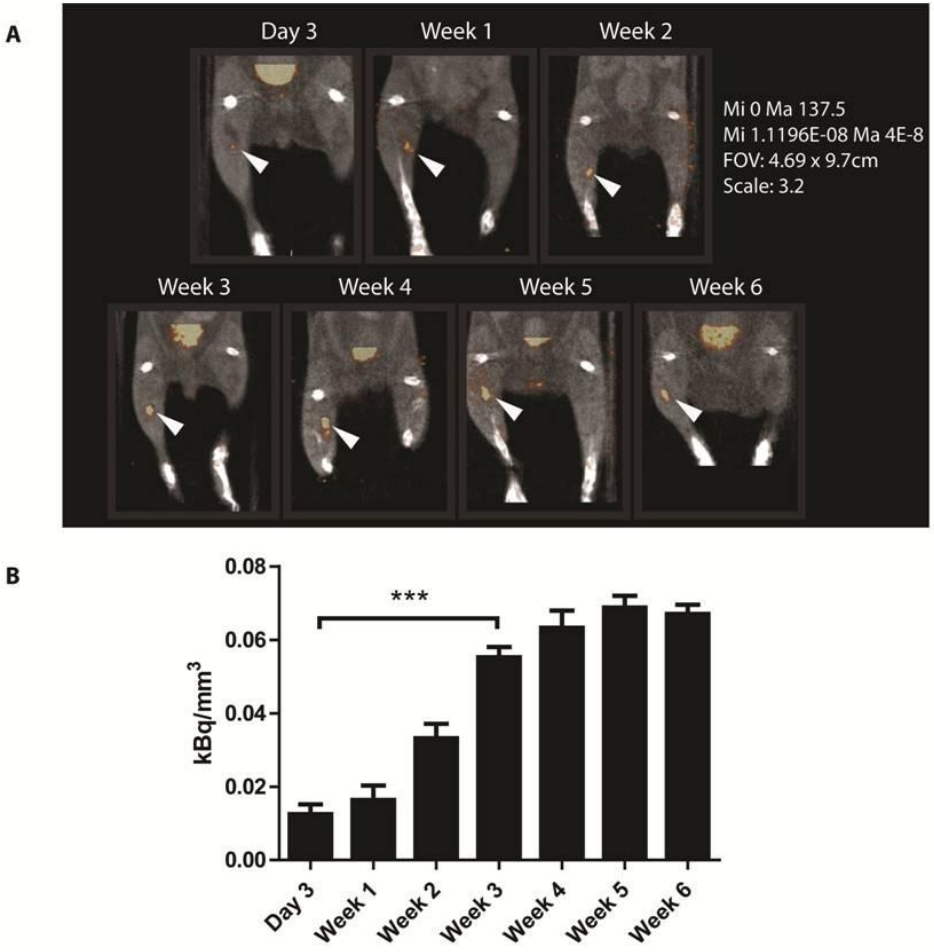

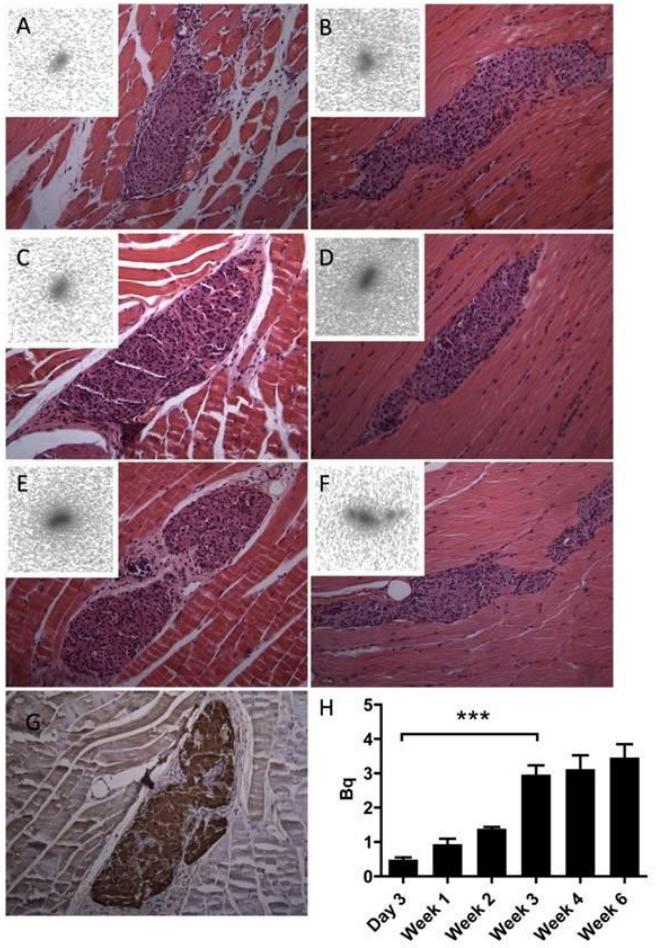

Eter et al., Sci Rep. 2015 Oct 22;5:15521. doi: 10.1038/srep15521

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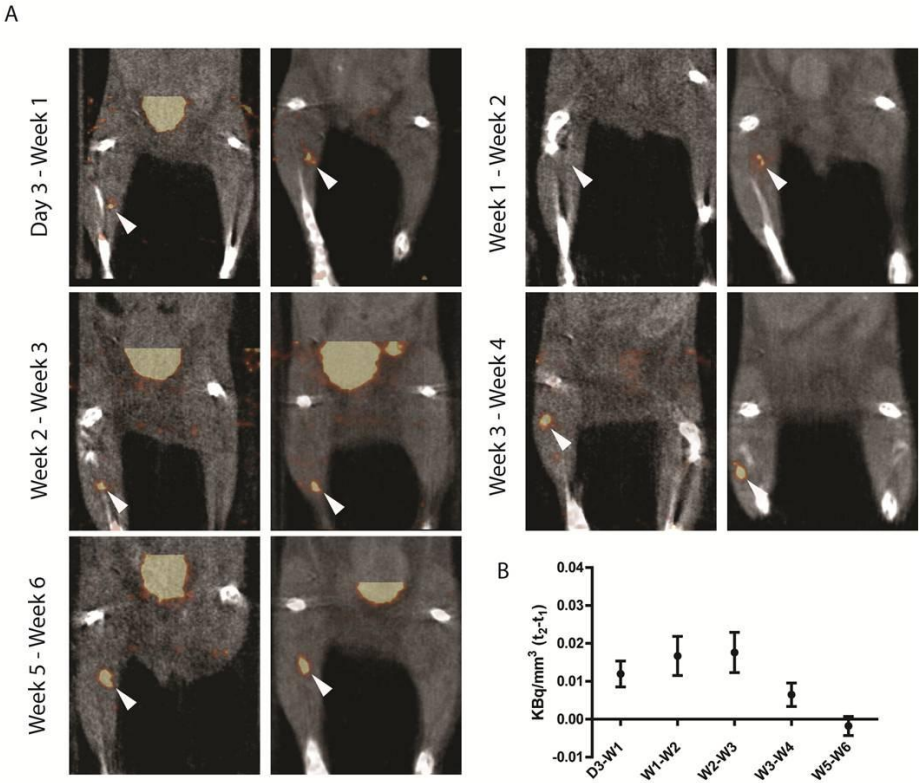

