

Models Imaging Visualization Perfusion Viability Inflammation Translation

Cardiovascular Disease – A Challenge Worldwide

Category	Percentage
CVD	52 %
Coronary heart disease	22%
Stroke	11%
Other CVD	15%
Diabetes	8%
All other causes	20%
Injuries and poisoning	4%
Respiratory disease	6%
Other cancer	10%
Breast cancer	2%
Long cancer	2%
Gastrointestinal cancer	1%

European Heart Network 2012

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Cardiovascular Disease Models

Small animals do typically not present with cardiovascular diseases



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Animal Models of Atherosclerosis

ApolipoproteinE^{-/-} mouse

ApoE^{-/-}

Genotype	Diet	Cholesterol _{plasma} (mg/dl)
WT	standard chow	~150
WT	HFC	~350
ApoE ^{-/-}	standard chow	~350
ApoE ^{-/-}	HFC	~2800

Nakashima, ATVB 1994

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Cuff Model – shear-stress induced local atherosclerosis

ApoE^{-/-} on HFC

heart

aortic arch

downstream

upstream

Oscillatory ESS Promotes development of stable plaques

Low ESS Promotes inflammation & development of unstable plaques

Kuhlmann et al., JoVE 2011

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Induction of Myocardial Infarction

Site of occlusion

scar formation
3 weeks after induction of MI

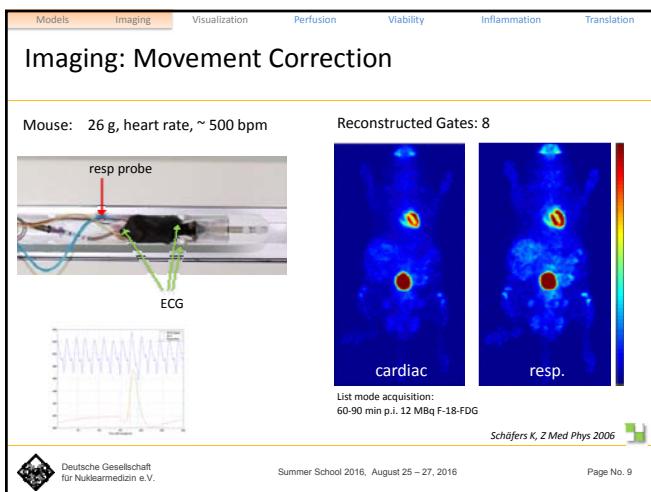
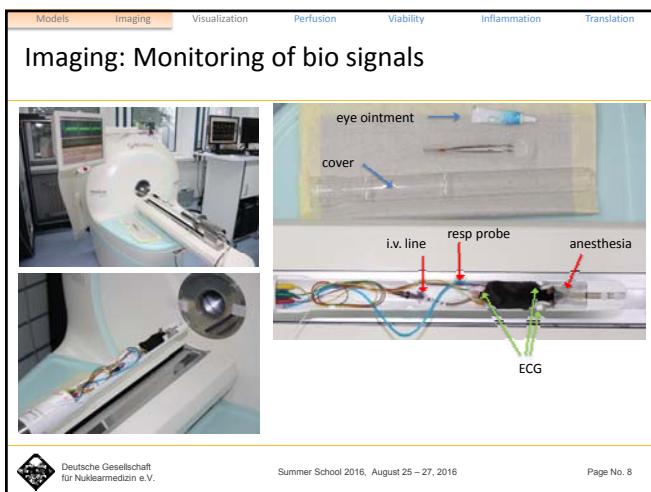
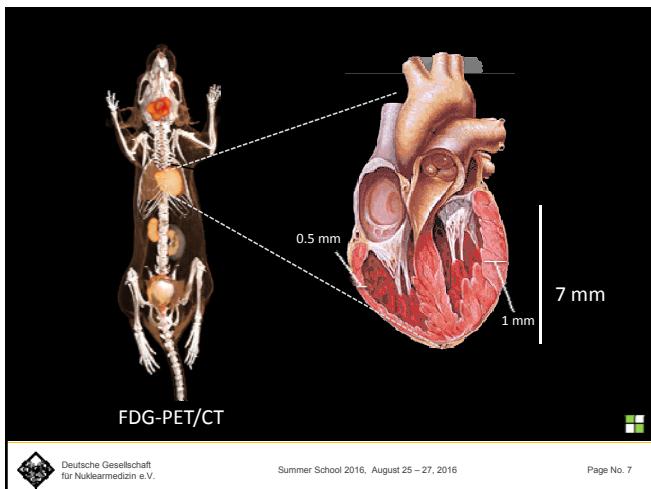
30 min ischemia

