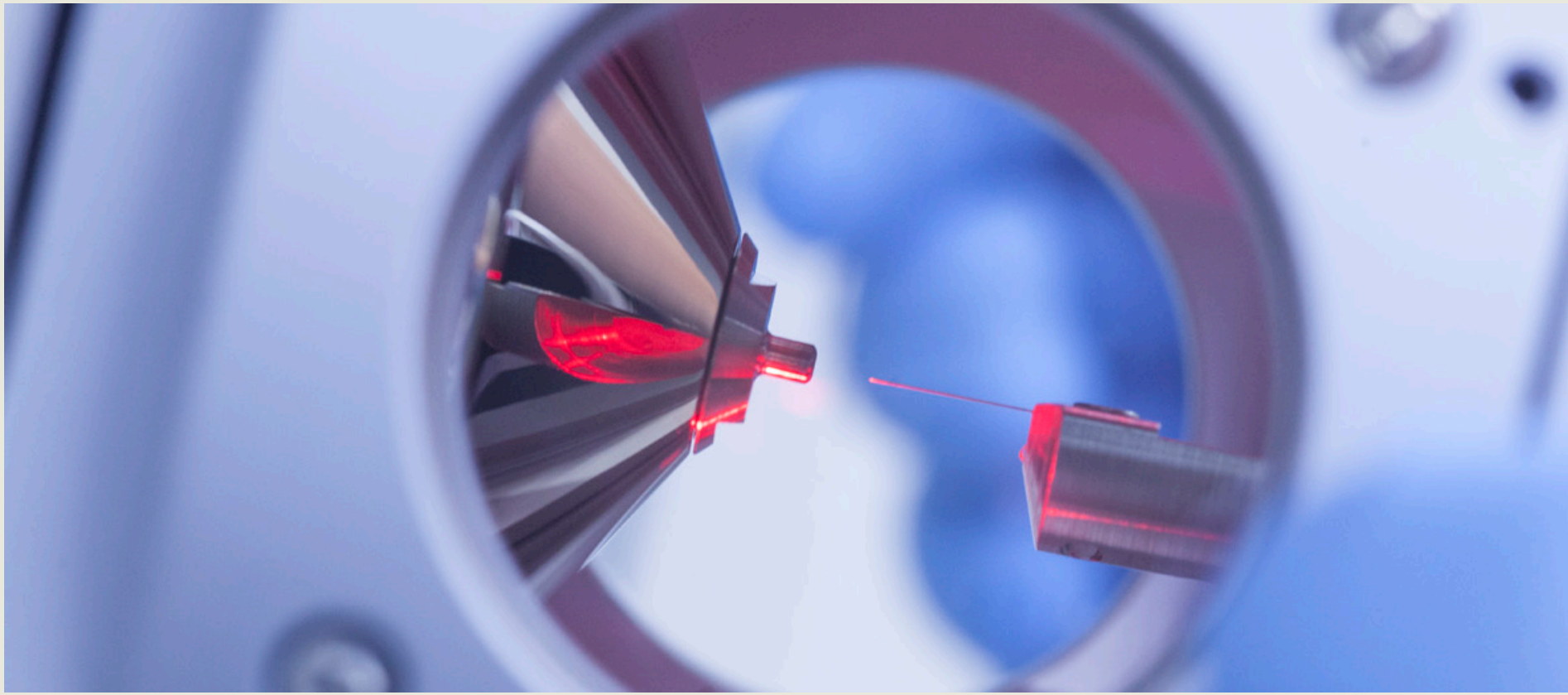
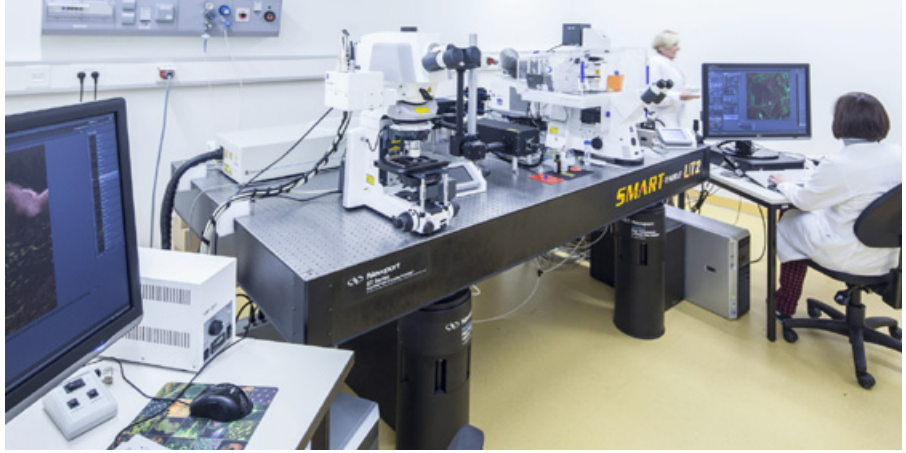


