IMAGING FROM MOLECULE TO MAN

A NATIONAL CORE FACILITY TO IMPROVE HEALTH

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1. Vision and scientific goals

A clear trait in biomedical imaging in Norway of today is that the individual researchers receive funding for imaging equipment according to the needs of their specific research projects. This fragmentation makes it difficult for other researches to get access to the whole range of modalities and the adherent necessary expertise despite a substantial number of imaging modalities scattered within the Norwegian research community. This in turns hampers development of novel imaging techniques and prevents the exploitation of the full potential of available and future technology.

During the past decades, medical and molecular imaging has proven to be crucial in our understanding of biological processes in pathology, in patient diagnosis and eventually in the development of new and improved treatment strategies. In response to this development strong research consortia in medical and biological imaging have been developed in the Bergen area with the partners Molecular Imaging Centre (MIC), Medviz and Christian Michelsen Research (CMR).

These strong, and in a Norwegian context already consolidated, imaging groups will now embark on an even closer collaboration with other imaging groups in Bergen merging their comprehensive spectrum of modalities and establish a nationally unique imaging cluster in Norway. Our vision is to remedy the above outlined situation through a concentration of expertise and modalities and continuous upgrading of both.

Long term scientific goals

We aim to fulfil our vision by building on existing imaging expertise and equipment and bringing in new imaging modalities and knowledge in order to develop imaging research infrastructure in the form of a large , but geographically very compact imaging core facility with open access for all researchers from Norway and their collaborators from abroad. This facility, covering the whole range of imaging modalities from molecular imaging to clinical imaging will be staffed by highly trained and specialized technical personnel. Such a core facility will be unique on the national level as well as excellent in an international setting and guarantee the best possible utilization of funds spent on equipment.

At a core facility as described here, the newest equipment and highly qualified and experienced technical staff will accelerate the exploitation and dissemination to the Norwegian research environment of the full potential benefits of current and future imaging technology and methods. It will create a strong link from basic research and education to biomedical and clinical applications where new technology is used to understand pathology at a molecular level, and to improve diagnosis and treatment of patients. The ultimate goal is to contribute towards moving the Norwegian translational research to the forefront.

2. Scientific and technological environment

Below we will address the main scientific challenges, the levels of existing research infrastructure and the need for new equipment for frontier research within different imaging modalities.

Ultrasound (US)

Ultrasound (US) is widely applied in basic biomedical and clinical research and constitutes a cornerstone in diagnostic management of a large spectrum of patients. However, the full potential of this technology is by far exploited.

Molecular ultrasound imaging and targeted treatment: Contrast-enhanced ultrasound (CEUS) is now in regular clinical use. Our knowledge of tumour perfusion and inflammation is greatly facilitated by using CEUS. However, there is a need to develop more robust post-processing software to aid interpretation of CEUS data. In the MedViz network, mathematicians and engineers are working closely with clinicians to improve perfusion algorithms. Targeted contrast agents may be filled with drugs or bioactive substances, or combined with drug filled nano particles (liposomes) and be released locally by US-induced sonoporation. Molecular US imaging of inflammation, ischemia-reperfusion injury, angiogenesis, and thrombosis is achieved in animal models. As tumour model, we have chosen acute myeloid leukaemia (AML), based on our establishment of several models in mouse and rat. These models are highly molecularly characterized, and their disease phenotype and clinical characteristics are highly reproducible. To extend this research beyond the existing level, state-of-the art equipment and laboratory facilities are needed.

Novel ultrasound technology with SURF imaging: The US group (Prof. Angelsen, NTNU) has worked on new methods for nonlinear US imaging of tissue and particularly detection of contrast agents at high frequencies. The new US methods, named SURF imaging, have shown the potential to extend the limitations of current US imaging applying advanced dual transmit pulses. This technique enables contrast detection with improved resolution, specificity, and sensitivity compared to traditional techniques, and has been demonstrated to work for small animal imaging. In collaboration with Sunnybrook Research Institute and the University of Toronto, Canada, the method also demonstrated to work for small animal imaging frequencies.

