Lund University Bioimaging Center (LBIC)
http://www.med.lu.se/bioimaging_center
Progress Report June 2011

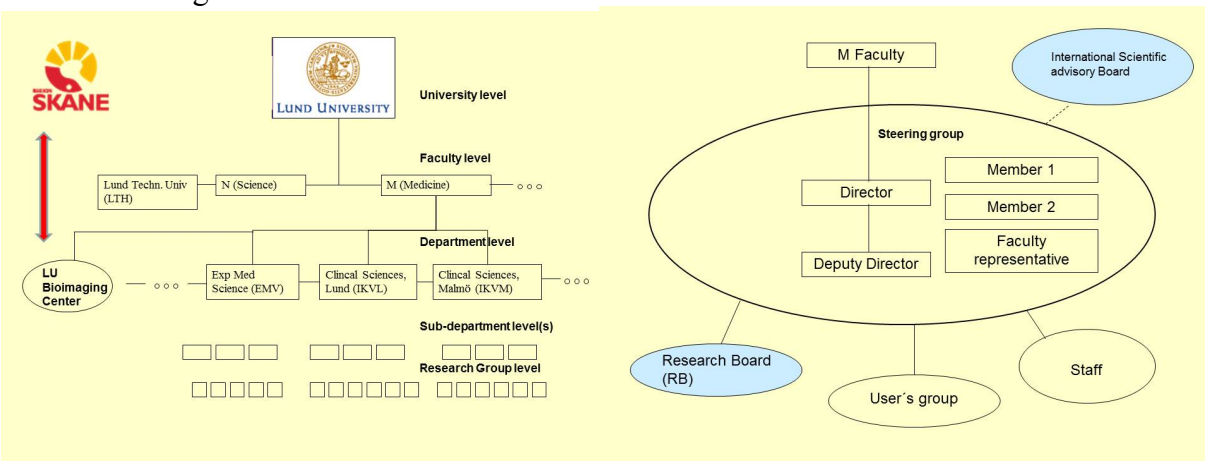
Goal

The overall goal of Lund University Bioimaging Center (LBIC) is to pursue in-depth knowledge of human metabolism and function by developing and combining advanced imaging techniques, primarily high-field MRI, PET and SPECT.

To achieve this goal, we provide technical platforms, knowledge and support in the development of new diagnostic methods from experimental models, while at the same time taking on unmet clinical problems to device patient-specific tailored therapies. LBIC techniques will be advanced both as individual modalities and also towards a merged use. We envision future simultaneous extraction of physiological and molecular information in a multimodal imaging environment for better understanding the impact of molecular events on cellular/tissue behavior. We believe that the development of the Lund University Bioimaging Center will have a significant impact on the research at Lund University. Locally, the center is intended to become a powerful resource for translational research at the medical faculty and at Skåne university hospital, with strong connections to planned larger research facilities in Lund, e.g. MAXIV and ESS Scandinavia. On a national and international level, the buildup of the proposed center can be foreseen to become an asset to the whole biomedical research community.

Structure

LBIC was established as a center within the medical faculty at Lund University in autumn 2008, directly under the faculty leadership and in parallel with the faculty departments as shown in the figures below:



Steering Group:

LBIC is led and coordinated by a steering group, where the competence reflects the different core imaging modalities within LBIC. The director and the deputy director represent competence in human imaging and experimental imaging, respectively, and share the responsibility of center leadership.

Steering group 2011:
Prof. Freddy Ståhlberg (director); Prof. Deniz Kirik (deputy director); Prof. Sven-Erik Strand; Assoc. prof. Isabella Björkman- Burtscher; Prof. Ingemar Carlstedt (faculty representative).

Research Board:
All projects are evaluated before acceptance with respect to possibility to perform the intended experiments successfully, given the available equipment at LBIC. This evaluation is performed by the LBIC research board (RB).

RB 2011:
Prof. Deniz Kirik (chair); Eva Nordin (secretary); Prof. Sven-Erik Strand; laboratory researchers Thuy Tran and Carina Dahlgren; Assoc. prof. Bo-Anders Jönsson (adjunct); research engineer Karin Wingårdh (adjunct).

