Towards *in vivo* visualization of pancreatic beta-cells in the mouse: Molecular imaging at 16.4 T

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Introduction Despite of decade-long research, the quantification of insulin producing beta-cells in the pancreas is still not ready for clinical application. Currently, no method exists that could either accurately or non-invasively determine the beta-cell mass in humans *[1]*. The quantification of beta-cells not only would allow to understand the pathophysiology of both type 1 and 2 diabetes in more detail, but also to identify pre-diabetic patients and to follow up cellular therapies (e.g. islet-transplantations). Several *in vivo* imaging approaches are being developed (e.g. fluorescence, positron emission tomography). But these methods have some inherent limitations (low depth in tissue penetration, ionizing radiation, low resolution). Magnetic Resonance Imaging (MRI) on the other hand offers the advantages of using non-ionizing radiation and having a high spatial resolution. Here we present *in vivo* MRI of the mouse abdomen and pancreas at ultra high fields (16.4T) and the first attempt to visualize pancreatic islets with a newly developed beta-cell specific superparamagnetic contrast agent based on a single chain antibody (kindly provided by PD Dr. S. Schneider, Bochum, Germany).

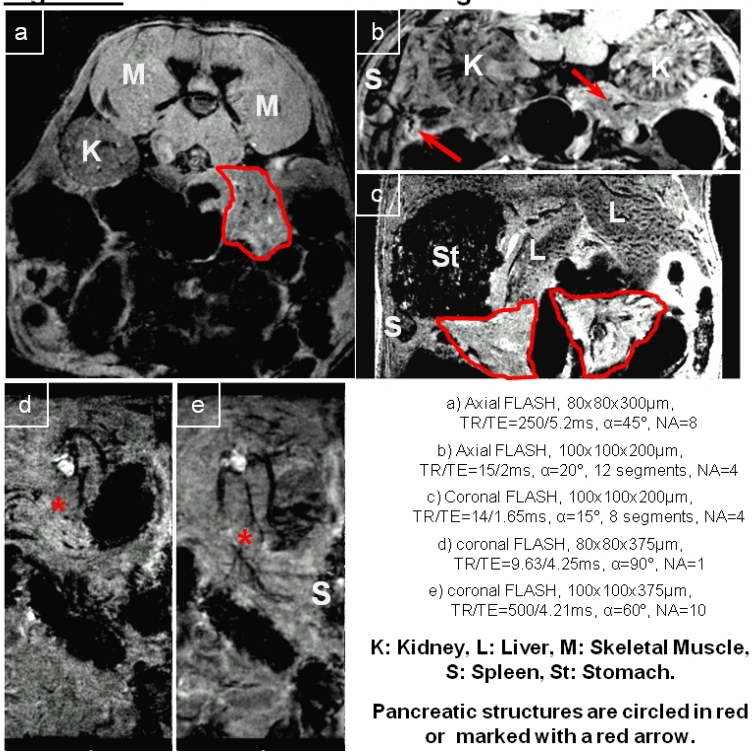
Methods C57BL/6J-mice were anaesthetized and a constant breathing rate was maintained. MR-images were recorded on a 16.4T horizontal animal system. The contrast agent was injected intravenously into the tail vein. Further details are given in the figures.

Results Fig. 1 shows anatomical *in vivo* images of the mouse abdomen. The measurements were triggered on breathing and acquired using volume (1a) or surface coils (all other images). All organs can be easily identified. Figures 1d and 1e show enhanced sections of the pancreas. The vasculature providing blood flow to the pancreas and the spleen can be seen (also visible on figure 1b next to the spleen, marked with an asterisk on d, e). By finding these structures first, the pancreas can be localized. Similar characteristic structures are also visible in images of a dissected pancreas (fig. 2a). Preliminary results using the targeted superparamagnetic contrast agent directed against beta-cells demonstrated punctuate loss of signal intensity in an excised pancreas 24h after intravenous injection (fig. 2b). The sizes of the areas with signal loss match the sizes of islets of Langerhans which are ~100µm in diameter. Although this signal-loss was not yet detectable *in vivo*, binding of the prospective contrast agent to beta-cells in the islets of the excised pancreas was verified by immunofluorescence (data not shown).

Conclusion For the first time we have shown the feasibility of *in vivo* MRI of the mouse abdomen at the ultra high field of 16.4T. This allowed the sensitivity of MR-microscopy for structures <100µm and anatomical details (e.g. the vasculature) of the pancreas were identified. Despite of the high possible spatial resolution at this field strength the cellular architecture of the pancreas, i.e. the location or amount of islets of Langerhans remains difficult to assess. Nevertheless, first results using a novel targeted contrast agent *in vivo* demonstrated that it might be possible to identify beta-cell containing islets of Langerhans.

[1] Schneider, S *Diabetes Obes Metab* **10(4)**(2008)109-18

Figure 1: Anatomical *in vivo* images



a) Axial FLASH, 80x80x300µm, TR/TE=250/5.2ms, α=45°, NA=8

b) Axial FLASH, 100x100x200µm, TR/TE=15/2ms, α=20°, 12 segments, NA=4

c) Coronal FLASH, 100x100x200µm, TR/TE=14/1.65ms, α=15°, 8 segments, NA=4

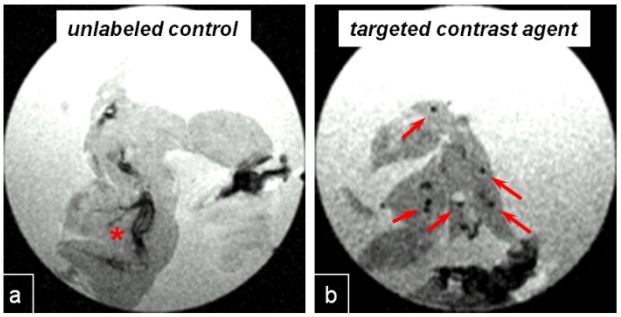
d) coronal FLASH, 80x80x375µm, TR/TE=9.63/4.25ms, α=90°, NA=1

e) coronal FLASH, 100x100x375µm, TR/TE=500/4.21ms, α=60°, NA=10

K: Kidney, L: Liver, M: Skeletal Muscle, S: Spleen, St: Stomach.

Pancreatic structures are circled in red or marked with a red arrow.

Figure 2: Dissected pancreas – *ex vivo*



a) FLASH, 50x50x317µm, TR/TE=500/4.21ms, α=40°, NA=10
b) FLASH, 50x50x200µm, TR/TE=500/4.21ms, α=40°, NA=10
(Labeled islets are marked with a red arrow.)