Research Infrastructure

A complementary innovation for strengthening scientific performance is the implementation of core facilities at the Medical Faculty of Ulm University that provide resources for shared cross-institutional use and for external partners.

These core facilities are specifically:

- Confocal and Multiphoton Microscopy Facility
- FACS (Fluorescence Activated Cell Sorting) Facility
- Genomics Facility
- Core Unit Mass Spectrometry and Proteomics
- Small Animal Imaging Facility
- Transgenic Mice Facility
- 3 Tesla MR Imaging in Human Neuroscience



The heart of the core unit:
LSM 710 (right); LSM 7 MP (left);
and fs-pulsed Ti:Sa laser (middle).

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Core Facility

Confocal and Multiphoton Microscopy

Head of Core Facility: Dr. Angelika Rueck

Keywords: Functional confocal imaging | multiphoton | FLIM | FRET | SHG

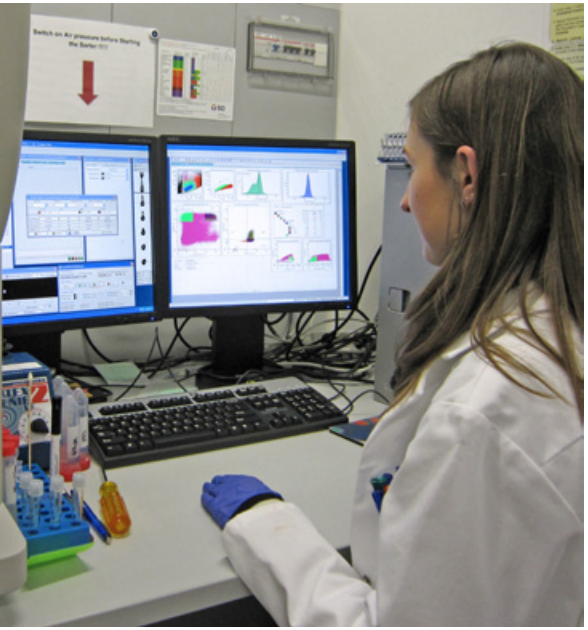
The core unit “Confocal and Multiphoton Microscopy” is located in the Medical Faculty of Ulm University. The heart of the unit consists of two laser scanning microscopes, one being an inverted LSM 710 and the other an upright microscope LSM 7 MP. Both microscopes are coupled to an fs-pulsed laser to provide multiphoton microscopy. Besides spectral detection and time-resolved detection, detailed fluorescence lifetime imaging (FLIM) is now possible with the newest generation of hybrid detectors and TCSPC electronics. In addition to the LSM 710, the LSM 510 META is equipped with a spectrometer for spectral imaging which is utilized at the facility. There are also labs available for cell culturing and molecular biology.

The core unit “Confocal and Multiphoton Microscopy” has existed in its current form since August 2013. It functions as a life cell imaging competence center, mainly for the purposes of biomedical research. At present there are seven people (five females and two males) working at the facility. Two of them (the head and the first assistant) have permanent positions while the others hold temporary positions in research projects. The aim of these projects is the development and adaption of new imaging techniques, for example phosphorescence lifetime imaging, that can be helpful for other users. Fees are requested for the use of this core unit.

