Biomedical Imaging

November 9 – 11, 2016

Technical University of Munich, Institute for Advanced Study
Lichtenbergstrasse 2 a, 85748 Garching, Germany

Collaborative Workshop Series on Biomedical Imaging of the Institute for Advanced Study of the Technical University of Munich and the Institute of Advanced Studies of the Nanyang Technological University, Singapore.
Program

WEDNESDAY, NOVEMBER 9, 2016
Faculty Club (4th floor)

8:45 – 9:15 a.m.   Welcome Address: Ernst Rank (Director TUM-IAS)
                   Introduction to the workshop: Franz Pfeiffer (Scientific Chair TUM),
                   Russell Gruen (Scientific Chair NTU)

9:15 – 10:00 a.m. Multimodal Molecular Imaging for Translational Research
                   Markus Schwaiger (Nuclear Medical Clinic and Policlinic, TUM)

10:00 – 11:00 a.m. Neuroimaging and multimodal molecular probe development at NTU
                    Balázs Gulyás (Translational Neuroscience, NTU)

11:00 – 11:30 a.m. Coffee Break
                    Faculty Club (4th floor)

11:30 – 12:30 p.m. In vivo imaging of neuronal cell biology in development and disease
                    Thomas Misgeld (Biomolecular Sensors, TUM)

12:30 – 1:30 p.m.  Lunch Break
                    Faculty Club (4th floor)

1:30 – 2:30 p.m.   Biological applications of organic semiconducting nanoparticles
                    in imaging, therapy and optogenetics
                    Swee Hin Teoh (School of Chemical and Biomedical Engineering, NTU)
                    Kanyi Pu (School of Chemical and Biomedical Engineering, NTU)

2:30 – 3:30 p.m.   From Medical Engineering (Medizintechnik) to Bioengineering at TUM
                    Axel Haase (Munich School of Bioengineering, TUM)

3:30 – 4:00 p.m.   Coffee Break
                    Faculty Club (4th floor)

4:00 – 5:00 p.m.   NTU’s approach to medical technologies
                    Russell Gruen, (Technology in Health and Medicine, NTU)
THURSDAY, NOVEMBER 10, 2016
Faculty Club (4th floor)

9:00 – 10:00 a.m.  X-ray Phase-Contrast and Dark-Field Imaging for Pre-Clinical and Clinical Applications
Franz Pfeiffer (Biomedical Physics, TUM)

10:00 – 11:00 a.m. Real-time high resolution imaging and experimental behavioural studies of the human microbiomes
Yehuda Cohen (Singapore Centre for Life Sciences Engineering, NTU)

11:00 – 11:30 a.m. Coffee Break
Faculty Club (4th floor)

11:30 – 12:30 p.m. Towards nanoscale DNA machines and robots - guided by EM imaging
Hendrik Dietz (Experimental Biophysics, TUM)

12:30 – 1:30 p.m. Lunch Break
Faculty Club (4th floor)

1:30 – 2:30 p.m. Single particle cryo-EM and correlative microscopy
Daniela Rhodes (School of Biological Sciences, NTU)
Sara Sandin (School of Biological Sciences, NTU)

2:30 – 3:30 p.m. Antiviral immunity in the liver visualized by dynamic imaging
Dirk Wohlleber (Molecular Medicine, TUM)
Percy Knolle (Molecular Medicine, TUM)

3:30 – 4:00 p.m. Coffee Break
Faculty Club (4th floor)

4:00 – 5:00 p.m. Multi and Hybrid Optical Imaging for Medical Diagnostics and Effects of Nano Revolution
Murukeshan Vadakke Matham (Center for Optical and Laser Engineering, NTU)
Friday, November 11, 2016
Laboratory Tours (several venues)

9:30 – 11:30 a.m. Guided tour of the TUM Institute for Medical Engineering (IMETUM)
Boltzmannstr. 11, Garching Campus

11:30 – 1:00 p.m. Lunch break
TUM-IAS, Faculty Club (4th floor)

1:00 p.m. Departure to Munich
Bus transfer

1:30 – 2:30 p.m. Guided tour of the TUM Institute for Translational Cancer Research (TranslaTUM)
Ismaninger Strasse 22, University Hospital Klinikum rechts der Isar, Munich

2:30 – 3:30 p.m. Guided tour of the TUM Institute of Molecular Immunology & Experimental Oncology
Ismaninger Strasse 22, University Hospital Klinikum rechts der Isar, Munich

*Visits are confirmed, there might be still adjustments in the schedule.
ABSTRACTS
Abstracts are arranged in the order of the talks. To find the speakers according to their names, please consult