Scientific Advisory Board:
Several world experts in the fields of MRI and PET form an international scientific advisory board (SAB):

SAB 2011:
Prof Magnus Dalhbom *(UCLA,USA)*, Prof Philippe Hantraye *(CEA, Orsay, France)*, Prof Hans Lundqvist *(Uppsala Univ, Sweden)*, Prof Kamil Ugurbil *(Univ of Minnesota, USA)* and Prof Larry Wald *(MGH, Boston, USA*.)

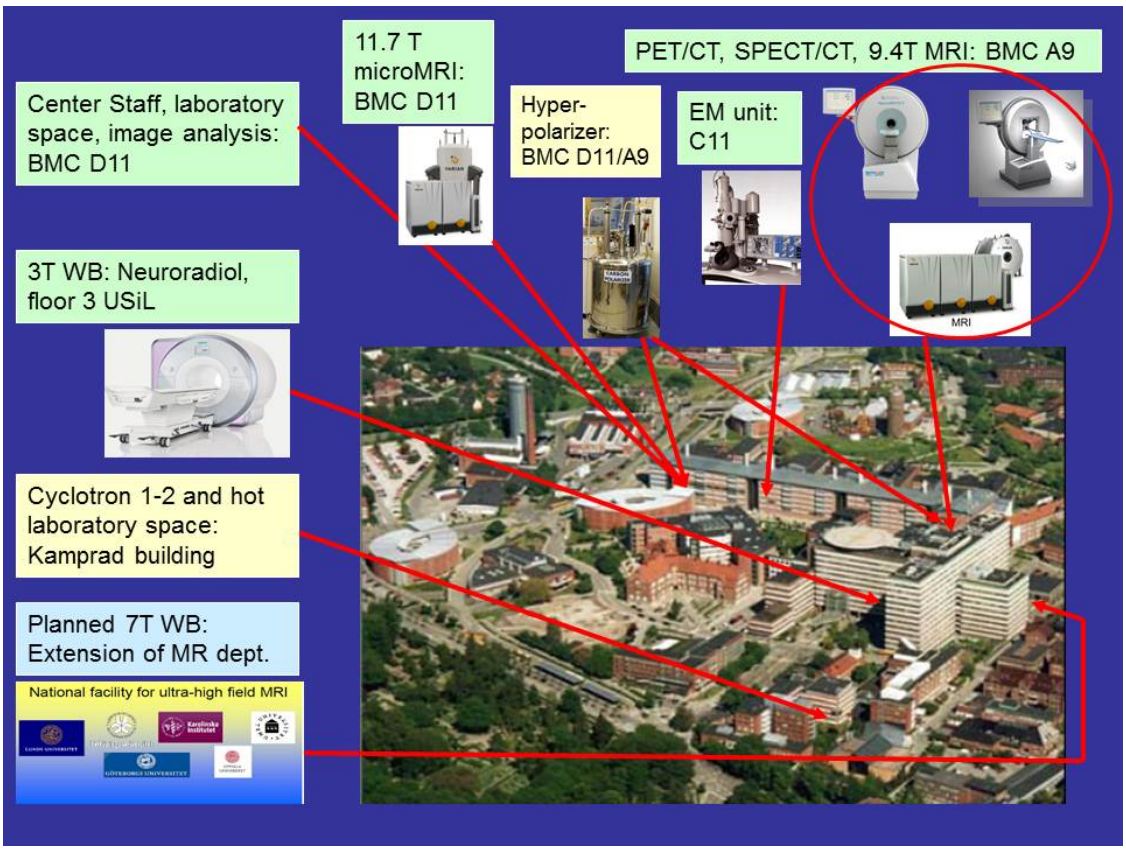
Equipment, funding and staff:

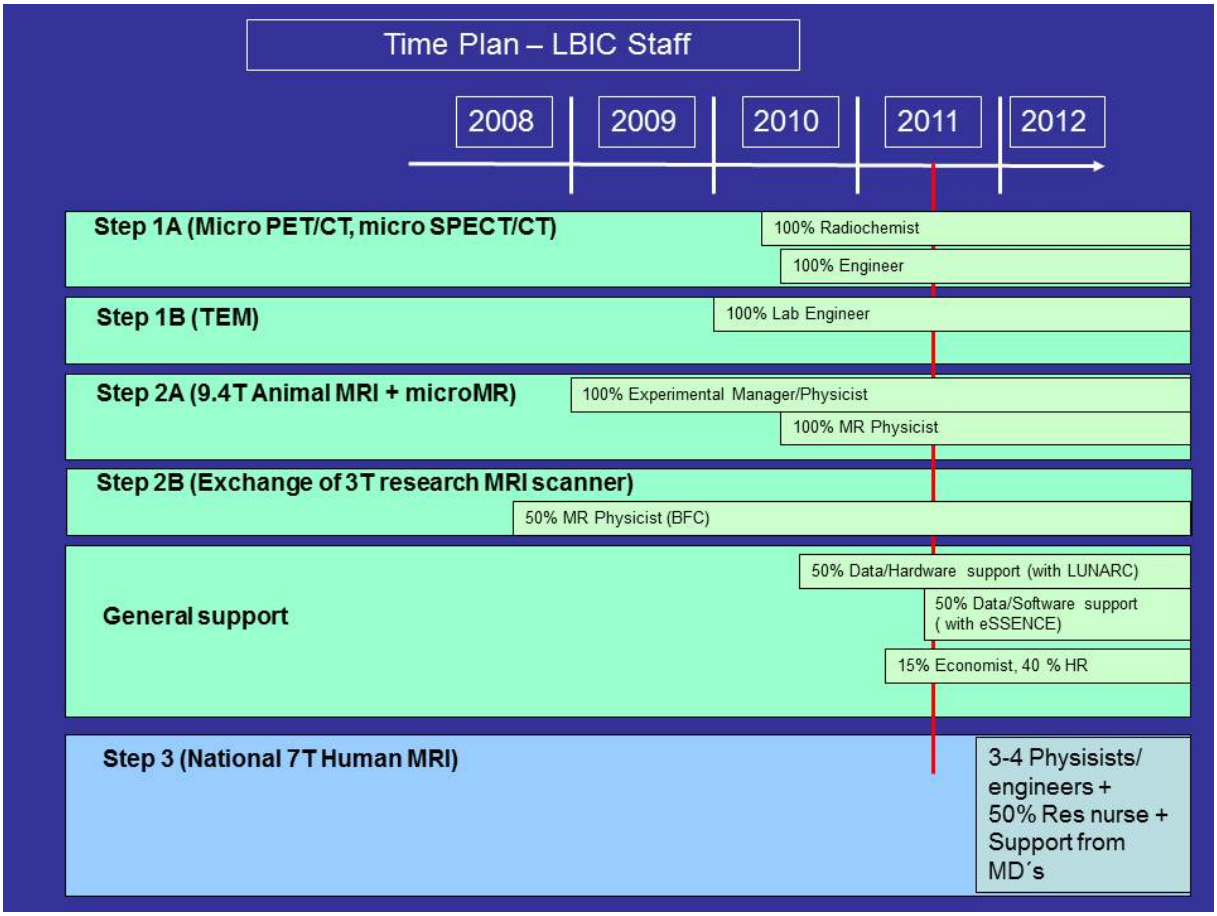
LBIC is still in its development phase, however several steps have to date been established and are active.

LBIC Steps 1-2: Subsequent to a major donation from the Knut and Alice Wallenberg foundation (40 MSEK) in March 2008, a purchase procedure led by the Lund university purchase and procurement department was initialized in late 2008 and finalized in mid-2009. With support also from other external funding sources up to a total of approximately 70 MSEK, the two first major steps (1 and 2) in LBIC are now being accomplished:
Step 1A: Experimental PET/CT and SPECT/CT
Step 1B: TEM
Step 2A: Experimental MRI at 9.4T and 11.7 T
Step 2B: Human MRI at 3T
In mid-2011, all equipment in steps 1-2 is expected to be available for researchers after final acceptance testing.