Elastography and Strain imaging. Another main scientific challenge is tissue characterisation using endoscopic ultrasonography (EUS),in combination with elastography. This would be of major clinical importance and reduce the need for obtaining biopsies. We aim to combine EUS-guided procedures, EUS-CEUS, and elastography and apply new equipment and software for frontier research. Strain imaging methods are also applied for accurate detection of subendocardial ischemia and detailed analysis of gastric contractions in patients with dyspepsia. Improving these methods would give more accurate diagnosis of myocardial ischemia and infarction, including grading of a dysfunctional myocardial segment and also a more accurate localization of the affected region. In gastric applications, these US methods have the potential of improving diagnosis of functional dyspepsia and thus aid management of this large patient population. We also plan to investigate patients with liver diseases, also using Fibroscan, and using US Duplex scanning in cerebrovascular stroke (The *Bergen Stroke Study).*

Magnetic Resonance Imaging (MRI)

Small animal MR imaging: Magnetic resonance (MR) imaging has become one of the gold standards in human and animal imaging, as well as in preclinical and clinical research. Considerable expertise in small animal MR imaging has been built up at MIC since the 7T animal scanner was installed in 2004. However, preclinical MR imaging performed in Bergen is limited in the ability to perform detailed physiological studies with the current MR machine. Also, the MR technology has moved considerably forwards the last 5 years, with stronger magnets, improved coil technology, better shimming strategies and more advanced scanning/analysis software. We therefore include a new high-field small animal MR scanner in our current application.

Human MR imaging: The trend in scientific and advanced clinical MR for humans is a migration from 1.5T machines to 3T machines. In Bergen we have a General Electric (GE) broadband 3.0 Tesla bought in 2002 at its disposal half time. The machine has been extensively used in functional MR imaging, and is the central tool for this successful research area in Bergen. However, our 3T technology is now obsolete and needs a major upgrading to a new hardware platform.

This upgrading will also include additional hardware and software for hyperpolarized carbon 13 imaging, which allow high resolution imaging of metabolites of sugar metabolism such as pyrovate and lactate. We see applications of carbon 13 imaging as a major possibility to improve imaging of ischemia and malignant tumours. Hyperpolarized carbon 13 imaging is still limited to very few sites on a world basis. We have, however, a close collaboration with Dr. Stephan Petterson, GE Sweden, which was central in the early development of carbon 13 imaging. The extremely high spatial resolution of sugar metabolism is likely to give significant contributions to the understanding of tumour growth and treatment. A major challenge will be to explore in an optimal way the multimodal information resulting from imaging pyrovate and its metabolites. This is true for both applications in animals and humans. Our GE 3T machine can be upgraded to handle hyperpolarized carbon 13 imaging because it is a broadband machine. GE is the only vendor producing this equipment, and so far only for scientific purposes. As sugar metabolism is the main focus of PET imaging with FDG, this project also has potential in bridging PET and MR research.

Live cell imaging

Due to the rapid development of the imaging field, we apply for a comprehensive upgrade of the Perkin-Elmer Ultra View RS spinning disk confocal microscope (SDCM) to maintain it as a state-of-the-art imaging tool. The SDCM is a real time imaging system, which due to its low photo toxicity allows long-time recording of dynamic processes in living cells and tissues at high spatial and time resolution that cannot be achieved using conventional CMs. The increased sensitivity of an upgraded, SDCM system would further facilitate the analysis of fast biological processes. The development of new fluorescent probes continuously leads to novel SDCM applications in functional genomics research. For example, SDCM is an integral part of correlative light and electron microscopy, combining live cell imaging of the dynamics of a cellular structure with its EM analysis. SDCM is in growing demand in cellular imaging, but remains to be established in Norway. Moreover, fluorescence recovery after photo bleaching (FRAP) and photo activation are powerful techniques to study molecular kinetics in living cells, and requires faster imaging than by conventional CM. We wish to supplement the present SDCM system with the FRAP and photo activation attachments, thereby broadening the biological applications of this imaging system.

Optical imaging (OI)

We have established a small animal OI unit within MIC, and initiated an optical image processing project within MedViz. The unit is financed by NRC and UiB, and developed in collaboration with ART Inc and GE Healthcare. Currently, three optical scanners based on pulsed laser/photo-multiplicator detectors equipped with gas anaesthesia and heated stages are operative, dedicated to green fluorescent protein, far red probes and multi-wavelength/chemoluminiscense, respectively.