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Markus Schwaiger
Nuclear Medical Clinic and Policlinic, TUM

Multimodal Molecular Imaging for Translational Research

After the clinical success of PET/CT as multimodal imaging instrumentation in the area of cancer, PET/MR emerged as an attractive research tool especially for neurological applications. Simultaneous imaging of regional brain function and metabolic activity allows unique exploration of neuronal processes during various cognitive tasks. In addition, PET/MR offers very attractive biomarkers for the non-invasive characterization of neurodegeneration. The combination of amyloid imaging and cerebral perfusion with MR provides new insights into the early changes occurring in patients with Alzheimer disease. Most current research focuses on the development and validation of new radiopharmaceuticals, addressing specific protein deposition in the brain of patients with neurodegeneration. In oncology, PET/MR has proven useful in the characterization of prostate cancer. Multiparametric MR images can be supplemented by specific molecular probes, using novel radiopharmaceuticals. Especially, the application of $^{68}$Ga-PSMA has gained rapid clinical acceptance as a specific marker for prostate cancer. Finally, PET/MR is used for cardiovascular research at our institution. MR characterization of acute ischemic injury in patients with acute myocardial infarction, supplemented by PET signals delineating cardiac metabolism or innervation, is attractive for research studies. Especially, the role of FDG imaging in characterizing acute inflammation has been a topic of intense research at our institution.

In conclusion, PET/MR is considered a superb research tool with emerging clinical application in neurology and oncology.

Balázs Gulyás
Translational Neuroscience, NTU

Neuroimaging and multimodal molecular probe development at NTU

Nanyang Technological University has set out to build up an advanced neuroimaging platform, comprising state-of-the-art pre-clinical and clinical neuroimaging capacity, the latter one including both and clinical neuroimaging (Centre for Neuroimaging Research at NTU or CeNReN). The first phase of the programme, focusing on cognitive neuroimaging, has started with the establishment of NTU’s Cognitive Neuroimaging Centre, housed in the Experimental Medicine Building on the NTU main campus and managed by NTU’s Lee Kong Chian School of Medicine. The instrumentation of the Centre includes a 3T Siemens Prisma MRI scanner with 128 receive channels, a 0T Siemens MRI scanner (i.e. a mock scanner), an Elekta Neuromag Triux system, as well as EEG (stand alone and MRI/MEG compatible), TMS, NIRS, OCT and portable head-mounted hyperimaging devices. The Centre will be operational from early next year. The following developmental phases of CeNReN will include the establishment of a pre-clinical and a clinical imaging facility.

At present, all pre-clinical imaging activities at NTU are performed in collaboration with other institutions in Singapore, including Singapore’s Defence Science Organisation (DSO), the National Neuroscience Institute (NNI0, the SingHealth Experimental Medical Centre (SEMC) and Singapore Radiopharmaceuticals (SRP). In collaboration with these institutions, our group has performed numerous experimental studies, focusing on small animal disease
models as well as traumatic brain injury (TBI) models in rodents and non-human primates. The lecture will give a short survey of some of these studies.

**Thomas Misgeld**

Biomolecular Sensors, TUM

**In vivo imaging of neuronal cell biology in development and disease**

The Misgeld lab at TUM uses structural and functional *in vivo* imaging in transgenic mice to analyze the cell biological mechanisms underlying axon development and degeneration. Currently the group has a major focus on devising assays of organelle dynamics and function and applying these assays to settings of axon dismantling in neuromuscular synapse elimination, spinal cord injury and neuroinflammation.

**Swee Hin Teoh & Kanyi Pu**

School of Chemical and Biomedical Engineering, NTU

**Biological Applications of Organic Semiconducting Nanoparticles in Imaging, Therapy and Optogenetics**

The convergence of medicine and nanotechnology is providing new opportunities to better understand fundamental biology, monitor health, perform diagnosis and treat diseases. Semiconducting polymer nanoparticles transformed from optically and electrically active polymers have emerged as a new class of optical nanomaterials. As those polymers are completely organic and biologically inert, SPNs essentially circumvent the issue of heavy metal ion-induced toxicity to living organisms, possessing good biocompatibility. In this talk, I will first present the recent advance of SPNs in imaging and therapy. Then, I will focus on discussing how to engineer the intraparticle nanostructure of SPNs to develop theranostics for amplified photoacoustic imaging and enhanced photothermal therapy of tumors in living mice. At last, I will demonstrate the utilization of SPNs as the photothermal nanomodulators to precisely control the thermosensitive ion channels in neurons, which forms a transgenesis-free approach to optogenetics.

