Pathological evaluation of diabetic retinopathy in mice using high-field MRI

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Diabetic Retinopathy (DR)

- 40-45% of people with diabetes are affected
- early stage: non-proliferated DR (retinal vascular dilation, tortuosity, capillary occlusion and increased permeability)
- late stage: proliferative DR (new blood vessels grow on the surface of the retina, increased leakiness)

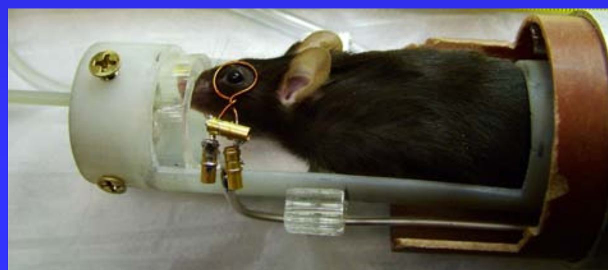
  => blurred vision, macular edema and visual loss
- clinical routine examinations detect disease-induced changes (fundus photography)
- a comprehensive study of the progression of the disease is not possible

Animal model

- pro:
  - study of the progression possible
  - models available
- contra:
  - small eyes
  - anesthesia necessary

Infrastructure

- 14 tesla Varian MRI system



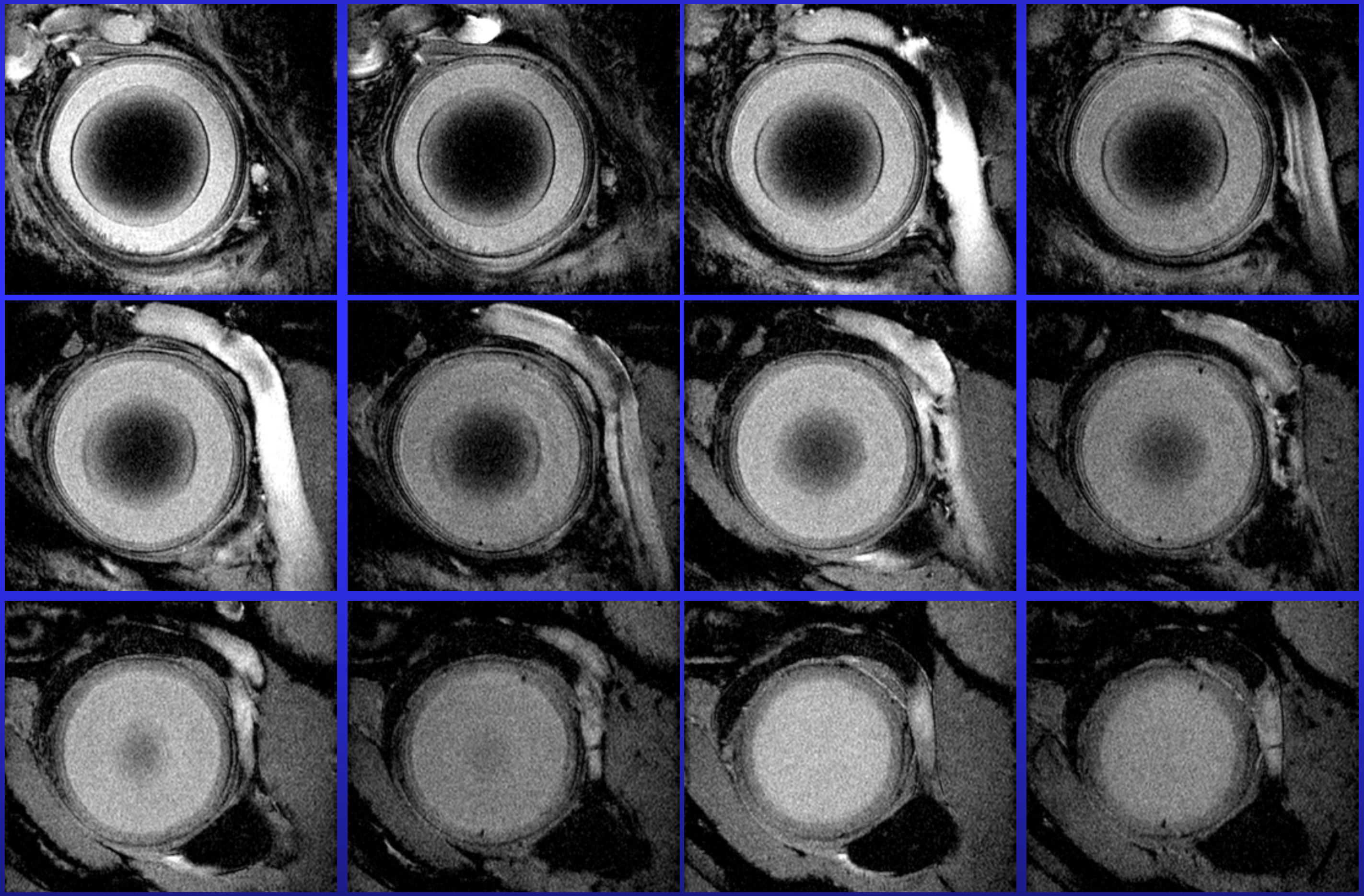
- electronic lab:
  => RF resonator design and construction