LBIC Step 3: The overall goal of LBIC step 3 is to establish Sweden´s first human 7T MR equipment, in order to pursue in-depth knowledge of human morphology, function and metabolism in health and disease by the utilization of ultra-high field (UHF) magnetic resonance imaging (MRI) and spectroscopy (MRS). The initiative is made in national collaboration between six Swedish universities/university hospitals (Umeå, Uppsala, Stockholm, Gothenburg, Linköping, Lund/Malmö), all possessing advanced bioimaging equipment in the fields of MRI and PET, but so far lacking UHF MR. The infrastructure will form a third and nationally open resource step in LBIC, and the initiative is made as part of the VR supported network Swedish Bioimaging (SBI).
LBIC step 3 is presently in its purchase phase, and the total budget for the scanner and the building is estimated to 104 Mkr. The equipment is to its major extent financed using an equipment grant from the Swedish Research Council´s board for research infrastructure, and the building is planned to be financed by Region Skåne.
An overview of LBIC equipment, placement and staff is given in the images below.

Platform and coordinator	Equipment	Delivery	Availability	Funding
Exp PET/SPECT Prof. Sven-Erik Strand	BioScan: Micro-PET/CT + Micro-SPECT/CT 	Spring 2011	Autumn 2011	KAW, Kamprad, Lundberg and the Swedish Cancer foundations; Science faculty, LU; ALF, LU
EM Prof. Ingemar Carlstedt	FEI: TEM (transmission electron microscope) 	Autumn 2010	Spring 2011	The Crafoord foundation
Exp MRI Prof. Deniz Kirik	Varian: 9.4 T MR 11.7 T micro-MR 	Spring/ summer 2010	Spring 2011	The Knut and Alice Wallenberg foundation
-"-	Hyperpolarizer for e.g. C-13 	2011/2012	2012	The Swedish Research Council
Human 3T: Assoc. Prof. Isabella Björkman-Burtscher	Siemens: Skyra 3T WB MRI 	Spring/ summer 2010	Spring 2011	The Knut and Alice Wallenberg foundation (50%), Region Skåne (50%)
Human 7T: Prof. Freddy Ståhlberg		2012/2013		The Swedish Research Council





On the following pages, the LBIC steps (platforms) 1-2 are described together with a short description of our initiative to develop a joint computer infrastructure for the center as a whole.

Step 1A: Preclinical PET/SPECT/CT and related radiochemistry

The overall objective is to provide a platform for research groups that need to develop novel molecular imaging probes and techniques for non-invasive detection of different diseases using microPET/SPECT/CT systems. The radiochemistry and the techniques developed will allow investigations of the molecular, cellular, metabolic and physiological features of certain diseases.

Instrumentation and laboratory buildings

The preclinical PET/SPECT/CT platform is equipped with a combined PET/CT and a combined SPECT/CT (both from BioScan) for in vivo imaging, with animal handling systems compatible with the MR imaging system. The SPECT has 4 detectors for highest spatial resolution and sensitivity. The PET camera has a spatial resolution of 1.0 mm, the SPECT of 0.4 mm and the CT of about 40 µm. The animal handling systems are equipped with sophisticated anesthesia and regulated temperature in a pathogen-free sterile environment.

The laboratory space in the BMC A09, conventional animal department has been rebuilt and completed in December 2010 to accommodate the two camera systems. In between the rooms, there is a preparation room for handling radiopharmaceuticals and tissue samples. The laboratory space at BMC D11 is now fully equipped with radiolabelling, cell culture, conjugation, auto-radiography and histology laboratory and a data evaluation room. In addition, a radiochemistry laboratory is being built at the cyclotron unit at the Kamprad Laboratory building and will be equipped with 3 hot cells for production of a variety of radionuclides and for production of novel radiotracers for clinical and research purposes.