**Axel Haase**

Munich School of Bioengineering, TUM

**From Medical Engineering (Medizintechnik) to Bioengineering at TUM**

The Technical University of Munich (TUM) covers fields of life sciences, medicine, engineering and natural sciences (chemistry, physics). TUM is therefore the best place to link these scientific disciplines together. Already in the year 2001, an Institute of Medical Engineering (IMETUM) was established at the TUM campus Garching which was traditionally focused on “Medizintechnik”, a highly innovative area related to the development of new devices and methods for medicine. “Medizintechnik” is one of the largest and fastest growing
industrial sector in Germany with many and still increasing jobs and a high export rate of 68% (world’s third largest). Many research groups at TUM are working in this field. In recent years it could be seen that modern Bioengineering evolves which is concentrated to quantitative measure and solve complex problems in biology and medicine. Bioengineering is a discipline that lives and operates within Life Sciences and Medicine but uses the problem-solving culture from engineering sciences. Many top ranking universities in the USA have established Bioengineering Departments. TUM has decided to develop the traditional “Medizintechnik” further and establish a new Munich School of Bioengineering (MSB) as the first University in Germany. Bioengineering is already very strong at TUM with many research groups having attracted top ranking awards and projects, like ERC grants from the EU.

In the area of research, MSB concentrates at the moment on the topics of:
- Sensing and Imaging
- Biological Information and Systems
- Cell Engineering

In this presentation, the new set-up of the Munich School of Bioengineering will be described both in terms of research activities and development of Postgraduate (Graduate School of Bioengineering) and new Master Programs.

Russell Gruen

Technology in Health and Medicine, NTU

NTU’s approach to medical technologies

NTU has one of the world’s largest engineering colleges, in which health-related technological innovation has been commonplace. In the past decade NTU has strengthened life sciences and medicine, through several entities such as the Singapore Centre for Environmental Life Sciences Engineering, the Institute of Structural Biology and, most recently, the Lee Kong Chian School of Medicine. Along with stronger linkages with Singapore’s health services, these have created new opportunities for health and medical research, innovation, and education. Key to harnessing these opportunities have been interdisciplinary ‘supercentres’: the Nanyang Institute of Technology in Health and Medicine and the Nanyang Integrated Medical Biology and Environmental Life Sciences Cluster. Challenging the conventional norms of university structure and hierarchy, NITHM and NIMBELS are providing the technology platforms, interdisciplinary teams and complex project management capabilities needed for the future.

Franz Pfeiffer

Biomedical Physics, TUM

X-ray Phase-Contrast and Dark-Field Imaging for Pre-Clinical and Clinical Applications

The basic principles of x-ray image formation in radiography have remained essentially unchanged since Röntgen first discovered x-rays over a hundred years ago. The conventional approach relies on x-ray attenuation as the sole source of contrast and draws
exclusively on ray or geometrical optics to describe and interpret image formation. This approach ignores another, potentially more useful source of contrast, namely the phase information. Phase-contrast imaging techniques, which can be understood using wave optics rather than ray optics, offer ways to augment or complement standard attenuation contrast by incorporating phase information.

This presentation will review the recent development and status of x-ray phase-contrast and dark-field imaging in general, and focus particularly on our recent efforts to evaluate x-ray phase-contrast for future clinical applications in radiography and computed tomography. A variety of experimental results will be shown that highlight the potential of this novel method for biomedical, clinical, and industrial applications. The presentation concludes with a presentation of first in-vivo results obtained with a small-animal phase-contrast CT scanner, recently developed in our lab.

Yehuda Cohen

Singapore Centre for Life Sciences Engineering (SCELSE), NTU

Real-time High Resolution Imaging and Experimental Behavioural Studies of the Human Microbiomes

Human microbiomes are central to all infectious diseases and contributing significantly to human wellbeing in heath and disease. Yet, our ability to control their communal function is limited because of lack to tools to investigate the evolution of microbiomes from a single attached bacterium to complex microbial communities. Microbiomes are structurally and functionally heterogeneous and their development is apparently interactively interrelated with their microenvironments. The dynamics of biofilm behaviour is governed by the physical dimensions of life in microscales dominated by fast diffusion and flow at low Reynolds number.

The study of the fundamentals of microbiome behavior requires precise tools and procedures for accurate and reproducible experiments. Such robust precise engineering approach allowing for the quantification of real-time, high-content imaging of biofilm behaviour under well-controlled flow conditions were developed and tested by using model opportunistic bacteria.