For further upgrades we propose a medium throughput Small animal imaging device (IVIS-like) for screening of larger number of animals, and a significant upgrade of our laser scanner/photomultiplicator device Small animal time-domain optical imager to secure standard operation and further development. Small animal time-domain optical imager upgrade in 2012 is necessary for technological edged and further development of technology.

Positron emission tomography (PET)

Animal PET imaging: Image data obtained from Positron Emission Tomography (PET) is used for non-invasive biochemical and physiologic activity measurements in humans and animals. Image data obtained from PET are functional in nature as they non-invasively measure biochemical and physiologic activity in humans and animals. Since April 2009, the PET Centre in Bergen has been operable with one clinical PET scanner. For animal use, μPET-CT has become a standard tool in the evaluation of preclinical studies and also in drug discovery. Although current human PET scanner has the best available spatial image resolution (around 3-4 mm), this is insufficient for imaging small animals like mice. Hence, for quality animal research a dedicated animal PET scanner is mandatory. It is important to have a combined PET and CT (PET-CT) animal scanning system, which allows the functional PET information to be superimposed on anatomical CT images.

Clinical PET-MR imaging: The clinical significance of PET in oncology has increased tremendously since the introduction of PET-CT a decade ago. For the central nervous system there is also

a wide range of radio chemicals that can be used to in basic research, clinical research and diagnostics. The problem has been to match the functional PET information precisely to the underlying anatomical structures, which are best delineated with MR. Today about 12 such systems are under testing on a world basis, but none in Scandinavia. Fusion of images recorded on separate MR and PET units does not provide sufficient spatial accuracy, and MR-PET systems will provide possibilities to relate biochemistry, function and anatomy in the normal state and in disease that is not possible today. We have a dedicated area for another PET-CT or PET-MR machine for humans. While Bergen now has all the additional infrastructure and manpower that is necessary to do the research described above, the central piece of equipment is missing, the integrated MR-PET scanner.

PET Radiochemistry: A radiopharmaceutical labelled with a positron emitting radioisotope (PET-tracer), is a fundamental part of the PET-technology. The most successful radiotracer so far has been [^{18}F]FDG, and about 90% of the PET-CT examinations worldwide use this PET-tracer. However, most biochemical processes cannot be visualised through glucose metabolism. Therefore several other PET-tracers have been made to image receptors, cell proliferation, apoptosis and other molecular events. The PET Centre in Bergen has an up-to-date cyclotron with the possibility of producing the common positron emitters F, C, N and O, and has dimensioned the cyclotron bunker also for more unusual positron emitters as Cu, I, Zi. This will enable radiochemistry which very few PET centres worldwide can match. Neurology is a field that is most demanding in terms of imaging. Not only does it require compounds that can cross the blood-brain-barrier, but also be receptor specific and have favourable receptor binding characteristics. A key goal will thus be to develop novel receptor ligands. This will be an essential component in schizophrenia research, especially with a PET-MR imaging system. For implementation of novel radiotracers in fields of oncology and neurology, a small animal PET/CT and a human PET-MR is essential in translational research.

Supporting infrastructure

Laboratory for Advanced image analysis and visualization Imaging informatics in medicine and biology is a rapidly evolving branch of information technology acting in the fields of clinical medicine and radiology, cell/tissue/organ physiology and molecular cell biology, with strong links to applied mathematics, statistics and computer science. In this context, imaging informatics is a distinct scientific and technological discipline that aims at the quantification, modelling and visualization of structural information and biological processes from images that are recorded at a wide range of spatial and temporal scales, and where the relevant tissue or cellular information is distributed in both space and time. Imaging informatics is shown to be increasingly important for quantitative analysis and interpretation of image data from both clinical scanners such as MRI, PET, CT and US, and bio imaging devices such as SEM and TEM, confocal, spinning disk, and multiphoton fluorescence microscopy. Such imaging equipment produces large collections of data in both 2-D, 3-D, 3-D+time (dynamic imaging, time-lapse imaging), and even multispectral or hyper spectral 3-D data in time, i.e. 5-D. Moreover, the technologies of high-throughput and high-content screening are critically dependent of image analysis algorithms and computing power regarding automation, processing capacity, and quality and robustness of results. The proposed Laboratory for Advanced image analysis and visualization will be equipped with high performance computing facilities (workstations with multi core CPUs and GPUs) and state-of-the-art software tools (C++/Python, Matlab, VTK/ITK, Imaris) to deal with a wide range of biological and medical imaging problems and visualization challenges posed by the users. Moreover, research and development will be conducted by a team of researchers and students that can build on interdisciplinary collaborations between Departments of Biomedicine, Informatics, and Mathematics over the last decade (cf. the interdepartmental Bergen image processing group - www.mi.uib.no/BBG, MedViz, and CMR).