- animal housing and breeding facility

  (Penn State College of Medicine Juvenile Diabetes Research Foundation Diabetic Retinopathy Center Animal Core)

MRI of a mouse eye

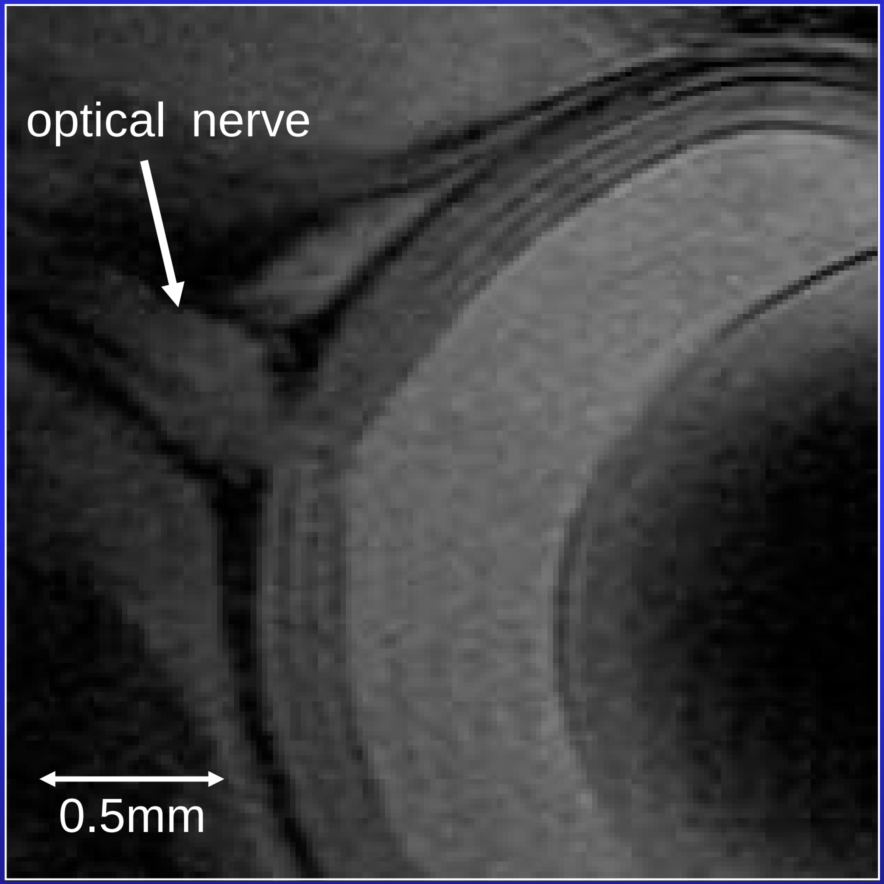
- different layers of the retina detectable in vivo