Some of the highlights of our scientific topics include cell-cell adhesion, protein interaction, transport processes, cell metabolism, nanoparticles, stem cell research, wound-healing, sepsis and developmental biology.

Selected Publications:

- *Rueck A, Hauser C, Lorenz S, Mosch S, Rotte S, Kessler M, Kalinina S (2013): Cell metabolism, tumour diagnosis and multispectral FLIM. Proc. SPIE DOI: 10.1117/12.2003729 (2013).*
- *Amin RM, Hauser C, Kinzler I, Scalfi-Happ C, Rueck A (2012): Evaluation of photodynamic treatment using Aluminum PhthalocyanineTetrasulfonate Chloride as a photosensitizer: New approach. Photochem. Photobiol. Sci., ID PP-ART-12-2011-005411.R1.*
- *Rueck A, Lorenz S, Hauser C, Mosch S, Kalinina S (2012): Multiwavelength FLIM: New concepts for fluorescence diagnosis. Proc. SPIE DOI: 10.1117/12. 906620.*
- *Florian MC, Dörr K, Niebel A, Daria D, Schrezenmeier H, Rojewski M, Filippi M-D, Hasenberg A, Gunzer M, Scharffetter-Kochanek K, Zheng Y, Geiger H (2012): Cdc42 Activity Regulates Hematopoietic Stem Cell Aging and Rejuvenation. Cell Stem Cell, 10 (5): 520 – 530.*
- *Strat D, Dolp F, von Einem B, Steinmetz C, von Arnim CAF and Rueck A (2011): Spectrally resolved fluorescence lifetime imaging: FRET Global Analysis with a one- and two-exponential donor model. Journal of Biomedical Optics, 16(2), 026002.*



Isolation of murine hematopoetic stem cells via complex multicolor FACS (Fluorescence Activated Cell Sorting) on a BDFACSAriaIII cell-sorting machine.

Core Facility

FACS – Fluorescence Activated Cell Sorting

Head of Core Facility: Prof. Dr. Christian Buske
Coordinator FACS: Prof. Dr. Christian Buske
Keywords: Fluorescence activated cell sorting | FACS

The newly established core facility of Fluorescence Activated Cell Sorting (CF-FACS) is part of the Medical Faculty of Ulm University. The facility is fully run by a coordinator and FACS operator and offers an advisory and complete sorting service for its users with the support of three FACS operators.

The CF-FACS is equipped with the following machines from the company Becton Dickinson: Sorter 1: FACS Aria 3 fitted with five lasers (375, 405, 488, 561 and 633 nm); Sorter 2: FACS Aria 3 fitted with four lasers (375, 405, 488 and 633 nm); Sorter 3: FACS Aria 2u fitted with three lasers (405, 488 and 633 nm); and Sorter 4: BD LSR II with four lasers (325, 405, 488 and 633 nm). Different filter combinations are available that enable the measurement of almost all fluorochromes available on the market. We own ceramic duct nozzles of different sizes (70, 85 and 100 um) that allow the sorting of cells of various diameters up to 25 µm. On all machines it is possible to sort up to four different cell populations out of one probe into 1ml, 5ml and 15ml tubes, as well as multi- or single-cell sorting into multi-well culture plates. Sorters 1 and 2 are additionally equipped with an aerosol vacuum device that enables sorting of infectious organisms and gene-modified cells classified as biosafety S2.

A large number of institutes of Ulm University and the University Hospital Ulm benefited from the service of the CF-FACS in the year 2013. The main focus of the research projects that run on the machines of the CF-FACS has centered on stem cell biology, cancer and aging.