We observed, for the first time, unpredicted complex pattern biofilm formations followed by total dispersal events that are closely related to the flow conditions. High spatiotemporal resolutions of single micrometers and minutes are crucial framework for the investigation into the mechanisms underpinning the environment-structure-function interactions of human microbiome.

Hendrik Dietz

Experimental Biophysics, TUM

Toward nanoscale DNA machines and robots

It is notoriously difficult to observe, let alone control, the position and orientation of molecules because of their small size and the constant thermal fluctuations that they experience in solution. Programmable self-assembly of DNA molecules provides a route for placing molecules and constraining their fluctuations in user-defined ways and with up to Angstroem-
scale precision. These positioning options open attractive and unprecedented avenues for scientific and technological exploration, in particular with respect to the creation of artificial molecular machines. High-resolution imaging with transmission electron microscopy plays an important role in these efforts. In my talk I will introduce some of the key concepts and methods, and highlight a number of recent developments.

Daniela Rhodes & Sara Sandin,
School of Biological Sciences, NTU

Single Particle Cryo-EM and Correlative Microscopy

We work on chromatin structure and nuclear architecture, applying high-resolution Electron Microscopy (EM) methods to obtain mechanistic insight into how proteins regulate DNA folding. Cryo-EM is a powerful technique for structure determination of isolated macromolecular complexes at near-atomic resolution. Several important developments have contributed to the recent ‘resolution revolution’ in cryo-EM, including direct electron detection, correction of beam-induced motion, as well as improved classification and 3D reconstruction procedures. I will discuss new applications and recently developed cryo methods, such as phase plate cryo-EM and cryo confocal imaging. Furthermore, I will present different labeling approaches to selectively stain DNA and DNA-binding proteins for correlative microscopy analysis. Together, these complementary techniques can provide important insight into the structure of protein-DNA complexes and higher-order levels of DNA folding.

Percy Knolle & Dirk Wohlleber

Molecular Medicine, TUM

Antiviral immunity in the liver visualized by dynamic imaging

The liver is an organ with unique immunological functions that is often target of chronic infections such as chronic hepatitis B or chronic hepatitis C. We have studied over the last years the cellular and molecular mechanisms that determine the immune response against hepatotropic viruses that target hepatocytes. Regulation of CD8 T cell activation and effector function by local antigen presenting cell populations are key to understand the principles of local immune control of infection in the liver. We have developed proprietary tools such as recombinant adenoviruses that target hepatocytes and express reporter genes that can be visualized and therefore allow to follow anti-viral immunity in real time. To this end, we employ in vivo bioluminescence imaging as well as optoacoustic imaging in close collaboration with the lab of Prof. Ntziachristos. The visualization of the dynamics of the immune response against infection with hepatotropic viruses will be instrumental in understanding the pathophysiology of chronic hepatitis virus infection and will help us to develop novel immune therapies that overcome the immune regulatory hurdles imposed by chronic viral infection of the liver.
Murukeshan Vadakke Matham

Center for Optical and Laser Engineering, School of Mechanical and Aerospace Engineering, NTU

Multi and Hybrid Optical Imaging for Medical Diagnostics and Effects of Nano Revolution

Biomedical optics which is an interdisciplinary branch of science and technology uses optics for improving the basic understanding of biological processes, enhancing the diagnostic efficiency and treatment of human diseases. The changes in tissues in the early disease stages are often subtle and can occur beneath the tissue surface. In most of the cases, conventional types of medical imaging may not be able to detect these changes easily. Each imaging modality has its own advantages and limitations and one cannot fit one single modality for all diagnostic applications. Therefore the need for a multi or hybrid modality imaging arises. Combining more than one imaging modality overcomes the limitation of individual imaging method and integrates the respective advantages into a single setting.

From this perspective, medical diagnostics in the recent past has seen the challenging trend to come up with dual and multi-modality imaging for implementing better diagnostic procedures. The advent of new generation broadband and coherent light sources, specialty optical fibers and the advancement in the imaging hardware and software became excellent enablers for this research trend. Also, the impact of nanotechnology has further induced a paradigm shift in medical diagnostics by way of enhancing different parameters of interest.

This talk in this context will be dedicated to these aspects from a fundamental and application point of view. The optical engineering and research challenges in developing the multi-modality platform will be discussed. A detailed analysis on the proposed schemes that can be explored based on the recent works carried out by the author’s group for early diagnosis of cancerous growth in colon, and ocular imaging targeting iridocorneal angle will also be reviewed. This will be followed by latest trends in multi and hyperspectral methodologies and their advantages in the proposed application. The talk will also briefly touch upon the evolution of nanoparticles and associated layered structures for improved light absorption and how it benefits energy harvesting applications.