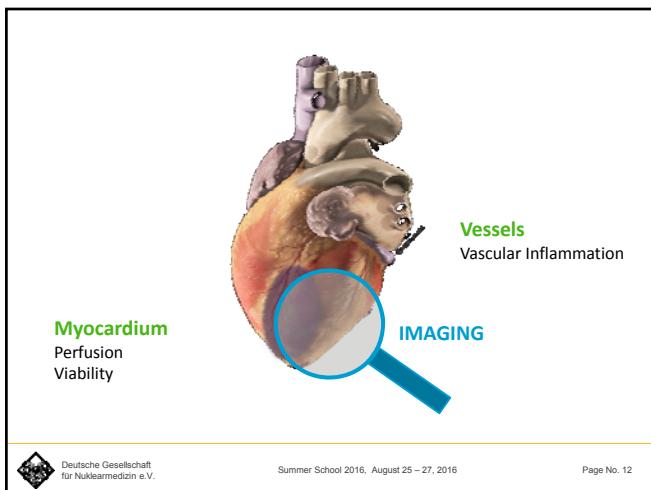
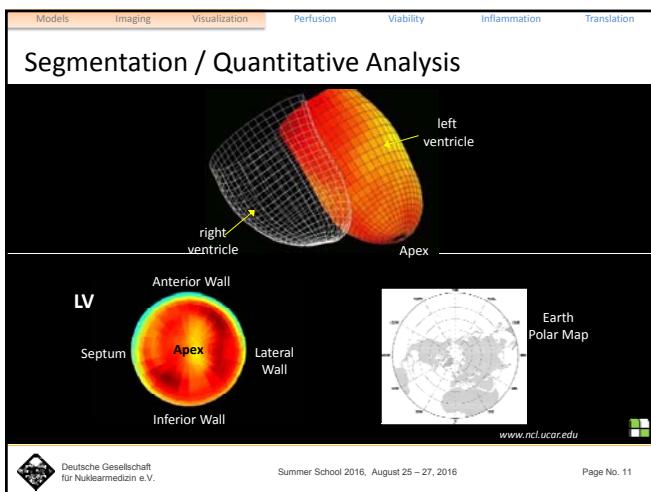
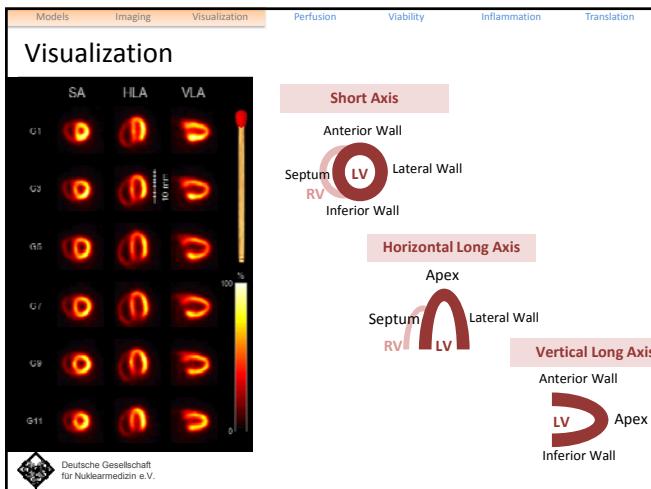
perm. ligation

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Models Imaging Visualization Perfusion **Perfusion** Viability Inflammation Translation

Myocardial Perfusion Imaging

Blood **Cardiomyocyte**

Tracer uptake (normal)

Coronary blood flow (ml/min/g)

Coronary blood flow (ml/min/g)	Rest (orange)	Exercise (blue)	Pharmacologic vasodilation (green)
0	~1.5	~2.0	~3.5
1	~2.0	~2.5	~3.8
2	~2.5	~3.0	~4.2
3	~3.0	~3.5	~4.5
4	~3.5	~4.0	~4.8
5	~4.0	~4.5	~5.0

Sogbein, Biomed Res Int. 2014

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Models Imaging Visualization Perfusion **Perfusion** Viability Inflammation Translation