Flow cytometry Multi-wavelength systems with high sensitivity and high-throughput ability for screening of (probe)libraries of molecules are few if not absent in Norway. Flow cytometry is a basic technology in contrast development for optical imaging. Also in other modalities, like ultrasound and MRI, flow cytometry has likely a potential for target cell validation and in vitro functional validation. Through MIC we have started establishment of a flow cytometry core facility. The cell sorter is state-of-the-art, but

analysis instrument are not adequate for a stronger working line in molecular contrast development. New multiparameter systems based on mass spectrometry determination of probe is at prototype stage (CyTOF), and should be considered in 2010 and beyond for state-of-the-art multiparameter single cell analysis. This methodology will have considerable advantages in probe development in MRI and PET, since (stable and unstable) isotopes are determined on a single cell basis in a time-of-flight mass spectrometry instrument.

Relevance with respect to existing European, national and local strategies

The 7th Framework Programme as well as the ESF underlines the importance of Medical imaging and visualisation as a highly significant topic for future research to improve human health care[1]. The European Advanced Translation Reseach Infrastructure (EATRIS), a European effort with its main focus on Translational research, states that "*Imaging facilities will need to be designed both for animal studies as well as for studies with human patients".* This corresponds exactly with the outlook of our new combined pre-clinical and clinical imaging core facility. EATRIS also states that "*A close interaction with the medical technology industry will take place to define the interface between the development of new imaging technology"*. This is already the case for the Medviz cluster as well for MIC. The latter is and will remain a reference and test centre for several equipment producers.

On the national level the NRC emphasises that the quality of Norwegian research has to be improved in order to be able to compete with international research institutions[2]. The Norwegian research environments as well as international evaluation committees, points out that there is a lack of open access to research infrastructure within Norway and that open access to infrastructure is of importance for Norwegian researchers who want to compete on an international level. In the same document UiB listed MedViz as an area of priority from UiB, capable of having great national and international impact. The NRC also states that imaging technologies is one of the areas which the NRC particularly wants to stimulate and in which there is an ever increasing degree of specialization and that cross disciplinary cooperation is increasingly important to facilitate research of high quality[3]. We conclude that our effort is in line both with the EU and NRC strategy.

This concurrence is also reflected in MIC's positive external evaluation in 2006, which resulted in further funding from the NRCs FUGE effort. The evaluation also stated clearly the need to develop tools for imaging bioinformatics which this and eInfrastructure application ES443590 seeks to remedy. The UiBs interest in the maintenance of MIC is illustrated e.g. through earmarked positions and funding and through the priorities of the Faculty of Medicine and Dentistry (MOF) and Department of Biomedicine.

Further, the MOF faculty board 20th May 2009 (*sak 117/09*) decided to adopt the core facility concept with universal access for the national research community to all its major equipment. MOF thus demands that all existing and future equipment should be included in core facilities and several times mentions MIC's setup as a model for this.

The partners in this application feels secure that our effort, both in terms of science, equipment and our organisational setup is safely embedded in European, national and local strategies. We also see this application as a very good answer to the criteria for evaluation issued by the NRC in connection with the INFRASTRUCTURE call.

3. Description of the Research Infrastructure

This proposal suggests to strengthen current infrastructure by replacing or upgrading the most used equipment and acquiring new equipment from the point of view of research strategic necessity. The currently available human recourses in experimental and clinical imaging are adequate or scalable, and the formal organization of future extended imaging will be absorbed by existing and envisaged structures. Existing infrastructure at MIC and other imaging relevant infrastructure owned by the Faculty of Medicine

[1] European Science Foundation's Science Policy Briefing "*Medical imaging can now play a central role in the global healthcare system as it contributes to improved patient outcome and more cost-efficient healthcare in all major disease entities. More and better research in medical imaging is needed in Europe to increase our knowledge about disease processes and therapy management with the long-term goal of improving the health of European citizens."*

[2] *Verktøy for forskning-Nasjonal strategi for forskningsinfrastruktur (2008-2017)*

[3] "*Medisinsk og helsefaglig forskning. Forskningsrådets policy for 2007-2012*"

and Dentistry at UiB will in its entirety be incorporated into the new core facility, being complemented by the equipment listed below. This will in effect constitute a national facility with most of the presently available imaging modalities. A more extensive description of which issues the below instruments are to address, is described in part 2, 4 and 5 of this application.