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Selected Publications:

- *Edmaier KE, Stahnke K, Vegi N, Mulaw M, Ihme S, Scheffold A, Rudolph KL, Buske C (2014): Expression of the lymphoid enhancer factor 1 is required for normal hematopoietic stem and progenitor cell function. Leukemia, 28(1):227-30.*
- *Zhou X, Florian MC, Arumugam P, Chen X, Cancelas JA, Lang R, Malik P, Geiger H, Zheng Y (2013): RhoA GTPase controls cytokinesis and programmed necrosis of hematopoietic progenitors. J Exp Med., 210 (11): 2371-85.*
- *Luche H, Nageswara Rao T, Kumar S, Tasdogan A, Beckel F, Blum C, Martins VC, Rodewald HR, Fehling HJ (2013): In vivo fate mapping identifies pre-TCRα expression as an intra- and extrathymic, but not prethymic, marker of T lymphopoiesis. J Exp Med., 210(4):699-714.*
- *Florian MC, Nattamai KJ, Dorr K, Marka G, Uberle B, Vas V, Eckl C, Andra I, Schiemann M, Oostendorp RA, Scharffetter-Kochanek K, Kestler HA, Zheng Y, Geiger H (2013): A canonical to non-canonical Wnt signalling switch in haematopoietic stem-cell ageing. Nature, 503 (7476), 392-6.*

Core Facility

Genomics

Head of Core Facility: Prof. Dr. Christian Buske

Keywords: Microarray Analysis | Next Generation Sequencing | Data Analysis | Microarray production

Isolation of murine hematopoetic stem cells via complex multicolor FACS (Fluorescent-Activated Cell Sorting) on a BDFACSAriaIII cell-sorting machine

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The Genomics Core Facility offers several genomic services, including traditional microarray analysis as well as Next Generation Sequencing both to investigators at Ulm University as well as to external users. Established in 2001, the Genomics Core Facility started with expression and copy number microarray analyses using self-spottet Oligo- and BAC arrays (Gene Machines Omnigrid Spotter). At the time, the Genomics Core Facility was especially engaged in the development of Matrix-CGH in close collaboration with the German Cancer Research Center, Heidelberg.

In 2006 the Genomics Core Facility acquired an Affymetrix GCS 3000 system and expanded its services with the complete range of analyses offered by Affymetrix. The Genomics Core Facility is especially focused on copy number analysis in different tumor types using Affymetrix SNP arrays, and on supporting international and collaborative projects.

In 2013 the range of applications was expanded to Next Generation Sequencing by using a state-of-the-art Illumina HiSeq2000 machine. In its first year the machine was used by more than eight groups on campus that have fostered research in the fields of cancer, stem cell biology, microbiology, virology and cardiology.

The core facility currently offers a broad range of applications :

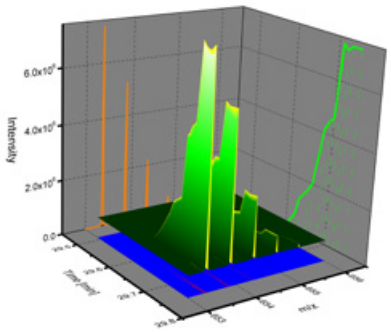
Microarray Analysis
- Expression profiling
- miRNA analyses
- SNP/Copy number analyses
- ChIP on Chip Analyses

Next Generation Sequencing
- Whole Genome Sequencing
- Exom Sequencing
- RNA Sequencing
- miRNA Sequencing
- ChIP Sequencing

Customer support includes complete assistance from sample preparation to data analysis in close collaboration with the group of H. Kestler at the Department of Bioinformatics (http://sysbio.uni-ulm.de/?Research).