Staff and associated researchers

PI for this platform is Prof Sven-Erik Strand. Present LBIC staff comprises one 100% employed radiochemist (Thuy Tran, MSc Pharm, PhD) and from the 1th July 2011, one 100% employed Medical Radiation Physicist for operating instruments and data analysis (Gustav Grafström, PhD). Associated researchers are senior lecturer Bo-Anders Jönsson and research engineer Karin Wingårdh, both at Dept of Medical Radiation Physics.

Radiochemistry

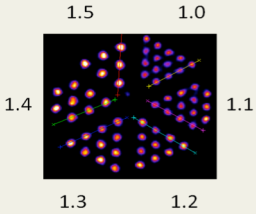
Before performing the *in vivo* animal imaging, radiosynthesis, optimization and quality control of different radiotracers are carried out. Biomarkers such as proteins, peptides and small ligands are labeled with a number of different radionuclides (for example ^{125}I, ^{111}In, ^{18}F, ^{68}Ga) are evaluated regarding their labeling yields, stability and radiochemical purity. The main research areas for developing radiotracers are oncology and neuro-diseases.

Current and foreseen projects 2011/2012

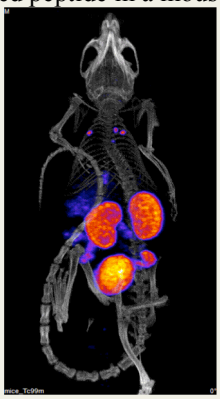
The equipment is up and running since April 2011. The current approved projects include prostate cancer, breast cancer, and neurodegenerative diseases. Parts of the projects have been initiated during the spring and will be fully started in the autumn 2011 when our laboratories are adapted for handling of immuno-compromised animals. Future projects will also include imaging of bone structures and structure changes in the bones using CT. Development of novel radiotracers for neuroPET will also be a major part in this platform in the next two years.

A.Laboratory buildings

B.Jaszczak phantom measured on SPECT



C. Biodistribution of a ^{99m}Tc-labelled peptide in a mouse



Step 1B: Electron microscopy (EM)

The overall research aim is to provide both the latest-state-of-the-art, as well as more routine facilities for electron microscopy users.

Instrumentation

The FEI Tecnai™ G2 Spirit BioTWIN transmission electron microscope at LBIC is a general-purpose, user-friendly instrument to be used in a multi-user core facility environment. It is designed for high resolution and contrast imaging and analysis of low contrast soft matter. It enables to explore the native state of low-contrast, beam-sensitive biological specimens, or other soft materials like polymers. Samples can be unstained or stained. It enables the 2D and 3D ultra-structure exploration of cells and cell constituents, as well as the morphology, chemical composition and function of natural or artificial materials. Low dose observation of beam sensitive and cryo samples is a key performance aspect. The technique of Cryo-TEM enables visualization of frozen-hydrated thin film preparations of particles where dehydration and negative staining is undesired. The feature of electron tomography is of paramount importance to obtain high magnification and high resolution 3D information of cells and organelles or even smaller cell constituents.

Staff and associated researchers

Coordinator for Step 1B is Prof. Ingemar Carlstedt. Present LBIC staff comprise one 100% employed research engineer (Lina Gefors). Associated researchers are senior lecturers Matthias Mörgelin, division of infection medicine and senior lecturer emeritus Eric Carlemalm.

Laboratory buildings

In the BMC building at floor C11 rooms are rebuilt to accommodate the instrument. As auxiliary equipment the facility will house a comprehensive preparation laboratory which includes a range of specialized sample preparation equipment, digital imaging facilities and computer workstations for image processing. Additionally, a somewhat older scanning electron microscope (Philips) is available at the present EM facility. Pending additional funding, it will be replaced by a modern state-of-art instrument.

