Neurocampus Tübingen

Werner Siemens Imaging Center

Department for Preclinical Imaging and Radiopharmacy
Group: Neuroimaging (molecular, metabolic and functional brain imaging)
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Infrastructure

The Werner Siemens Imaging Center is located next to the woman's hospital and equipped with:

- **3 high-resolution small animal PET systems**
- 1 small animal PET/SPECT/CT system
- 2 whole body optical imaging systems
- **2 7-T small animal MRI systems** equipped with specific brain coils for rats and mice (**fMRI**, **MR spectroscopy**, **contrast enhanced MRI, diffusion weighted imaging and diffusion tensor imaging)**
- **PET insert** to measure PET and MR simultaneously
- aesthesia systems, cardiac and respiratory gating units, a ventilator
- **2 cell culture labs** including laminar flow and incubator,
- **1 gamma counter** and 1 **phosphor imager**,
- 1 **histology** and **microscopy lab** including cryostat and histological slide scanner for digital pathology
- 1 molecular biology lab
- **On-site cyclotron** with PET tracers, both for preclinical and clinical use (Table 1). These include PET tracers for the dopaminergic, serotonergic, GABAergic and glutamatergic system (Figure 1) as well as [^{18}F]FDG, [^{15}O]Water. **PET tracers for other targets in the brain, published in the literature can be established.**
- **2 Behavioral rooms** for several behavioral tests: Open Field, Plus Maze, T-Maze, Beam Walk, Rotometer, Grip Strengh, Skinner Box, Zylinder Test

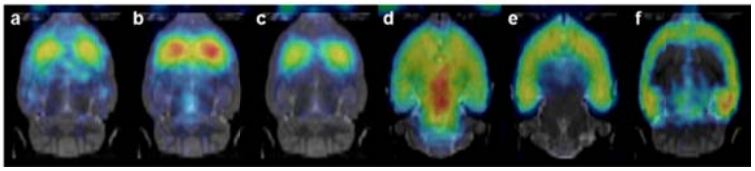

Figure 1: PET images of brain tracer available at the WSIC. From left to right: **(a)** [^{11}C]methylphenidate (dopamine transporter), **(b)** [^{11}C]DTBZ (vesicular monoamine transporter 2), **(c)** [^{11}C]raclopride (dopamine D2 receptor), **(d)** [^{11}C]DASB (serotonin transporter), **(e)** [^{18}F]PSS232 (metabotropic glutamate receptor 5), **(f)** [^{11}C]flumazenil ($GABA_A$ receptor).

Table 1: CNS PET tracers available in Tübingen

Tracer	Target	Available for preclinical research	Available for clinical studies in GMP Grade
[^{11}C]Raclopride	dopamine receptor (D2)	x	x
[^{18}F]Fallypride	dopamine receptor (D2)	x	
d-threo-[^{11}C]Methylphenidate	DA transporter	x	x
[^{11}C]DTBZ	vesicular monoamine transporter 2	x	
[^{11}C]DASB	serotonin transporter	x	
[^{11}C]Flumazenil	benzodiazepine receptor	x	
[^{11}C]PIB	amyloid beta	x	x
[^{18}F]PSS232	metabotropic glutamate receptor (mGluR5)	x	
[^{18}F]FDG	Glucose metabolism	x	x
[^{15}O]Water	Perfusion	x	

The neuroimaging group currently consists of 4 PhD students, several undergraduate students and myself. A W2 professorship is funded by the Carl Zeiss Foundation and the candidate selection process is currently ongoing. Our main research interest compromises the following topics:

Study of synaptic dysfunctions in animal models of neurological disorders using simultaneous PET/BOLD-fMRI. Structural disruptions and loss of synapses are a major hallmark of neurodegenerative disorders and result in network disruptions and loss of neuronal signaling. How early in the process of neurodegeneration synaptic dysfunctions appear is not yet understood. Our aim is to develop and apply protocols and methods (including **pharmacological** and **optogenetic stimulations**) to assess molecular changes of **receptor expression by PET** and **functional changes by BOLD-fMRI** at different time points of the disease to develop early read-outs of disease progression (Figure 2). For this purpose, we use different rat models and **genome engineering technologies (CRISPR/Cas9)** to target specific genes and proteins *in vitro* (cell culture and primary neurons) and ***in vivo* in the rat brain**. For data analysis of PET and MRI data we use several data analysis methods, including **kinetic modeling** and **machine learning** approaches.

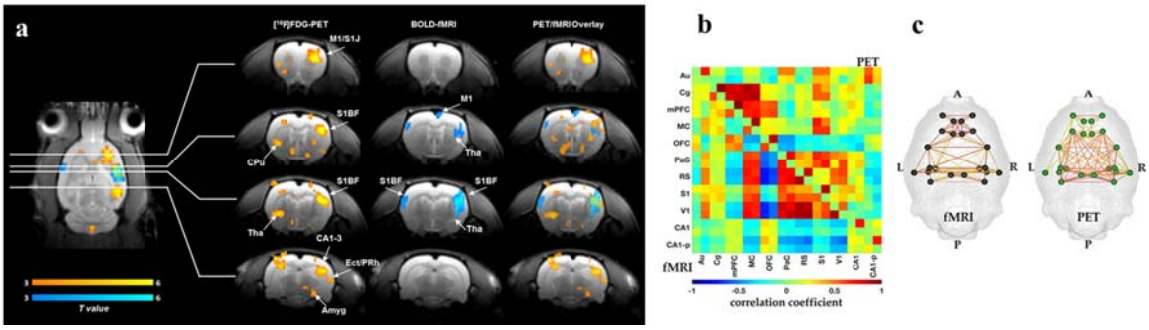

Figure 2: Simultaneously acquired [^{18}F]FDG PET and BOLD fMRI activation pattern after left whisker stimulation shows functional and metabolic activity in S1 barrel field (S1BF) and Thalamus (Tha) **(a)**. Metabolic changes are observed in several additional brain regions (Caudate Putamen (CPu), hippocampal region (CA1-3), amygdala (Amyg) and ectorhinal cortex (Ect). Correlation matrix **(b)** and functional and metabolic connectivities **(c)** of the default mode network at resting state.