MedViz infrastructure over 5 yrs	Cost/yr.	Tot. Cost	Own Cont.	NRC	Year
Ultrasound					
Ultrasound small animal scanner		3,8	0,8	3	2010
High-frequency US scanner for large animal drug delivery		1,6		1,6	2011
High-frequency US scanner for clinical drug delivery		1,6		1,6	2010
Ultrasound scanner for experimental and in vitro studies		1,6		1,6	2010
Duplex Scanner in transcranial stroke imaging		1,2		1,2	2012
Research scanner for cardiology		1,6		1,6	2010
Elastography Unit (US scanner and Fibro scan)		2		2	2010
Endosonography scanner		1,5		1,5	2011
SURF technology development package (UiB + NTNU)		5		5	2010-2012
Magnetic Resonance Imaging					
Upgrade of GE 3T HDx MR scanner to MR750 platform		2,5		2,5	1010
3-Tesla MR scanner for human experimental research		20	3	17	2012
New small animal MR scanner		20		20	2011
Live Cell Imaging					
Upgrading RS Spinning disk with FRAP		2,1		2,1	2010
Optical Imaging				0	
Small animal time-domain Optical Imaging replacement		2,4		2,4	2010
Small animal optical imaging (IVIS-like)		3		3	2011
PET					
PET-CT small animal scanner		20,2	6,2	14	2010
PET-MR scanner		30	5	25	2013
PET-radiochemistry		6		6	2010
Supporting infrastructure					
LAB for advanced imaging analysis and visualisation		2		2	2010
Flow cytometry-analyzer with robotization		5,5		5,5	2010
Running Costs					
General running costs for the MedViz /MIC platform	1,8	9		9	2010-2014
Infrastructure rental	0,5	2,5		2,5	2010-2014
Image analysis/applications to protein dynamics	0,5	2,5		2,5	2010-2014
Operational costs MRI, µPET/CT, US, OI	1	5		5	2010-2014
Service contracts for OI, MR, PET, US	2	10		10	2010-2014
Personnel					
5 technical positions (OI, MR, PET, US, FCM, Image analysis)	3,16	15,8	0	15,8	2010-2014
5 research positions (OI, MR, PET, US, FCM, Image analysis)	4,1	20,5	20,5	0	2010-2014
Total	**13,06**	**198,9**	**35,5**	**163,4**	**2010-2014**

Localization

The equipment will be localised in well-prepared facilities at UiB and HUS. A new clinical PET centre was operational at HUS/UiB from April 2009. The future PET-MR scanner and the animal PET-CT will be placed in these locations. The small and large animal ultrasound scanners will be integrated in modern UiB animal facilities and the clinical research scanners at National Centre for Ultrasound in Gastroenterology (NCUG), and Depts. of Cardiology and Neurology. Optical imaging equipment, flow cytometry-analyzer, and experimental US scanner will be placed in the new laboratory building. Image analysis and visualization lab will be integrated at Dept of Radiology or in the up-coming Interventional Centre at HUS. The upgraded Spinning Disc as well as a new high-field small animal MR scanner will be localised in areas belonging to MIC. The 3T MR scanner for research with fMRI and related methods is located at the Dept of Radiology.

E-Infrastructure

The current eInfrastructure at MIC and accessible throughout Medviz combined with the supporting infrastructure of “LAB for advanced imaging analysis and visualisation” in this application and

the eInfrastructure application “Bioimaging Informatics” (sketch nr 253, project number 195219) will cater for the needs with regards to storage, tools for data handling/analysis and electronic services. With the present and future image acquisition equipment such eInfrastructure is absolutely crucial to bridge the gap between efficient/automatized image acquisition on the one hand and manual analysis on the other.

The structuring effect

By creating a nationally unique cluster of imaging infrastructure under a common organizational umbrella, offering a very wide range of imaging modalities at a pay-per-service basis without the researchers having to employ technical staff, nor buying their own equipment, the suggested core facility will constitute a very efficient way of organizing research infrastructure.