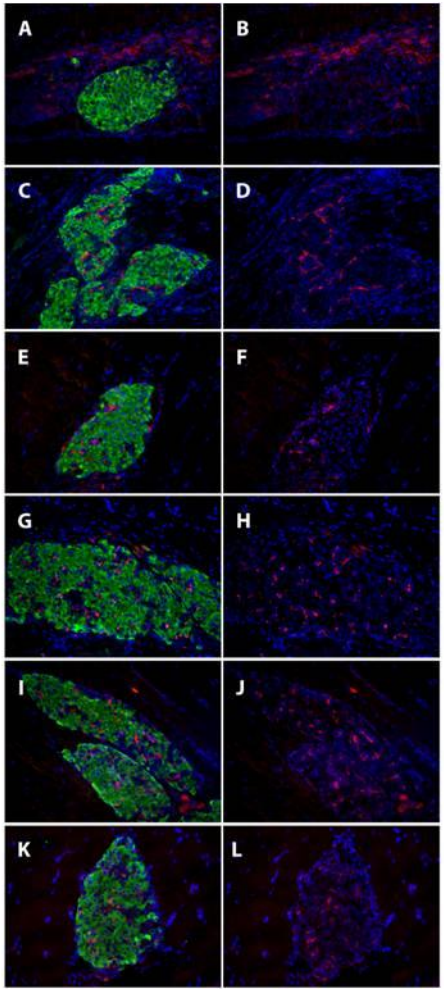

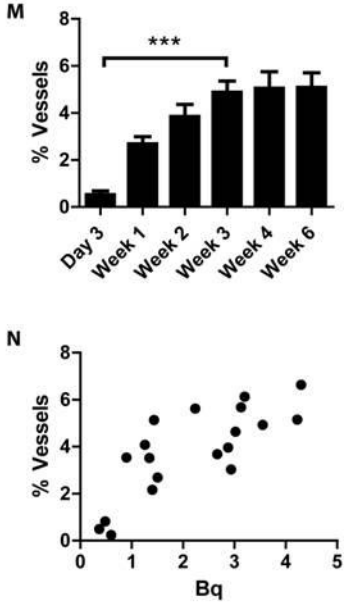

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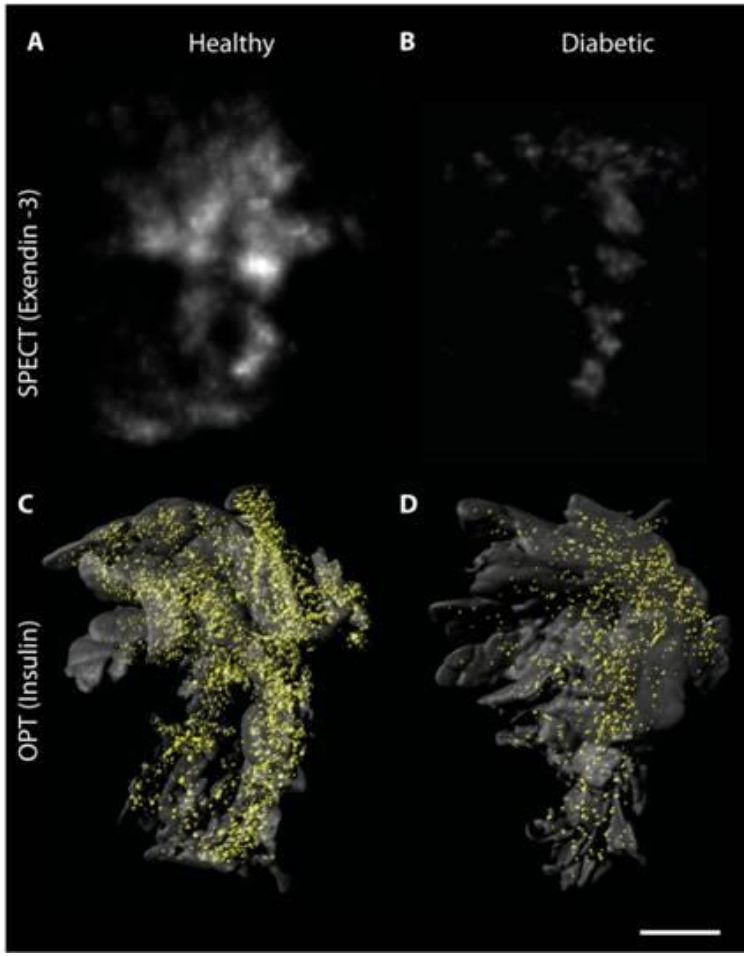


SPECT and OPT reflect beta cell mass better than histology!

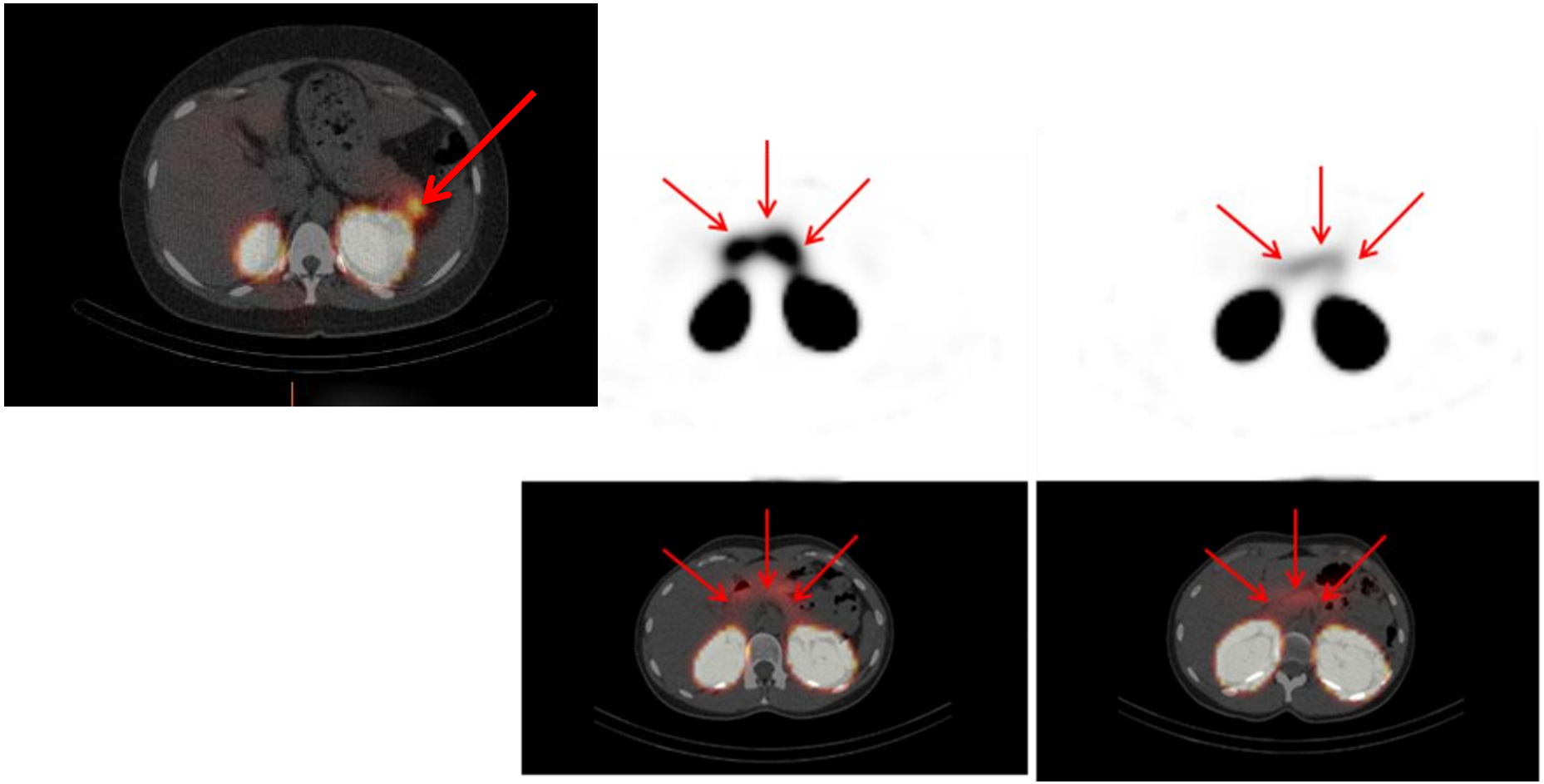
W. A. Eter, S. Parween, L. Joosten, C. Frielink, M. Eriksson, M. Brom, U. Ahlgren, M. Gotthardt, SPECT-OPT multimodal imaging enables accurate evaluation of radiotracers for beta-cell mass assessments. Scientific reports 6, 24576 (2016)10.1038/srep24576).