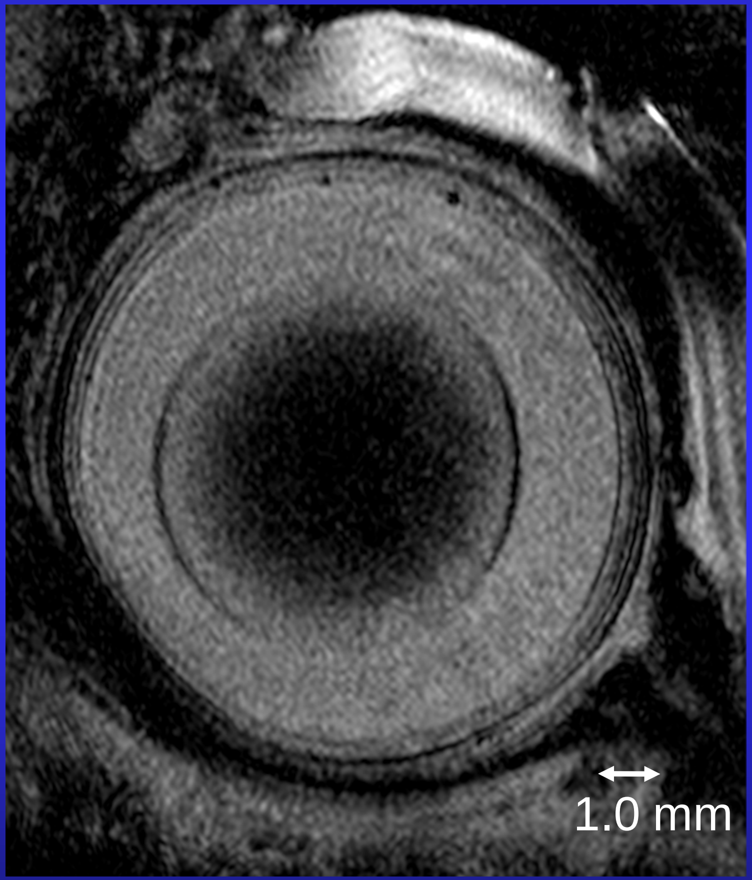


gradient echo, TR 200 ms, TE 8.56 ms, matrix size 192 x 264 (3/4 partial Fourier), FOV 6 x 8 mm^2, 16 averages, T_{exp} 10.6 min, in-plane resolution 30 x 30 μm^2, slice thickness 100 μm

MRI of a mouse eye

- different layers of the retina detectable in vivo

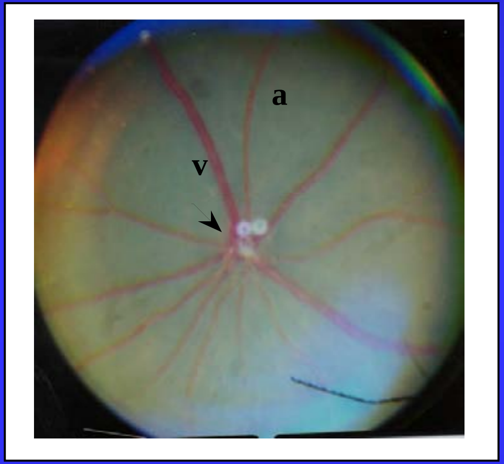




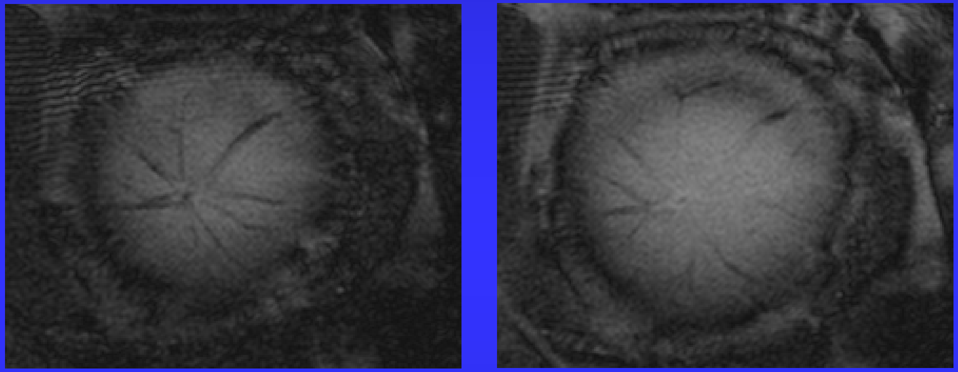
gradient echo, TR 200 ms, TE 8.56 ms, matrix size 192 x 264 (3/4 partial Fourier), FOV 6 x 8 mm^2, 16 averages, T_{exp} 10.6 min, in-plane resolution 30 x 30 μm^2, slice thickness 200/100 μm