4. Plan for access and use, data and knowledge management

Access and the national character

The suggested core facility will conduct both R&D and provide service at a pay-per-service basis on equal terms to the Norwegian research community and their international collaborators. One will not distinguish between internal and external users and industry partners will also be given access, albeit paying higher user fees. The success of MIC in attracting users from the whole UiB and institute sector as well as from the other universities in Norway proves the viability of the concept of pay-per-service core facilities. The services will be explicitly advertised and presented in all relevant scientific forums, included in MICs marketing effort and presented at all occasions where Medviz or MIC is represented in the university and hospital environments. These networks are natural first line arenas into which to disseminate our work and put our developments and service to good use towards potential users.

Data and knowledge management

Data generated through the use of our instrumentation will be the property of the respective researcher until an agreed upon date, thereafter the data will be made available to the benefit of the general research community. Generated data will be securely stored centrally, and simultaneously safeguarded. This also secures later release of the data to the benefit of the wider research community. Methods developed at the core facility will be offered as service.

5. Impact on research and innovation

A comprehensive and compact imaging core facility will be a strong resource for the whole Norwegian community with interest in biomedical and translational research since it represents a common technology base and discussion forum for and between available imaging and analysis methods. It will advance interdisciplinary work between Norwegian universities and hospitals, and also across educational borders since the facility will require the input from biology, medicine, mathematics, informatics, physics and technology.

The facility offers good opportunities to incorporate recruitment and education of students and younger scientists within medicine, biology, technology, mathematics, and computer science by assigning them well-defined and specific projects related to the services of the facilities. The leadership of the Imaging Infrastructure will in collaboration with the National Interdisciplinary PhD School in Medical Imaging in Norway ensure that innovative and cutting-edge projects related to imaging are defined and carried out.

We envisage that new technology together with our outstanding human resources will be used to improve diagnosis and treatment of patients towards:

- multilevel imaging in translational research integrating all the links from molecular to whole body imaging
- new acquisition technology will be explored clinically and pre-clinically.
- novel multimodal imaging methods that will be possible through novel techniques in co-registration.
- developing multi parametric imaging modalities, exemplified by ultrasound with determination of tissue elasticity that combine information about anatomy and (pato)physiology of organs.
- innovative new therapies that will be developed through target determination and smart delivery. Most imaging modalities give negligible energy exposure to the human body. Focused heat/infrared light has been used as therapeutic modality in clinical trials at Haukeland University Hospital. The therapeutic

potential of MRI and ultrasound is in its infancy, including the use of therapeutic contrasts that enhance the energy deposit.

- personalized medicine may demand a new set of imaging and contrast techniques for feasibility. Molecular imaging will determine early response monitoring of novel therapeutics, exemplified by the use of expensive enzyme inhibitors and therapeutic antibodies.

Ultrasound (US)

Worldwide, there is a growing understanding that US has a great advantage in that the distance from "bench to bedside" can be made very short. This is because the same type of scanners and transducers can be applied both on animals and in humans giving rapid transfer of basic research into clinical practice. We want to utilise this advantage by offering researchers access to a well-equipped animal facility (Vivarium, UiB) and clinical environments with parallel facilities for advanced US scanning. In addition, a specially designed US scanner (VisualSonics) for small-animal applications with very high frequencies and frame-rates will complete the translational chain from very detailed experimental imaging to patient management. We will build a national research network that will enable Norway to be competitive internationally and pave the way for cutting-edge research in US imaging. By means of new infrastructure, we are capable of offering state-of-the art facilities to attract researchers at the international arena.

Magnetic Resonance Imaging (MRI)

Animal MR imaging: By installing a new, high-field animal MR scanner, we will be able to perform preclinical imaging with a much higher sensitivity and specificity in assessing for instance drug response and treatment effects. The new coil technologies combined with a stronger magnet and better shimming will allow us to do MR techniques currently not available in Bergen, such as chemical shift imaging and phosphorus spectroscopy, ultrafine anatomical imaging and improved perfusion studies. We are currently collaborating with the MR Centre in Trondheim, Max Planck Institute in Cologne and Institute of Experimental Medicine in Prague. By installing a new animal MR scanner as described, we will likely receive several inquiries from Norwegian and foreign scientists.