Myocardial Perfusion Imaging

Healthy mouse, 26g

LV SA

RV HLA

LV VLA

10 min 20 min 30 min 40 min 50 min 60 min

time after injection

Vrachimis A, EJNMMI Res. 2012

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Models Imaging Visualization Perfusion **Perfusion** Viability Inflammation Translation

Myocardial Perfusion Imaging

Mouse, 24g Ischemia !

ant base

RV lat

inf

apex

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Models Imaging Visualization Perfusion **Perfusion** Viability Inflammation Translation

Perfusion Imaging: Application

Monocyte migration

Day	Infarct	Remote
Day 1	~0.55	~0.45
Day 7	~0.45	~0.35

Honold L, Gran S, Roth J, Schäfers M, *in preparation*

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Models Imaging Visualization Perfusion **Viability** Viability Translation

Viability

Mouse, 24g, permanent MI **¹⁸F-FDG-PET**

Time Point	Scar [%]	FF [%]
baseline	na	43
day 1	34	25
day 14	34	15

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Models Imaging Visualization Perfusion Viability **Viability** Inflammation Translation

Influence of anesthesia on cardiac ¹⁸F-FDG uptake

Anesthesia Condition	Healthy	3d post MI
Standard Isoflurane	~3x10 ⁶	~3x10 ⁶
Conscious Injection/Uptake	~3x10 ⁶	~3x10 ⁶
Conscious Fasting	~3x10 ⁶	~3x10 ⁶
Conscious Fasting, Heparin	~3x10 ⁶	~3x10 ⁶
Ketamine/Xylazine	~3x10 ⁶	~3x10 ⁶

Thackeray et al., EINMMI 2015

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Atherosclerosis – targets

The diagram illustrates the complex nature of atherosclerosis at the cellular level. It shows a cross-section of a blood vessel wall with various cells and molecules involved:

- Monocytes**, **Macrophages**, and **Foam cells** are shown within the plaque.
- Apoptotic cells** are depicted as yellowish bodies.
- T-lymphocytes** are shown with **IL-2-R**.
- Smooth muscle cells** are shown with **Mannose-R**.
- Fibroblasts** are shown with **LOX-1**.
- Lipid core** is labeled.
- Micro-calification** is shown as small white dots.
- Hypoxia** is indicated by a red area.
- Choline transport** is shown with **GLUT**.
- SST-R** and **Folate-R** are also labeled.
- FDG** (Fluorodeoxyglucose) is shown being taken up by the cells.
- MMP** (Matrix Metalloproteinase) is shown degrading the extracellular matrix.
- VEGF** (Vascular Endothelial Growth Factor) and $\alpha\beta_1$ integrins are shown promoting angiogenesis and adhesion.
- Apoptosis, PS** (Phosphatidylserine) is shown on apoptotic cells.

Vrachimis et al. QJNM 2016

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FDG-PET/CT in Carotid Cuff Model

This figure compares PET, PET/CT, and CT imaging in a carotid cuff model. It includes:

- PET**: Coronal and sagittal slices showing FDG uptake in plaques. White arrows point to specific uptake sites.
- PET/CT**: Coronal and sagittal slices showing anatomical structures. Labels indicate **DS** (Dense plaque) and **US** (Ulcerated plaque).
- CT**: Coronal and sagittal slices showing the vascular anatomy.
- MAC-3**: Histological sections stained for macrophages, showing MAC-3 positive cells in the plaques.
- C**: Bar graph showing %ID/ml for plaque US, plaque DS, and contralateral CCA at 8 weeks. Sample sizes (n=23) are indicated for each group. Significance levels are shown between plaque US and plaque DS ($p < 0.01$), and between plaque DS and contralateral CCA ($p < 0.05$).