fundus of a mouse eye

fundus photography*



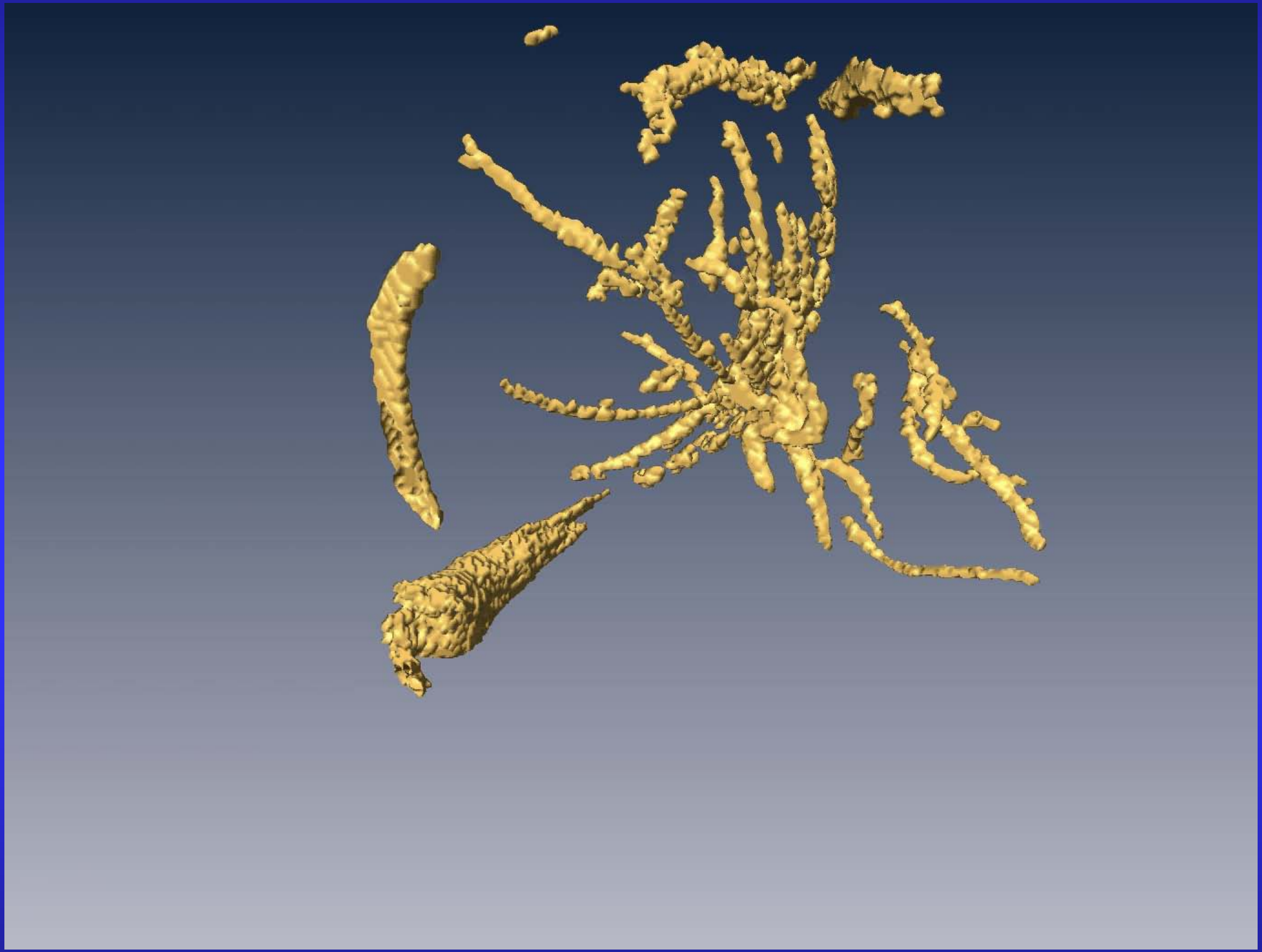
MRI of the fundus



depending on the slice thickness and position
different vessels can be observed

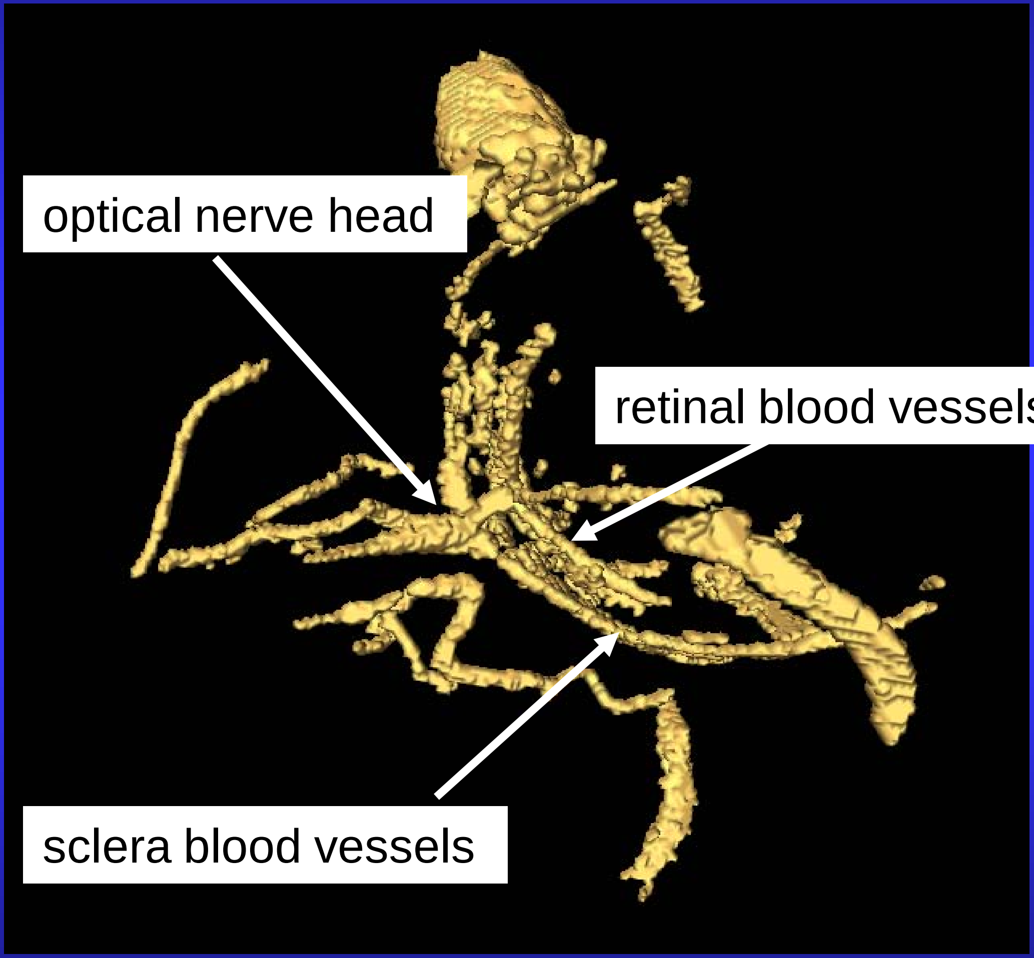
*Ramalho et al. BMC Cell Biology 2002 3:26

angiogram of a mouse eye



three dimensional time-of-flight (TOF) gradient echo sequence: TR=40 ms, TE=5.5ms, NT=8, matrix: 128 x 150 (200) x 162, FOV= 5 x 8 x 6.5 mm^3, Res = $(40\mu m)^3$, Texp =2.2 h