Development of a radiotracer for SPECT imaging: from bench to bedside

Development of a kit for clinical imaging

- Requirements:
  - –GMP produced ligand
  - –IMPD
  - –GMP labeling procedure
- Kit formulation to which only ^{111}InCl needs to be added, labeling by incubation at room temperature for 20 minutes
- Can be distributed within Europe for clinical imaging after approval by QP

Development of a radiotracer for SPECT imaging: from bench to bedside



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Quantitative imaging with SPECT: why not?

SPECT is not quantitative while …

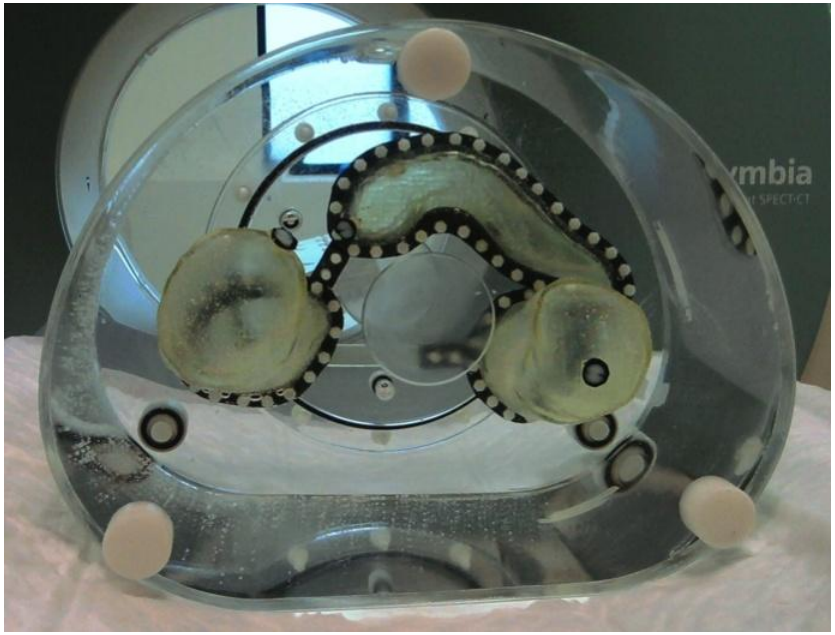
PET is quantitative by definition

Quantitative imaging with SPECT: why not?

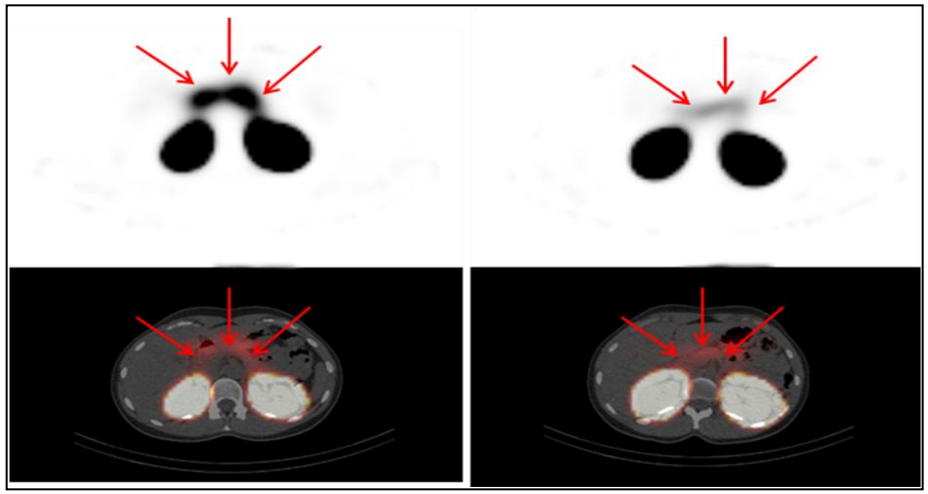
Phantom for **protocol optimization**, for enabling quantitative data analysis

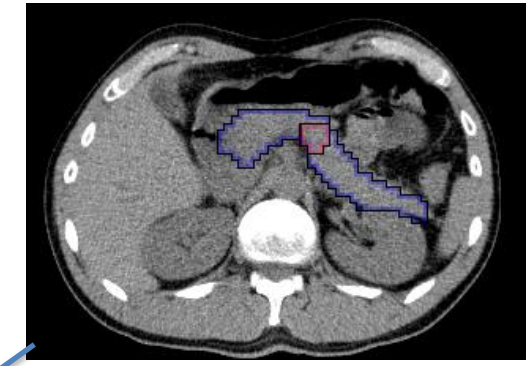
Reconstruction (Hermes Hybrid Recon)

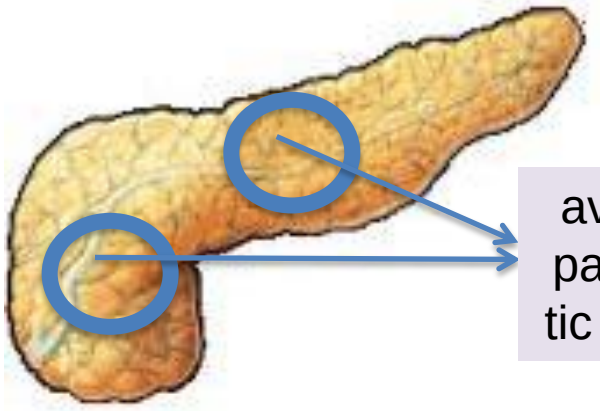
- OSEM 16 iterations, 6 subsets
- Attenuation correction
- Scatter correction
- Collimator correction



Quantitative imaging with SPECT: why not?