Selected Publications:

- *Pannicke U, Baumann B, Fuchs S, Henneke P, Rensing-Ehl A, Rizzi M, Janda A, Hese K, Schlesier M, Holzmann K, Borte S, Laux C, Rump EM, Rosenberg A, Zelinski T, Schrezenmeier H, Wirth T, Ehl S, Schroeder ML, Schwarz K. Deficiency of innate and acquired immunity caused by an IKBKB mutation. N Engl J Med. 2013 Dec 26;369(26):2504-14.*
- *Flossbach L, Holzmann K, Mattfeldt T, Buck M, Lanz K, Held M, Möller P, Barth TF. High-resolution genomic profiling reveals clonal evolution and competition in gastrointestinal marginal zone B-cell lymphoma and its large cell variant. Int J Cancer. 2013 Feb 1;132(3):E116-27.*
- *Kuehner S, Holzmann K, Speit G. Characterization of formaldehyde's genotoxic mode of action by gene expression analysis in TK6 cells. Arch Toxicol. 2013 Nov;87(11):1999-2012.*
- *Edelmann J, Holzmann K, Miller F, Winkler D, Bühler A, Zenz T, Bullinger L, Kühn MW, Gerhardinger A, Bloehdorn J, Radtke I, Su X, Ma J, Pounds S, Hallek M, Lichter P, Korbel J, Busch R, Mertens D, Downing JR, Stilgenbauer S, Döhner H. High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. Blood. 2012 Dec 6;120(24):4783-94.*
- *Sander S, Calado DP, Srinivasan L, Köchert K, Zhang B, Rosolowski M, Rodig SJ, Holzmann K, Stilgenbauer S, Siebert R, Bullinger L, Rajewsky K. Synergy between PI3K signaling and MYC in Burkitt lymphomagenesis. Cancer Cell. 2012 Aug 14;22(2):167-79.*



3D-plot of a doubly charged peptide from a tryptic digest of bovine serum albumin as observed during LC/MS-analysis.

Core Unit

Mass Spectrometry and Proteomics

Head of Core Unit: Dr. Sebastian Wiese

Keywords: Proteomics | Mass Spectrometry | quantitative | PTM analysis

The Core Unit of Mass Spectrometry and Proteomics (CUMP) is the most recent addition to the Medical Faculty's core facilities. The services, offered to all interested scientists, cover all aspects of proteomic research, from assistance during the initial planning phase, to sample preparation and sample fractionation, and to mass spectrometric analysis and subsequent statistical and bioinformatic analysis of primary data and downstream functional changes.

CUMP currently operates a Thermo Scientific LTQ Orbitrap Velos Pro mass spectrometer (MS) online coupled to a Dionex RSLCnano liquid chromatography (LC) system. In addition, a multi-dimensional LC system is used for SCX-driven peptide fractionation. This instrumentation allows state-of-the-art proteomic research, allowing the parallel identification and quantification of thousands of proteins.

The use of a broad range of quantitative proteomic techniques, such as SILAC (stable isotope labeling of amino acids in cell culture), label-free analyses, and isobaric tags, allows the elucidation of protein dynamics in a broad range of medical and biological fields. By using specific peptide enrichment, such as TiO_2-enrichment of phosphorylated peptides, CUMP is able to qualitatively and quantitatively analyze a number of various post-translational modifications (PTMs) and thus to shed light on cellular events involving protein processing.

In addition to the described methods, CUMP maintains a close collaboration with all scientists involved in order to devise novel solutions to newly arising questions.

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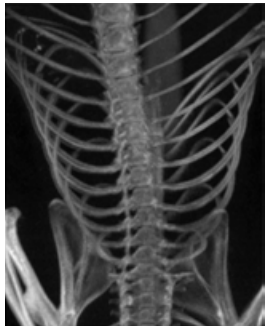
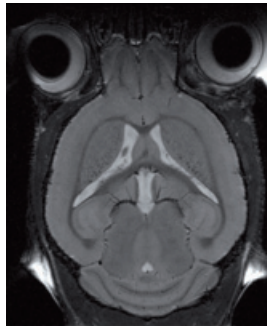
Selected Publications:

- *Gronemeyer, T., Wiese, S., Ofman, R., Bunse, C., Pawlas, M., Hayen, H., Eisenacher, M., Stephan, C., Meyer, H. E., Waterham, H. R., Erdmann, R., Wanders, R. J., and Warscheid, B. (2013): The proteome of human liver peroxisomes: identification of five new peroxisomal constituents by a label-free quantitative proteomics survey. PLoS. One. 8, e57395.*
- *Niemann, M., Wiese, S., Mani, J., Chanfon, A., Jackson, C., Meisinger, C., Warscheid, B., and Schneider, A. (2013): Mitochondrial outer membrane proteome of Trypanosoma brucei reveals novel factors required to maintain mitochondrial morphology. Mol. Cell Proteomics. 12, 515-528.*
- *Qiu, J., Wenz, L. S., Zerbes, R. M., Oeljeklaus, S., Bohnert, M., Stroud, D. A., Wirth, C., Ellenrieder, L., Thornton, N., Kutik, S., Wiese, S., Schulze-Specking, A., Zufall, N., Chacinska, A., Guiard, B., Hunte, C., Warscheid, B., van der Laan, M., Pfanner, N., Wiedemann, N., and Becker, T. (2013): Coupling of mitochondrial import and export translocases by receptor-mediated supercomplex formation. Cell 154, 596-608.*

Quantitative evaluation of a cardiac functional examination in a mouse model.



High-resolution µCT bone imaging.



High-resolution T2-weight magnetic resonance imaging of a mouse brain.

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Core Facility

Small Animal Imaging

Head of Core Facility: Prof. Dr. Volker Rasche

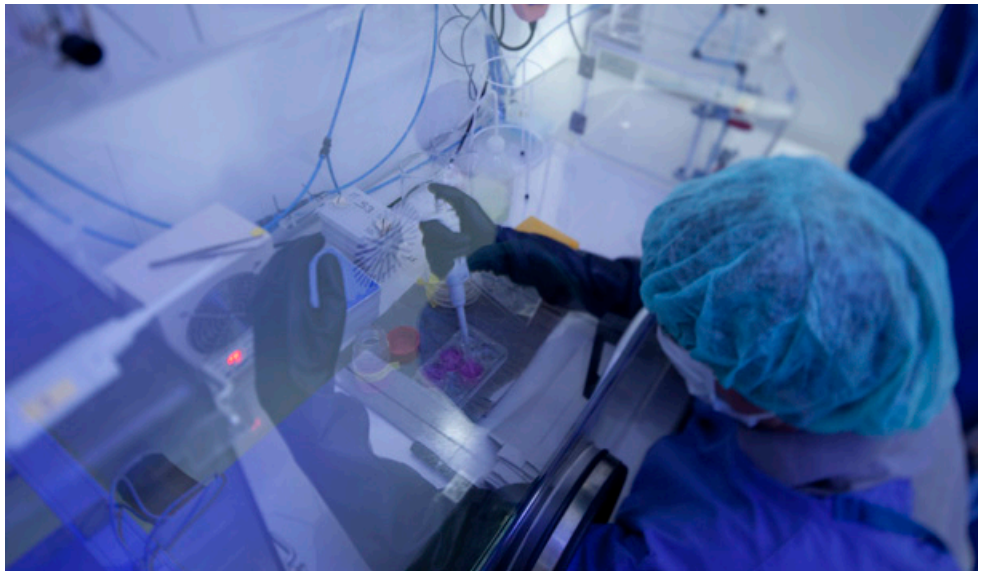
Keywords: Small animal imaging | magnetic resonance imaging | magnetic resonance spectroscopy | computer tomography

The mission of the core facility of Small Animal Imaging (SANI) is to provide a dynamic and productive environment for researchers at Ulm University, for collaborating research groups at other institutions, and for industrial partners to peform non-invasive imaging of small animals. There are currently two PhDs and one technician active at the facility and these are supported by a variety of other PhD and master students. The facility offers guidance for the planning and implementation of small animal imaging experiments by supporting applications for approval from relevant authorities and by providing the means for the post-processing and evaluation of images. Further activities include research for advanced imaging methods as well as advanced applications of MRI and MRS for the investigation of new fields in biomedical research.