angiogram of a mouse eye



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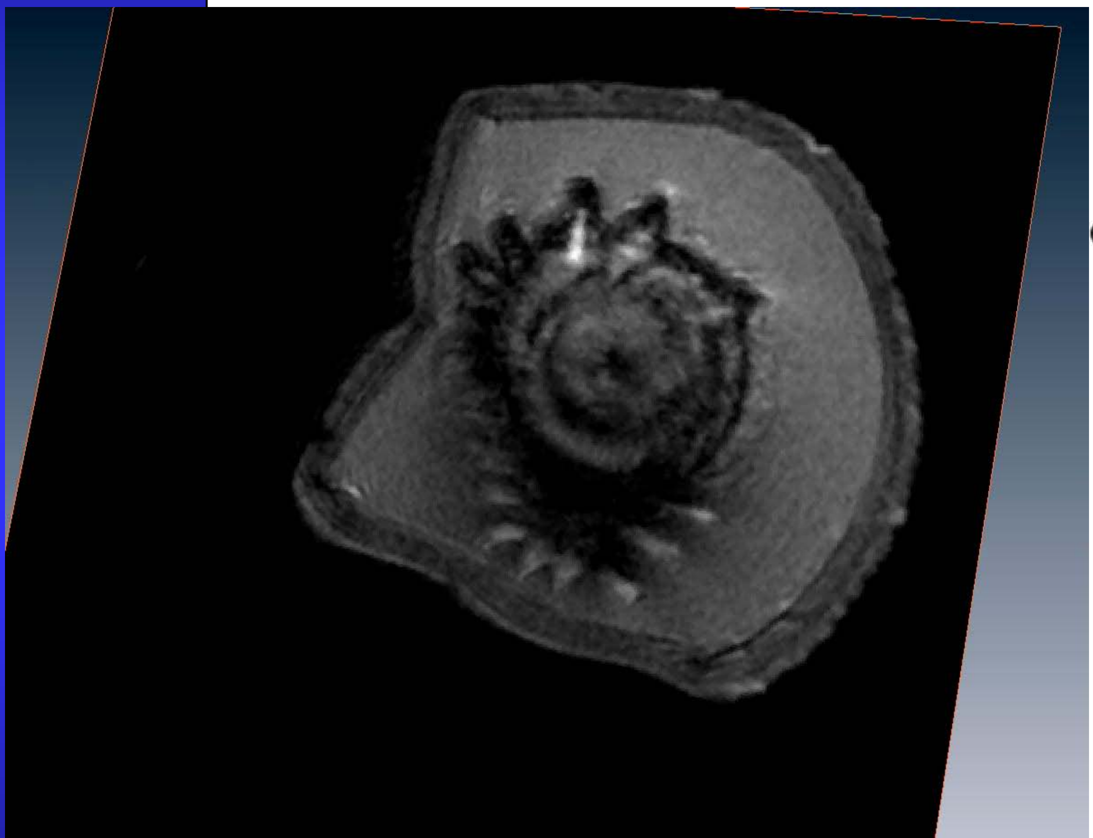
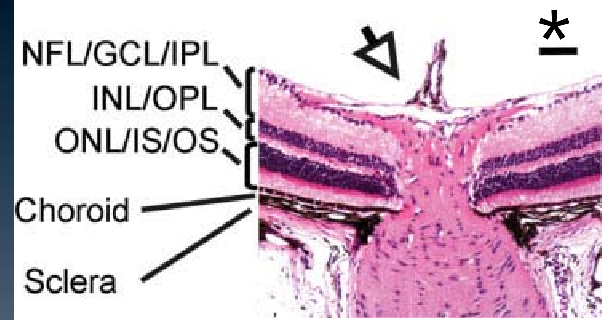
mouse eye ex vivo





NFL: nerve fiber layer
GCL: ganglion cell layer
IPL: inner plexiform layer
INL: inner nuclear layer
OPL: outer plexiform layer
IS: inner segments
OS: outer segments

resolution: 18 x 18 x 18 μm^3

*histology from: Chen J, et al, MRM 2008 59:731-738

Aim 1: longitudinal study of the progression of BRB breakdown in a mouse eye in vivo when exposed to VEGF.

- VEGF (3 nM to 250 nM) injection induces endothelial permeability
- acquire 3D angiogram
- dynamic contrast enhanced (DCE) MRI @ different time points after VEGF injection (up to 72h)
- contrast agents: Gd-DTPA (590 Da) and Gadolinium labeled albumin (~ 74k Da)
- co registration of angio and DCE data set

=> results will show the proximity of the signal enhanced regions acquired in the DCE MRI to the major inner and outer retinal vessels acquired in the angiography

Aim 2: Study of the breakdown of the BRB in a mouse model

- C57BL/6 Ins^{2Akita} mice
- monitoring the thickness of the retina with high res MRI
- acquire 3D angiogram
- starting 8 weeks after birth DCE MRI will be performed every 2 weeks
- contrast agent: Gd-DTPA

=> determine at which time point during the disease and at which location in the eye increased permeability occurs within the same animal