Wenning et al., Atherosclerosis 2014

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FDG-PET in patients

This figure shows FDG-PET imaging and histological analysis of patient carotid samples:

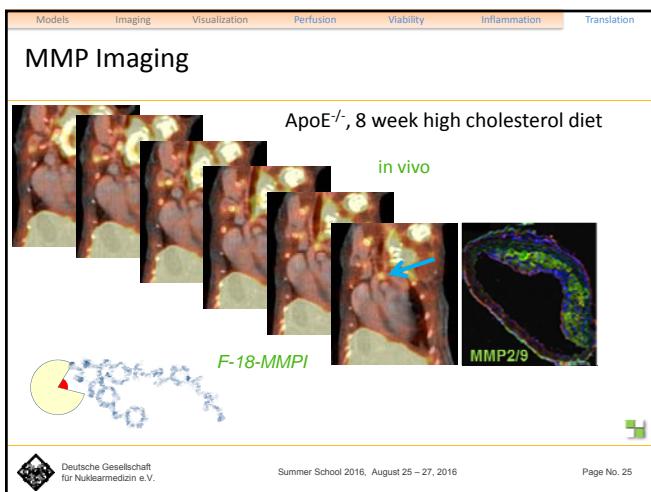
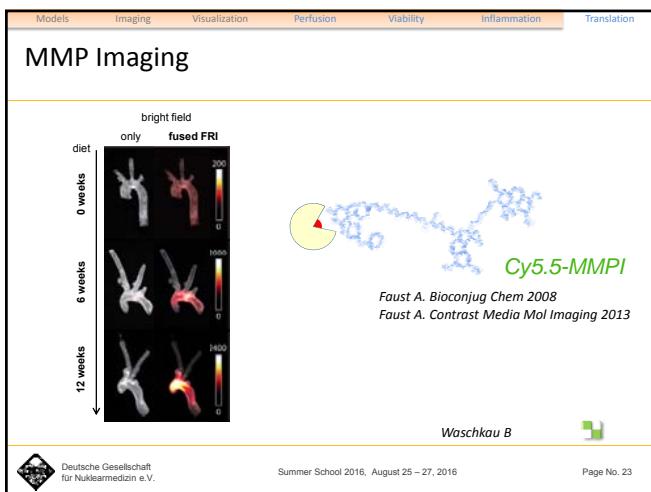
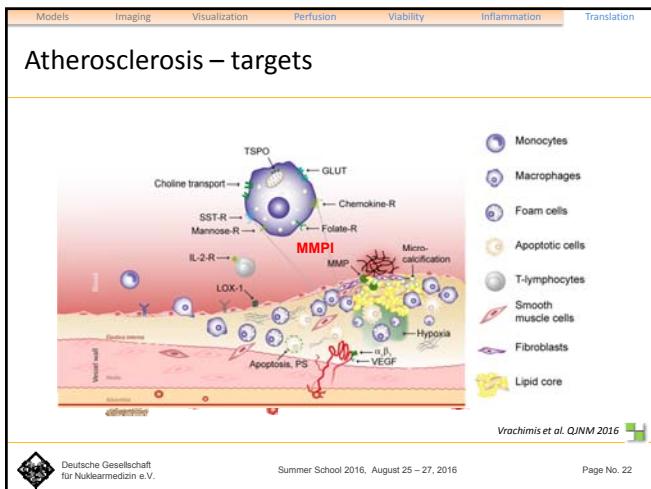
- A**: Coronal CT and PET slices. Arrows point to areas of interest.
- B**: Coronal CT and PET slices. Arrows point to areas of interest.
- Scatter plot**: FDG signal (SUVmax) versus macrophage density (% CD68 staining). A positive correlation is shown with $R^2 = 0.79$ and $p = 0.001$.
- Text**: → FDG signal correlates with macrophage density in excised carotid samples
- Text**: But: true nature of FDG signal is still unclear (macrophages vs. surrounding fat vs. ???)

Tawakol et al. J.Am.Coll.Cardiol. 2006

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Translational MMP Imaging in MS

Gelatinases MMP-2 & MMP-9 CNS tissue
Migrating leukocytes
CD45/Gel ZYM

Cy5.5-MMPI **Cy5.5-MMPI** **Gel zymo/PLM/CD45**

Gerwien H, Hermann S, Schäfers M, Sorkin L, in revision

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Translational MMP Imaging in MS

Gelatinases MMP-2 & MMP-9 CNS tissue
Migrating leukocytes
CD45/Gel ZYM

Gd-T1-MRI **MMP-PET** **PET-MRI**

baseline **35 days post Tx**

30-60 min p.i. of 250 MBq MMP radiotracer ¹⁸F-BR351

Gerwien H, Hermann S, Schäfers M, Sorkin L, in revision

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Atherosclerosis – targets

- Monocytes
- Macrophages
- Foam cells
- Apoptotic cells
- T-lymphocytes
- Smooth muscle cells
- Fibroblasts
- Lipid core