The facility offers the latest technology in small animal MRI imaging and spectroscopy as well as dedicated small animal computer tomography imaging. It operates an ultrahigh field 11.7T MR imaging and spectroscopy system (BioSpec 117/16) equipped with high-sensitive cryogenically cooled receive coils and multi-channel capability. It provides technology for neurology, abdominal and thoracic imaging (MRI) in mice, rats and tissue samples. The means for physiological gating enables high-quality quantification of cardiac and other functional parameters. Advanced rapid MR spectroscopy (MRS) facilitates the study of a multitude of metabolic processes. Target nuclei include 1H, 13C, 19F, 23Na, and 31P. For X-ray imaging, mice and rats can further be scanned by µ-CT (GE eXplore Locus) and this provides the means for high-resolution anatomic imaging of, for example, bones or lung parenchyma. Animal facilities are also provided for longitudinal studies.

Selected Publications:

- *Vernikouskaya I, Fekete N, Erle A, Bannwarth M, Landfester K, Rojewski M, Schnmidtke-Schrezenmeier G, Schrezenmeier H, Rasche V. Iron-loaded PLLA (iPLLA) Nanoparticles as Highly Efficient Intracellular Markers for Visualization of Mesenchymal Stromal Cells by MRI. Contrast Media Mol Imaging. 2014 Mar-Apr;9(2):109-21.*
- *Mueller HP, Vernikouskaya I, Kassubek J, Ludolph AC, Stller D, Rasche V. Diffusion tensor magnetic resonance imaging of the brain in APP transgenic mice: a cohort study. PlosOne 2013;8(6):e67630.*
- *Martins VC, Busch K, Juraeva D, Blum C, Ludwig C, Rasche V, Lasitschka F, Mastitsky S, Brors B, Hielscher T, Fehling HJ, Rodewald HR. Cell competition is a tumour suppressor mechanism in the thymus. Nature 2014, Nature. 2014 May 22;509(7501):465-70.*
- *Weiger M, Pruessmann KP, Bracher AK, Köhler S, Lehmann V, Wolfram U, Hennel F, Rasche V. High-resolution ZTE imaging of human teeth. NMR Biomed. 2012;25(10):1144-51.*
- *Begus-Nahrmann Y, Hartmann D, Kraus J, Scheffold A, Grieb M, Rasche V, Schirmacher P, Lee HW, Kestler H, Lechel A, Rudolph KL. Transient telomere dysfunction induces chromosomal instability and promotes carcinogenesis in telomerase-proficient mice. J Clin Invest. 2012;122(6):2283-8.*



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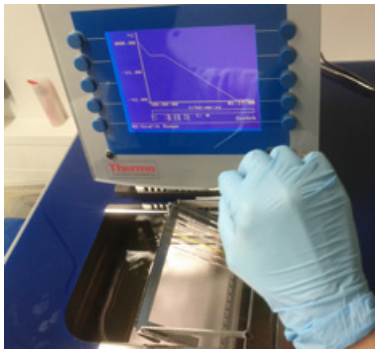
Core Facility

Transgenic Mice

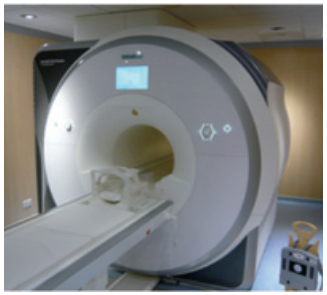
Head of Core Facility: Prof. Dr. Thomas Wirth/Mrs. Olena Sakk

Keywords: Embryo transfer | cryoconservation | pronucleus injection | in vitro fertilization



Embryofreezing

The technical manager of this core facility, which was established in July 2011, is Olena Sakk. The facility offers standard mouse technologies such as embryo transfer for hygienic sanitation, cryoconservation and the revitalization of embryos, in vitro fertilization, oophorectomy, and the generation of novel transgenic mouse lines by pronucleus injection. In addition, novel techniques, such as sperm freezing, are currently being established. The facility is supported by core funding from the Medical Faculty and thereby allows us to offer services to the researchers at Ulm University at competitive prices. In addition, services are available for external users. There has been a constant increase in demand of services from the core facility and as a consequence the facility is currently approaching its full capacity.