Foreseen projects 2011

The new EM equipment constitutes an essential research support to all other steps in LBIC, in particular step 1A. Furthermore, the present EM facility, which will be moved to BMC C11 when the new TEM microscope arrives, is actively involved in a wide range of research topics across the Medical Faculty and contributes to about 20 scientific publications per year in high profile biological journals. Major research areas that can be foreseen during the next year are: Bacterial infection and proteomics; host-pathogen interactions – primary adhesion, inflammation, sepsis, innate and adaptive immunity, biofilm and quorum sensing, antimicrobial and anti-inflammatory agents; chronic obstructive lung disease (COPD), pulmonary fibrosis and extracellular matrix remodeling; connective tissue structure and dynamics; oxidative stress and antioxidants; intracellular signaling in diabetes and cancer. Already active groups and projects are: Prof. Lars Björck, dept of infection medicine, host-pathogen interactions; Prof. Heiko Herwald, dept of infection medicine, innate immunity; Prof. Artur Schmidtchen, dept of dermatology and venereology, antimicrobial and anti-inflammatory agents; Prof. Kristian Riesbeck, dept of laboratory medicine, SUS Malmö, pulmonary pathogens; Dr. Ole Sörensen, dept of infection medicine, antimicrobial and anti-inflammatory agents; Dr. Joost Meijers, dept of vascular medicine, University of Amsterdam; Dr .Arne Egesten, dept of respiratory medicine and allergology, antimicrobial agents in pulmonary fibrosis; Dr. Stefan Hansson, dept of obstetrics and gynecology, oxidative stress in preeclampsia.

Step 2A: In vivo animal MRI/MRS and in vitro micro-MRI/MRS

The goal of the platform is to establish preclinical MR imaging and MR spectroscopy facilities at the Biomedical Center (BMC) at Lund University. The platform is envisioned as an open core facility and a competence center for advanced imaging techniques. The ability to perform first-class high resolution MRI and MRS research both in vivo and ex vivo will be provided to research groups from both academia and industry.

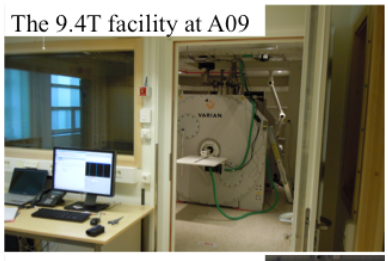
Instrumentation and laboratory buildings

Two well-equipped state of the art units, one 9.4T (horizontal bore) and one 11.7T (vertical bore), have been installed in newly renovated laboratory spaces in the A and D buildings of BMC. The use of the same software platform on both units allows seamless transfer of experience and know-how.

The animal 9.4T scanner with a bore size of 30 cm and gradient strengths between 300 mT/m and 1000 mT/m enables high-quality images of small mice to rats and even rabbits or cats in vivo. In addition to proton detection, the capabilities of X-nuclei MRI/MRS makes it perfectly suited in a variety of experimental applications from neuroscience to oncology and stem cell biology. Special attention has been paid to optimizing animal handling routines within the unit and between the MR and PET/SPECT/CT units.

The 11.7T integrated microimaging/liquids system allows the combination of in vitro high-resolution microimaging and high resolved liquid spectroscopy. This system enables detection of 1H, 2H, 13C, 15N, 19F and 31P. The laboratory space at D11 will also include an RF coil lab and post-processing units for modeling and image analysis.

The 9.4T facility at A09

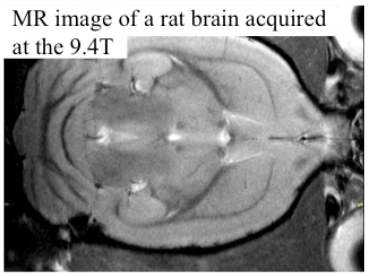


The 11.7T facility at D11

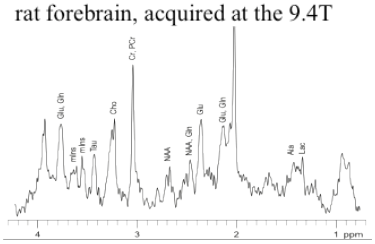
Staff and associated researchers

Coordinator for the platform is Prof. Deniz Kirik. Present LBIC staff comprises three MR physicists (Carina Dahlberg, PhD, René in ‘t Zandt, PhD, and Vladimir Denisov, PhD). Prof. Freddy Ståhlberg acts as associated researcher.