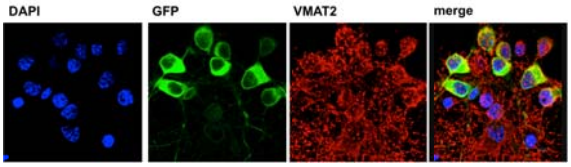

Figure 3: Immunofluorescent staining of rat primary neurons.

Tracer development and preclinical evaluation in neurology. In the past, we have established several ***in vitro*** **and** ***in vivo*** **screening assays** to validate novel PET imaging agents. As our group holds a strong collaboration to the Radiopharmacy research group, we are always looking for novel interesting targets in the brain. One important target is the protein **alpha-synuclein**, which plays a major role in the pathology of Parkinson´s disease (PD). In contrast to the situation in Alzheimer´s disease, PET tracers to detect alpha-synuclein oligomers or aggregates in PD are still missing. Therefore, we aim to develop a PET tracer to non-invasively assess alpha-synuclein aggregation in the brain of patients with Parkinson´s disease.
In addition, we are working on a **PET brain reporter gene system** to follow **gene expression** over time ***in vivo***. This reporter gene may be very useful for basic science applications as well as clinical implementation of gene and cell therapy in the CNS.

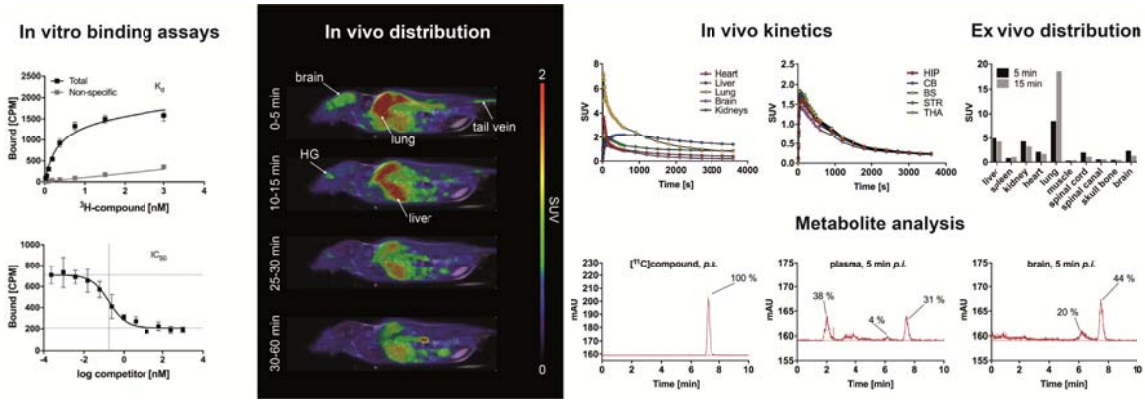

Figure 4: PET tracer development studies: from *in vitro* binding assays to *in vivo* kinetic analysis to *ex vivo* bio-distribution and metabolite analysis.

National and International Collaborations

Prof. Dr. Deniz Kirik, Lund University (Schweden)
Prof. Dr. Armin Giese, LMU Munich
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Prof. Dr. Simon Ametamey, ETH Zürich, Switzerland

Clinical Translation

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Prof. Ernemann, Department of Neuroradiologie, University Hospital Tübingen
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Selected literature from our lab

Lettfuss N.Y. and Fischer et al., Imaging DA release in a rat model of L-DOPA-induced dyskinesias: A longitudinal in vivo PET investigation of the antidyskinetic effect of MDMA. **Neuroimage**. 2012. Oct, 63(1):423-33.

Fischer K. et al., In vivo quantification of dopamine transporters in mice with unilateral 6-OHDA lesions using [11C]methylphenidate and PET. **Neuroimage**. 2012 Feb; 59(3):2413-22.

Fischer K., et al. Non-Invasive Nuclear Imaging Enables the in vivo Quantification of Striatal Dopamine Receptor Expression and Raclopride Affinity in Mice. **J Nucl Med.** 2011 Jul; 52(7):1133-41.

Walker M., et al., In vivo Evaluation of 11C-DASB for Quantitative SERT Imaging in Rats and Mice. **J Nucl Med.** 2016 Jan; 57(1):115-21. IF: 6.646

Maier F. et al., Longitudinal PET-MRI reveals β-amyloid deposition and rCBF dynamics and connects vascular amyloidosis to quantitative loss of perfusion, **Nat. Med.** 2014, 20: 1485-92.

Wehrl H. et al., Simultaneous PET-MRI reveals brain function in activated and resting state on metabolic, hemodynamic and multiple temporal scales, **Nat. Med.** 2013, 19: 1184-9.

We are very interested in collaborating with research groups focusing on mouse and rat models of neurodegenerative and neuropsychological disorders and combining *in vivo* molecular and functional brain imaging with other molecular imaging technologies and methods from molecular biology, microscopy, electrophysiology and others.