Front view of the new 3 Tesla whole-body magnetic resonance scanner harbored in the HF-cabin in the basement of the Department of Psychiatry.

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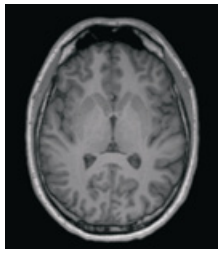
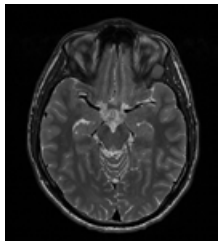
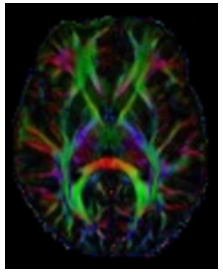


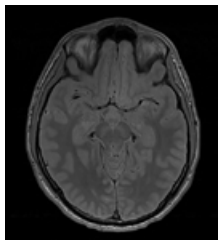
High resolution 3-dimensional T1 weighted brain image of a young male volunteer.



High resolution 3-dimensional T2 weighted brain image of a young male volunteer.



Colored fractional anisotropy mapping of a young male volunteer.



Proton density weighted brain image of a young male volunteer.

Core Facility

3 Tesla MR Imaging in Human Neuroscience

Head of Core Facility: Prof. Dr. Georg Grön

Keywords: Magnetic resonance imaging (MRI) | fMRI | perfusion MRI | structural MRI | diffusion MRI

In December 2014 the new core facility for magnetic resonance imaging in human neuroscience was established to run a new state-of-the-art 3 Tesla whole-body magnetic resonance scanner and is dedicated to research in the field of human neuroscience. The new Siemens MAGNETOM Prisma was funded equally by the German Research Foundation (*Deutsche Forschungsgemeinschaft, DFG*) and the Medical Faculty of Ulm University. The system is located in the basement of the Department of Psychiatry at Ulm University.

The mission of the core facility is to provide a campus-wide, efficient and scientific environment for research groups at Ulm University that is also open to collaborating research groups from other federal institutions as well as industrial partners. The core facility works in close collaboration with the departments of Neurology and Radiology of Ulm Medical Faculty.

The new MR scanner offers the latest technology in human brain imaging and is equipped with 20-channel and 64-channel head coils for fast parallel imaging in combination with an outstanding gradient system for high performance even under prolonged high-strain conditions. The facility provides the opportunity for in vivo brain imaging at high anatomical resolution. In particular, brain imaging under functional challenges either with “classical” BOLD (blood oxygen level dependent) or MR-based perfusion imaging by means of arterial spin labeling techniques can be provided by the facility. Several MR compatible devices for visual, acoustic and haptic stimulation are available in addition to devices that collect the responses of subjects during fMRI. The infrastructure has also been designed to run complex and elaborate pharmacological fMRI studies.

Selected Publications:

- *Ulrich M, Keller J, Hoenig K, Waller C, Grön G (2014): Neural correlates of experimentally induced flow experiences. Neuroimage, 86:194-202.*
- *Fladung AK, Schulze UM, Schöll F, Bauer K, Grön G (2013): Role of the ventral striatum in developing anorexia nervosa. Transl Psychiatry, 3:e315.*
- *Abler B, Grön G, Hartmann A, Metzger C, Walter M (2012): Modulation of frontostriatal interaction aligns with reduced primary reward processing under serotonergic drugs. J Neurosci., 32:1329-35.*
- *Cárdenas-Morales L, Grön G, Kammer T (2011): Exploring the after-effects of theta burst magnetic stimulation on the human motor cortex: a functional imaging study. Hum Brain Mapp, 32:1948-60.*
- *Graf H, Abler B, Freudenmann R, Beschoner P, Schaeffeler E, Spitzer M, Schwab M, Grön G (2011): Neural correlates of error monitoring modulated by atomoxetine in healthy volunteers. Biol Psychiatry, 69:890-7.*