MR image of a rat brain acquired at the 9.4T



MR spectrum from a region in the rat forebrain, acquired at the 9.4T



Current and foreseen projects 2011/2012

Several projects have been initiated since the acceptance of both scanners in September 2010. We have currently approved five projects for the 11.7T and nine for the 9.4T with a wide range of interest areas (such as bone, nanoparticles, cartilage, plaque, neurotransmitters, cardiac, brain, lymphatic system, and blood flow characterization). During 2010/2011, the major focus has been cardiac imaging of mice and brain spectroscopy of rats for the 9.4T. In the context of the latter, a collaboration with Prof. Rolf Gruetter (EPFL, Lausanne) has been initiated. For the 11.7T the focus has been on cartilage imaging, plaque imaging/spectroscopy and 15N-choline spectroscopy of neurotransmitter synthesis. The fruitful collaboration with Dr. Arnaud Comment (EPFL, Lausanne) has been intensified as the project of establishing hyperpolarization-enhanced MR spectroscopy has progressed successfully.

Step 2B: 3T MRI for neuro research

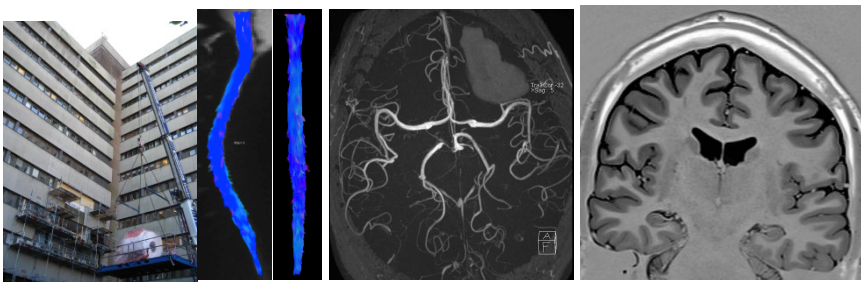
In 2001, Sweden's first 3T scanner was installed in Lund for 50% neuro research (funded by KAW), combined with 50% clinical operation (funded by Region Skåne). The goal of LBIC step 2B was to continue this successful research path by replacing this equipment and installing a new state-of-the art 3T scanner at the Dept. of Neuroradiology, Skåne University Hospital, Lund.

Intrumentation and laboratory buildings

The Siemens Magnetom Skyra 3.0T was, as the first equipment of its kind in Europe, delivered to Lund June 2, 2010 and installed into a comprehensive clinical surrounding including 11 trained neuroradiologists, one 64-slice CT and 2 angiography labs for interventional neuroradiology in close proximity and an additional 4 MRs and 4 CTs within the BFC (Center for Imaging and Physiology) organization. The Skyra is a whole-body scanner with 70 cm bore size and a gradient system operating at 45mT/m@200µs. It has a digital RF system fully integrated in the magnet housing, 48 receive channels and it is prepared for parallel transmit technology (8ch Tx). The system utilizes the TIM 4G coil technology and is equipped with 32-channel head-, 20-channel head&neck- and 32-channel spine-receiver coils. The tender includes a comprehensive research agreement supporting on-going and future research activities within the field of neuroimaging and technical development. The system has during spring 2011 already been upgraded to an even more advanced software platform and new modalities such as spine diffusion tensor imaging (DTI) are introduced.

Staff and associated researchers

Coordinator for Step 2B is Assoc. Prof. I Björkman-Burtscher. Associated researchers/groups are Prof. P. Maly-Sundgren and Dr. D. van Westen, Dept. of Neuoradiology and the MR Physics group at Lund University. Several national and international groups have been visiting the facility and the system has been presented at the annual user meeting of the manufacturer held in Lund, May 2011.



June 2011, the new 3T system is installed and excellent imaging quality guarantees outstanding research prerequisites: Kurtosis DTI tractography of the human spinal cord (sagital and coronal projections), MR angiography of intracranial vessels and high resolution IR MRI.