DOTATATE **SST-R** **Mannose-R** **IL-2-R** **LOX-1** **MMP** **Microcalcification** **Hypoxia** **Apoptosis, PS** **VEGF**

TSPO **GLUT** **Chemokine-R** **Folate-R**

Vessel wall **Intimal** **Media**

Vrachimis et al. QJNM 2016

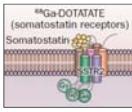
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Somatostatin-receptor imaging with DOTATATE



Somatostatin (SST): Circulating peptide with neuroendocrine, immunomodulatory and cell-regulatory functions



SSTRs: Overexpressed in a number of diseases, particularly neuroendocrine tumors

DOTATATE: SST analog with SSTR2 specificity
68Ga or 64Cu labeled

Tarkin et al. *Nat. Reviews Card.*, 2014

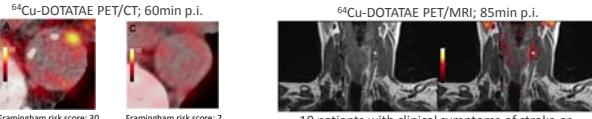
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DOTATATE PET in patients



64Cu-DOTATATE PET/CT; 60min p.i. Framingham risk score: 30

64Cu-DOTATATE PET/MRI; 85min p.i. 10 patients with clinical symptoms of stroke or transient ischemic attack

Several retrospective studies report DOTATATE PET (68Ga or 64Cu) signal to correlate with presence of plaques and cardiovascular risk factors

In vivo imaging and gene expression analysis of plaque regions after carotid endarterectomy

Strong correlation between *in vivo* signal and *ex vivo* markers of activated macrophages (CD163)

→ Detection of vulnerable plaques?

Rominger et al. 2010, *JNM*; Li et al. 2012, *EJNMMI*; Malmberg et al. *JNM* 2015

Pedersen et al. *Arterioscl. Throm. Vas.* 2015

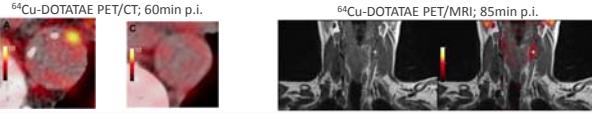
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DOTATATE PET in patients



64Cu-DOTATATE PET/CT; 60min p.i.

64Cu-DOTATATE PET/MRI; 85min p.i.

VISION study
(Vascular Inflammation imaging using Somatostatin receptor psitron emisson tomography)

50 subjects with atherosclerosis,
sequential PET/CT imaging with 68Ga-DOTATATE and 18F-FDG,
contrast angiography of carotid and coronary arteries,
autoradiography and immunohistochemistry of excised carotid plaques

US National Library of Medicine. ClinicalTrials.gov. <http://clinicaltrials.gov/show/NCT02021188> (2013)

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SSTR2 imaging – bedside to bench - to bedside?

Specific tracer uptake on tissue level? What cells in the plaque express SSTR2?

Digested aorta from ApoE^{-/-}: > 60 % of monocytes/macrophages
SSTR-2: > 28% of T-cells > 95% of endothelial cells

Li et al. Atheroscl., 2013

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SSTR2 imaging – bedside to bench - to bedside?

Tracer improvements?

Rinne et al. MOL IMAGING BIOL., 2016

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European Institute for Molecular Imaging

UKM Klinik für Nuklearmedizin

CRC 656 Molecular Cardiovascular Imaging

CELLS IN MOTION Cluster of Excellence

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Mouse Imaging Workshop 14-18 November 2016

Topics

- **Animal handling:** i.v./i.p. injection, tail vein catheter, anesthesia, surgery
- **μ PET/ μ SPECT:** static and dynamic scanning, CT fusion
- **μ CT:** *in vivo* scans +/- contrast agents, respiratory gating
- **μ MRI:** *in vivo* scans +/- contrast agents, cardiac & respiratory gating
- **Ultrasound:** hands-on scanning +/- contrast agents
- **Optical imaging:** fluorescence, bioluminescence
- **Multimodal imaging:** PET/CT, PET/MRI, SPECT/CT
- **Image analysis:** methods, coregistration, quantification (VisualLab)



<http://www.uni-muenster.de/EIMI/teaching/mia/>



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