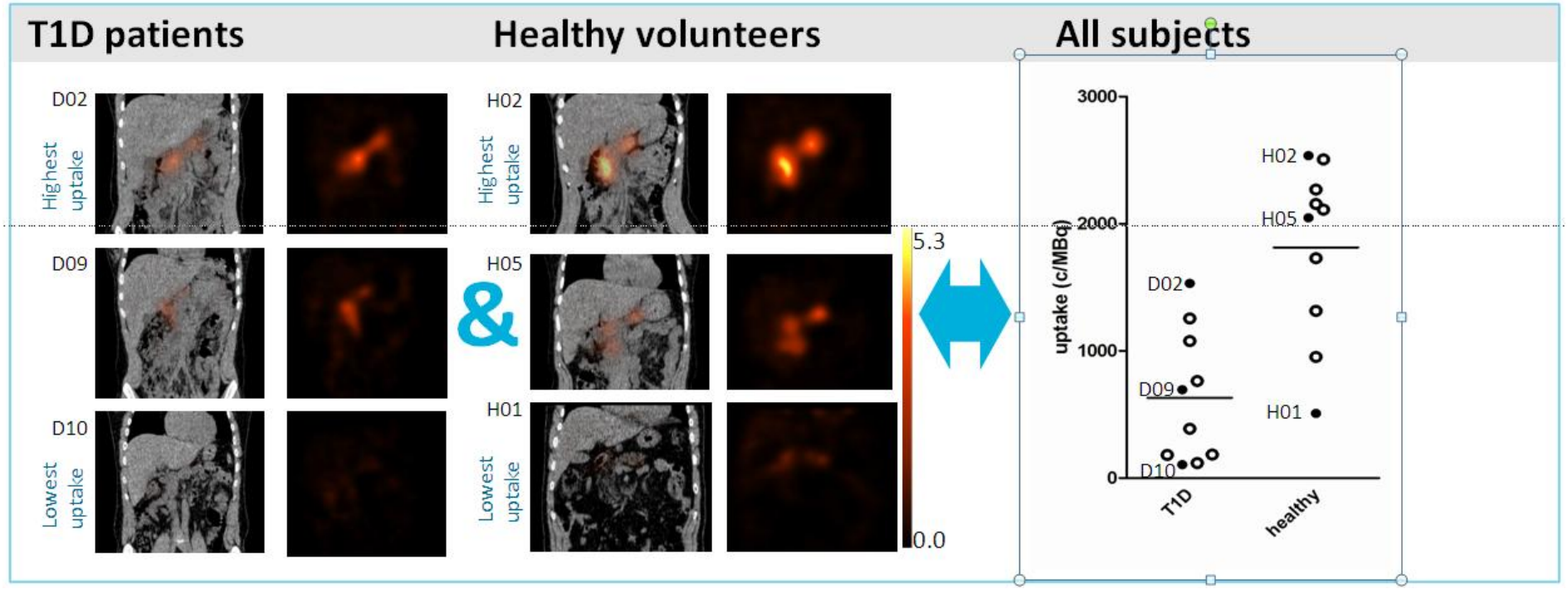






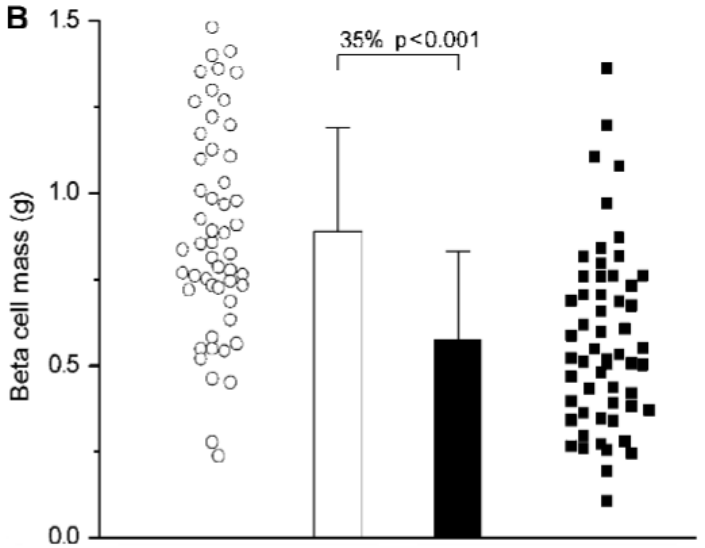
average pancrea-tic uptake × CT-based pancreas volume = uptake whole pancreas

Quantitative imaging with SPECT: why not?