Human MR imaging: The upgrading to the new hardware and software platform on the GE 3T MR scanner will allow functional imaging with a much broader scope and depth than can be done today. In particular, the upgrading is necessary to allow classical functional imaging techniques to be used outside the central nervous system, for example in the gastrointestinal tract. New techniques such as fibre tracking will be improved substantially. Hyperpolarized carbon 13 imaging is really functional imaging of biochemical pathways in health and disease, unmatched by any other imaging modality. New insight into diagnosis and treatment of ischemia and cancer is expected. This imaging technique is also central for development of MR compatible interventive tools. Upgrading of the 3T system will certainly be a major factor in attracting young scientists from Norway and abroad. Hyperpolarized carbon 13 imaging will be a major attractor for collaboration on a world basis.

Optical Imaging (OI):

OI has been used to recruit international and national students in therapy developmental projects. An interesting avenue is the recent build up of pharmacy in Bergen and Tromsø, where the Bergen milieu is outlining a strategy in pharmacy to prepare tomorrows pharmacists for molecular contrast agents and novel targeted therapeutics. OI will provide Norwegian scientists with a flexible tool, and we are established as interesting international collaborators (EU COST actions CANGENIN and EuGESMA) due to the current instrumentation and technological skills, indicating the positive effect of further development and investment.

Live Cell imaging:

The upgraded SDCM will constitute an important part of the combined imaging infrastructure offered by HUS/UiB. This cluster of broad imaging modalities would be defective in the absence of a modern real time imaging equipment. No other location in Norway can offer today the level of expertise, combined with the large variety of supporting and complementing imaging techniques, available at MIC, MedViz and HUS in Bergen. A state-of-the-art live cell imaging instrument is a key component of this technical repertoire, ensuring the national uniqueness of this imaging cluster. The upgraded instrument will

enable MIC to provide the latest technology in molecular imaging. Through MIC the SDCM will be included in the FUGE-funded Norwegian Molecular Imaging (NorMIC) Consortium, consisting of imaging nodes at the Universities in Bergen, Oslo, Trondheim, Stavanger and Tromsø, and headed by MIC (http://www.uib.no/med/nor-mic/).

Positron emission tomography (PET)

Animal PET imaging: A major challenge in preclinical imaging is a functional monitoring of treatment effects. By combining animal PET-CT with the current expertise in MRI and optical imaging in Bergen, we will establish a strong imaging facility, and thus a synergic effect in animal research is achieved by combining these modalities. It will bring Bergen in the forefront of translational research, and cause several new collaborations in Norway and abroad.

Clinical PET-MR Imaging: Norway has a very long and strong tradition in neuroscience. However, almost all biochemical and physiological neuroscience research has used animal models or cell cultures. The integrated MR-PET scanner will give possibilities to relate parts of this research directly to humans. The ongoing functional research on the human brain in Bergen will be supplied with a range of new possibilities. Undoubtedly, this will be a strong attractor for neuroscience research in Norway and Bergen in particular. The integrated MR-PET system will be unique in Scandinavia. Thus, it will be a strong attractor for basic and applied researchers wanting to investigate the human brain directly concerning biochemistry, drug response and physiology.

PET Radiochemistry: Norway has a short track record in PET-radiochemistry, and all current radio chemists working with PET in Norway have been trained abroad. This has however led to the establishment of international contacts and collaborations, which should be further strengthened by the development of a core radiochemistry facility. In order to attract student and researchers nationally and from abroad, it is of importance to have the best possible facilities, which offers access to exotic positron emitters usually not available in clinical PET centres. The proposed combination of modalities in this application would be unique in Scandinavia. It should thus be attractive institution to study radiochemistry in an international perspective. With an animal PET/CT and a PET-MR the attractiveness would be even greater by including the oncology and neuroscience imaging community as well.

Flow cytometry:

Currently we arrange 1-2 courses in basic and advanced flow cytometry per year with international participation. Through international speakers we are facilitating international collaboration with scientists all over Norway.