Foreseen projects 2010/2011

The clinical MR research in Lund has, since 2001, been governed by a local MR council, selecting research projects based on scientific quality. On-going research transferred to the new system and now in its operative phase comprises development of perfusion quantification techniques (DSC and time-resolved ASL), development of new biomarkers based on high b-value diffusion imaging and optimization of fMRI methods. Among clinical projects in our pipe-line are translational clinical research projects on Parkinson's disease, dementia, neuropsychology, brain plasticity as well as psychiatry related projects in cooperation with basic and clinical neurosciences. Furthermore, research focuses on stroke and neurovascular disease as well as neuro MRI in the newborn.

Computer Infrastructure

A scalable computer infrastructure including an off-site backup solution has been architected and implemented during the past year. Important aspects are security and data integrity as well as scalability driven by actual needs that will vary over time.
One of the main design goals has been to create a flexible and user-friendly environment enabling the LBIC staff to perform their work in an intuitive way focusing on the scientific research instead of computer related issues.

The heterogeneous computer environment consists of a variety of hardware and software including proprietary systems and interfaces used for data acquisition. The operating systems currently in use are Microsoft Windows 7, Microsoft Windows XP, Red Hat Enterprise Linux, Ubuntu and MAC OS X. All data stored must be accessible in a transparent way independent of operating system used.
The primary storage solution consists of a virtualized server environment based on VMware ESX4 vSphere running on three physical 2U servers each equipped with dual quad core Intel Nahalem processors and 24 GB RAM. The main storage is based on three high availability RAID-6 disk arrays (block-level striping with double distributed parity) that provides fault tolerance from two drives failure i.e. two drives are allowed to fail without affecting the array. The RAID array communicates with the host systems using iSCSI protocol. Total storage space is 66 TB.

Primary server operating system is Microsoft Windows Server 2008 using Microsoft Active Directory as directory service. Currently six virtual server instances plus two domain controllers are deployed managing both user- and sensor data acquired using LBIC's medical sensor devices.
Nightly backups are performed to off-site servers with direct attached RAID storage hosted in Lunarc's data center located in a separate building 0.2 km away from LBIC premises.

Next-phase R&D projects have also been defined in different areas with purpose to further improve the bioimaging workflow including both existing equipment and the upcoming national 7T ultra-high-field human MRI system. Examples are enhanced computer and graphics techniques and secure (remote) data access.

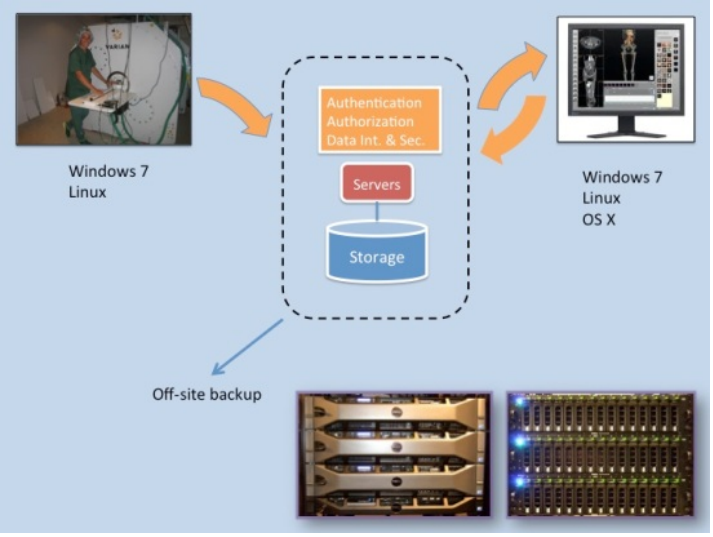


***Figure 1**: LBIC basic workflow and main storage system*

Staff and associated researchers

Coordinator for LBIC computer infrastructure is Anders Follin, Lic. Eng. , Project Manager / Solution Architect. Recruitment is presently ongoing for an additional IT staff person. Cooperation with researchers at SUS Lund (Johan Olsrud, PhD) and within the national network Swedish Bioimaging is presently being built up regarding the above mentioned 7T MRI project.