Quantitative imaging with SPECT: why not?

- Pancreatic uptake varies by a factor of ~5 between individuals and there is an overlap between healthy and diabetic individuals (Rahier et al. 2008; Ritzel et al. 2006; Meier et al. 2009)



- T1D patients seem to have remaining (afunctional) BCM (Coppieters et al, J. Exp. Med. 2012) and 40% BCM reduction may already lead to overt T1D in adults (Klinke et al, PLoS ONE 2008)

- Stem cell transplantation can reverse T1D and render patients insulin-independent, suggesting the presence of functionally inactive BCM (Voltarelli et al, JAMA 2007; Couri et al. JAMA. 2009)

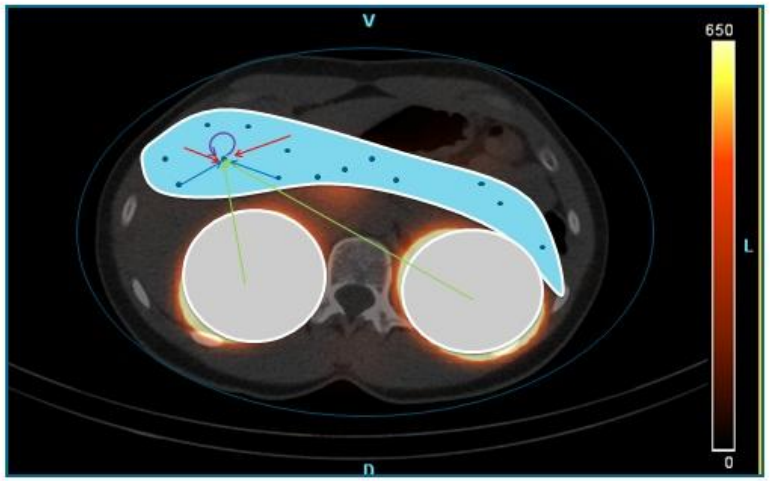
Quantitative imaging with SPECT: why not?

How dangerous is GLP-1R scanning for the islets?

Methods

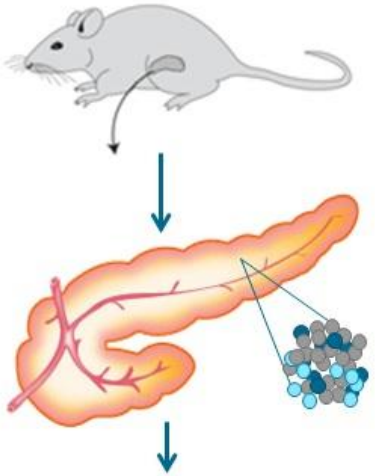
The model

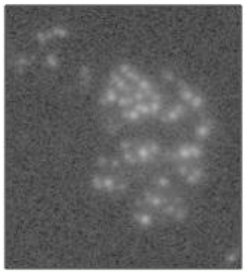
1. Selfdose islet
2. Dose due to other islets
3. Dose due to exocrine tissue
4. Dose due to kidneys



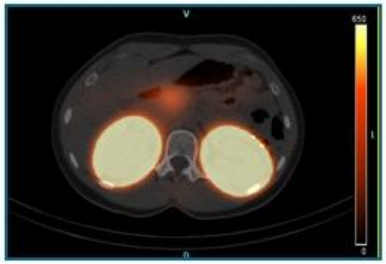
Input

Rat:





Human:



Calculations:

- Uptake ratio exocrine/islets
- Residence time each source
- Contribution each source to islet radiation dose

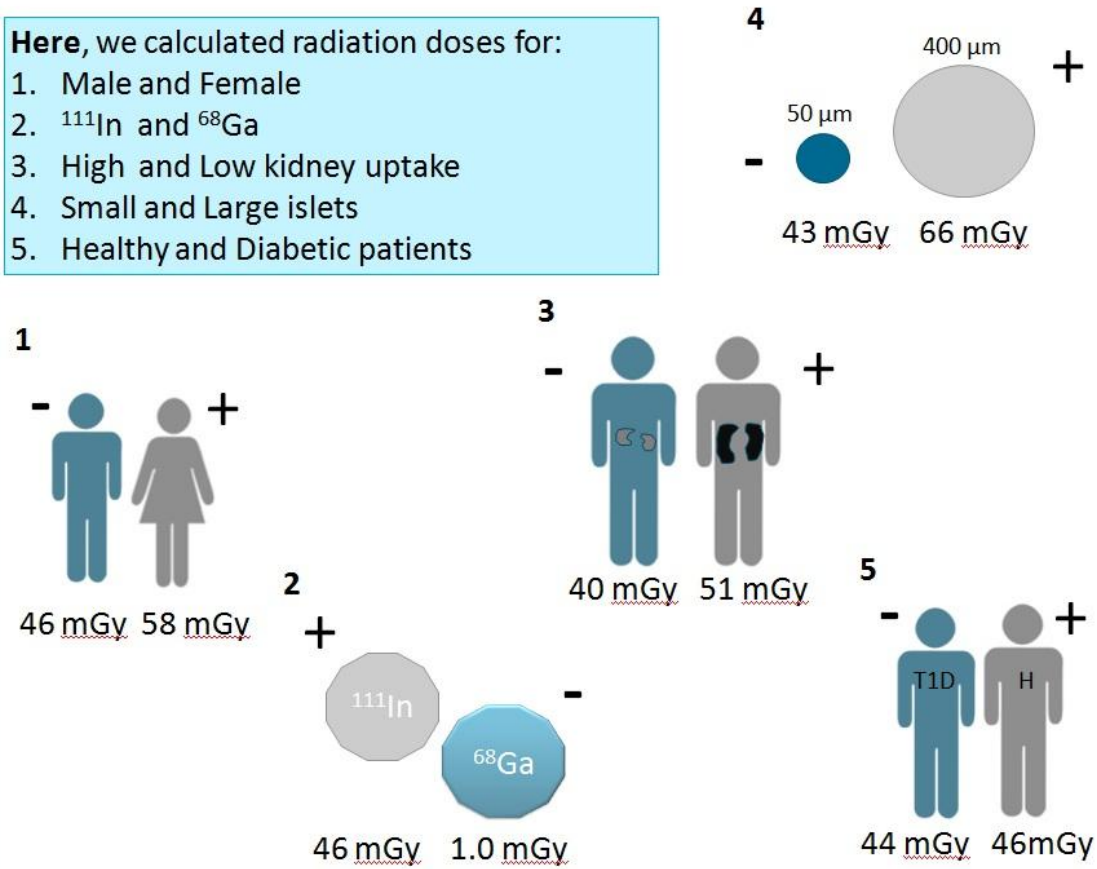
Quantitative imaging with SPECT: why not?