6. Partners and scientific institutions

MedViz is a cluster of research groups from many departments at UiB (Mathematics, Informatics, Physics and Technology, Biomedicine, Medicine, Surgery), Haukeland University Hospital (et al Dept, of Radiology, The PET/CT Centre, National Competence Centre for Functional MRI, National Centre for Ultrasound in Gastroenterology, and Dept of Oncology and Medical Physics). The MedViz network also includes MIC. Further, CMR Computing is well known for its state-of-the art solutions in advanced data visualisation. The MedViz cluster is an ideal mix of younger and senior scientists that have outstanding publication record on functional MRI and ultrasound. Optical imaging and multimodality acquisition is backed by strong PI in model development and biology, indicating high probability for success.

The Molecular Imaging Centre in Bergen (MIC) is a FUGE funded core facility which maintain and develop modern imaging modalities, and make them available to scientists to be applied in specific projects carried out in different research fields (http://www.uib.no/med/mic/). As a core facility MIC is open and provides equipment and expertise in molecular and preclinical imaging to the whole Norwegian research environment. MIC is the leading node in the FUGE-funded NorMIC consortium. MIC has proved its success through an excellent rating in the external evaluation report of 2006, and the resulting renewed financial support for operational cost for 2007-2012. MIC is an active partner in the Nordic Network on Imaging in Medicine and Biology funded by NordForsk (http://www.nordic-imaging.net).

7. User groups and international cooperation

MIC at present has users from all Norwegian universities and other major research institutions and is massively used by users from the Bergen area from all relevant disciplines in medicine and natural sciences. Its paid services are often preferred before free services at other institutions/departments due to its excellent quality and level of service.

The optical imaging group has signed a collaboration contract with ART Inc (manufacturer of eXplore Optics small animal imager) and have collaborated over several years with scientists from ART to optimize software and acquisition. A strategic collaboration has been made with GE Healthcare in development of new preclinical contrast agents. We also se it relevant to mention that various modalities have potential in earth science, and facilities at the hospital have been used for analysis of geological samples. Similarly, ultrasound has an important application in industry quality control and material science in addition to applications in earth science. We will emphasize this ability for additional use through our partnership with CMR and in cooperation with earth science research programmes.

The participating groups in this project proposal have currently several ongoing collaborations. MedViz is collaborating with Dundee University, Technische Universität München, Turku PET Centre, University of Brno, University of Aalborg, UCLA School of Medicine, Weill Cornell Medical College NY, and University of Adelaide. MIC has ongoing international collaboration with scientists in the Scandinavian countries through the Nordic Imaging Network in Medicine and Biology, as well as with Institute of Experimental Medicine, Prague, Radboud University in Nijmegen, and Max Planck Institute in Cologne. MedViz also has collaborators from industrial companies like Nordic Neuro Lab, GE Vingmed AS and Statoil-Hydro. Through collaboration with Angelsen's group we also have interface to University of Toronto. The new Imaging Infrastructure will be of great interest to and available for all ongoing collaborations established by the partners and other imaging groups in Norway. This investment will enhance the activity and quality of running and approved international projects, including EU projects, COST initiative, and several NordForsk activities. Where no collaboration exists today the investment will greatly improve the basis from which one can engage upon collaboration. Dissemination of project results in highly ranked, peer-review international journals, participation in scientific meetings, arrangement of international courses and workshops and presentation of the Infrastructure through the project web site will likely also attract attention from other research institutions abroad.

8. Time-schedule and deliverables

The above table under part 3 illustrates also the main deliverables. The acquisition of an instrument here implies setting this instrument up with technical staff, informing the research community of the possibility of using the instrument in question, either on its own or in combination with its staff and setting up booking etc for the instrument. We aim to have the core facility's organizational structure set up by the beginning of 2010. For further and more detailed milestones, please consult the e-applications project time table.

9. Budget and funding plan

The above table under part 3 illustrates that of the total of 198,9 mill NOK over five years, we apply for 164,4 mill NOK with the NRC. Over the course of the project period this includes 118,6 mill NOK for equipment and equipment upgrades, 29 mill NOK in running costs and 15,8 mill financing five technical positions on the senior engineer level. Own contributions totals 35,5 million divided on 15 mill NOK for equipment and 20,1 mill NOK in personnel costs, the latter being five scientific positions on the associate professor level. We wish to emphasize that the running costs applied for only will cover parts of the total running and maintenance costs. The remainder we aim to cover by the means of user fees which are not included in this budget. If user fees are generated in excess of running costs, these will be directed towards upgrades and new equipment within the fields in question.