GLP-1R scanning is not dangerous for islets!

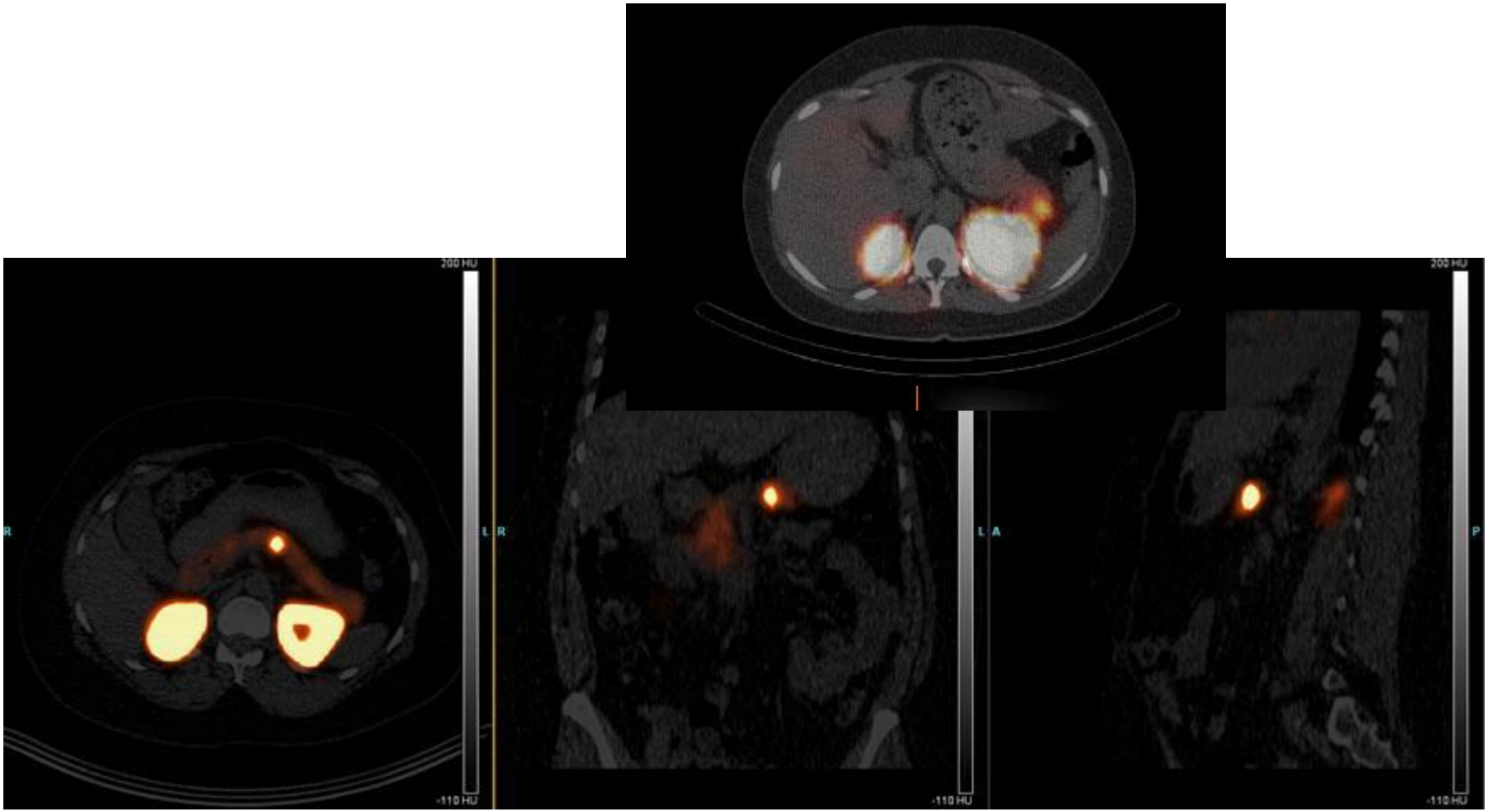
Results

Here, we calculated radiation doses for:

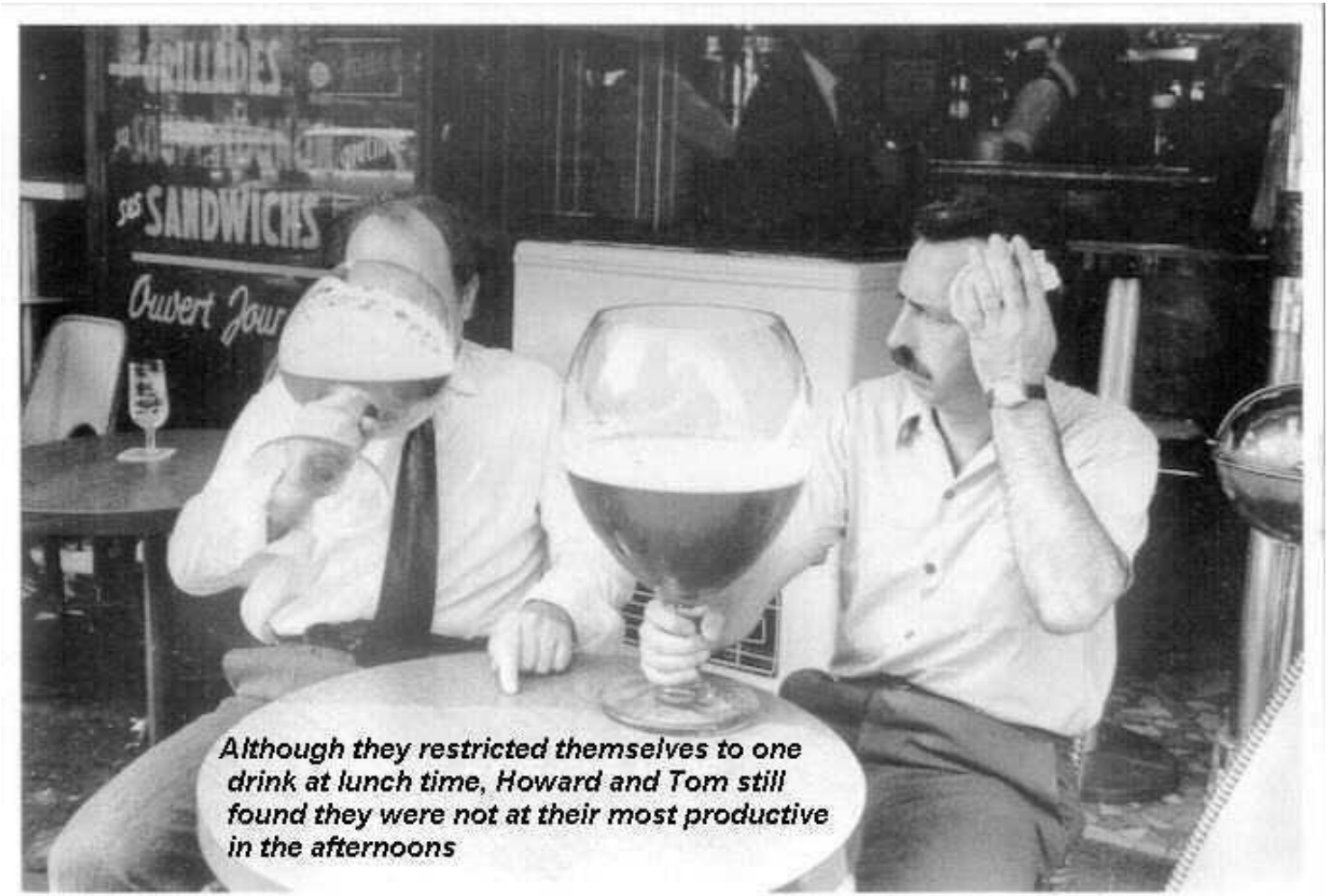
1. Male and Female
2. ^{111}In and ^{68}Ga
3. High and Low kidney uptake
4. Small and Large islets
5. Healthy and Diabetic patients



In the clinics, PET performs better……



Thank you very much for your attention



Acknowledgements

Radboud University Medical Center:

Dept. of Radiology and Nuclear Medicine

Wietske Woliner-van der Weg
Marcel Janssen
Wael Arabi Eter
Maarten Brom
Lieke Claessens-Joosten
Otto Boerman

Dept. of Internal Medicine

Cees Tack
Bastiaan de Galan
Heleen de Wit

University of Twente:

MIRA – Institute for Biomedical Technology and Technical Medicine

Cornelis Slump
Maaike Koenrades
Laura Peeters
Laura Deden

Funded by

- *the European Community's Seventh Framework Programme FP7, project BetaImage, BetaTrain, BetaCure*
- *The National Institutes of Health, Bethesda, MD, USA*
- *The Juvenile Diabetes Research Foundation, New York, USA*
- *Deutsche Forschngsgemeinschaft*
- *Diabetes Fonds*

EU FP 7 No 222980

EU FP 7 No 289932

EU FP 7 No 602812