Programme

Main Event: "First Mediterranean Thematic Workshop: Advanced Molecular Brain Imaging with Compact High Performance MRI-Compatible PET and SPECT Imagers - Potential for a Paradigm Shift"

Giardini di Naxos (Taormina, Sicily) - September 1-2, 2012

Saturday September 1

Registration is open on Friday (6 p.m. – 8 p.m.) and continues starting at 8. a.m. on Saturday.

8.45 am Welcome address (*F. Garibaldi* (15'))

9.00-10.10 a.m Introductory session (Chairpersons F. Garibaldi, Vesna Sossi)

1. **Molecular brain imaging: history and state of the art (V. Sossi, Vancouver) (*30')***

Abstract. *First FGD PET images date to the mid '70. While revolutionary, as their allowed for the very first time a glimpse into body and brain function in a living subject in a non invasive fashion, they offered very limited resolution. This talk will describe the major milestones in PET imaging that led from those very first, fuzzy, ^{18}F-fluorodeoxyglucose brain images to images obtained with a resolution better than (2 mm)^3 where exquisite detail of brain sub-regions can be observed. Hardware and software development, such as rapidly increasing computing power, development of 3D reconstruction algorithms, detector block design, use of LSO and finally time of flight PET, all contributed to an increase is resolution and sensitivity and a decrease in noise. The most recent milestone is the development of hybrid imaging scanners, that are able to take advantage of complementary strengths of different modalities; in this area the latest development is hybrid PET/MRI enabled by the rapid development of SiPM technology. There is an enormous growth of research in this area and some examples will be presented*

2. **Neuroimaging: what can we learn from qualitative and quantitative functional brain imaging (V. Sossi, Vancouver) *(30')***

Abstract. *There are two important steps that transform imaging of PET tracers into biologically relevant information: data quantification and kinetic modeling of the tracer time course. Data quantification requires accurate corrections for physical and instrumentation performance aspects, while kinetic modeling requires good understanding of tracer binding properties and their characteristics over time. Given the naturally coarse nature of the PET data (i.e. limited time and spatial resolution), the biologically relevant outcomes (such as binding potentials and uptake rate constants) are often only proportional to the processes under observation and their validity must be confirmed for each tracer. In spite of these intrinsic limitations PET data have provided invaluable insights into brain behavior in health and disease. Of*

particular relevance are instances where brain disease can be studied before the manifestation of clinical symptoms, thus providing a unique window on early changes, where disease origin might be discover or treatment might be most effective. Disease progression can be determined with quantitative brain images as is the interplay between different brain systems affected by disease. Likewise the effect of treatments can be measured in an objective fashion and correlated between brain function and personality traits can be teased out. Finally, pre-clinical brain imaging can also serve as a translational tool bridging invasive post-mortem observations done in rodent models of disease with imaging data obtained in humans.

Coffee break (10.10 – 10.40)

3. PET in Neuroscience and Drug Development (Christer Halldin, Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden) ***(30')***

Abstract. *PET provides a new way to image the function of a target and by elevating the mass, to pharmacologically modify the function of the target. The main applications of radioligands in brain research concern human neuropsychopharmacology and the discovery and development of novel drugs to be used in the therapy of psychiatric and neurological disorders. A basic problem in PET brain receptor studies is the lack of useful radioligands with ideal binding characteristics. Prerequisite criteria, such as high affinity and selectivity, need to be satisfied for a radioligand to reveal target binding sites in vivo. During the past decade over a hundred neurotransmitters have been identified in the human brain. Most of the currently used drugs for the treatment of psychiatric and neurological disorders interact with central neurotransmission. Several receptor subtypes, transmitter carriers, and enzymes have proven to be useful targets for drug treatment. Molecular biological techniques have now revealed the existence of hundreds of novel targets for which little or no prior pharmacological or functional data existed. Due to the lack of data on the functional significance of these sites, pharmacologists are now challenged to find the physiological roles of these receptors and identify selective agents and possible therapeutic indications. During the past decade various ^{11}C- and ^{18}F-labeled radioligands have been developed for labeling some of the major central neuroreceptor systems. There is still a need to develop pure selective PET tracers for all the targets of the human brain. This presentation will review recent examples in neuroreceptor radioligand development and the clinical potential of in vivo imaging of neurotransmitter systems. The review will focus on studies with PET radiotracers in neuropsychopharmacological drug development. A basic problem in the discovery and development of novel drugs to be used in for example the therapy of neurological and psychiatric disorders is the absence of relevant in vitro or in vivo animal models that can yield results to be extrapolated to man. Drug research now benefits from the fast development of functional imaging techniques such as PET.*

4. **Multimodality operation of PET detectors with MRI/fMRI (B. Pichler, Tubingen*) (30')*)**

Cerebrovascular diseases (Chairpersons F. Orzi, A. Varrone)

5. **Physiopathology of cerebral ischemia and clinical need for Imaging (F. Orzi, Department of Neurosciences, Mental Health and Sensory Organs, University of Rome "La Sapienza", Rome) (*25'*)**

Abstract. *Following an ischemic insult, brain tissue looses functional activity in a few seconds and undergoes irreversible damage and eventually cell death in a few minutes. In case of incomplete ischemia, associated with critical reduction of the cerebral blood flow, the brain damage consists of a process rather than a sudden event, and cellular recovery or death is attained after an intricate cascade of results. Quite consistently, in stroke patients, dishomogeneous areas of damaged, potentially viable, tissue surround an immediately necrotic area. Identifying the viable tissue in the hours following the ischemic onset is a major challenge in the stroke field. The increasing knowledge into the relevance of the neurovascular unit as a whole functional system, and into the mechanisms of the different kinds of programmed cell deaths, which are thought to mediate the ischemia-induced tissue damage, has produced a new conceptual framework, which includes several systemic or local variables relevant to the fate of the damaged tissue. Residual perfusing blood flow, however, remains the most relevant predicting factor of functional recovery. A number of methods have been devised to attain cerebral blood flow-related neuroimages. Very few approaches allow measurements of cerebral blood flow in terms of volume of blood which perfuses the brain per unit of time, per unit of mass.*

Lunch break (12.05 – 13.30)

13.30–15.55 Neurodegenerative diseases and clinical need for Imaging (Chairpersons F. Orzi, A. Varrone)

6. FDG and Amyloid imaging in Alzheimer's disease (A. Chiaravalloti, University of Tor Vergata-Rome) *(35')*

Abstract.

The pathophysiological hallmark of Alzheimer's disease (AD) is the accumulation of amyloid plaques in the brain with a fairly constant distribution pattern involving the basal portions of the frontal, temporal and occipital lobe with a partial saving of the hippocampal formation and primary sensory areas[1]. In vivo 2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG) PET is a minimally invasive diagnostic imaging procedure used that evaluate cerebral glucose metabolism[2] while SPECT with 99mTc-exametazime (HMPAO) and 99mTc-bicisate (ethyl cystine dimer [ECD]) reflects regional cerebral perfusion[3]. 18F-FDG PET is superior to perfusional SPECT in its ability to separate healthy controls from patients with true dementing illnesses[2] detecting functional changes that results in a reduced brain glucose metabolism due to amyloid deposition as neuronal injury and disfunction and cell death[4] .

In Mild Cognitive Impairment (MCI), different brain glucose metabolism patterns have been found between converters and non converters patients[5]. MCI converters usually show a greater brain glucose metabolism involvement in parietal, cingulated hippocampus and parahippocampus cortex as compared to MCI non converters which brain metabolic pattern is characterized by a selected involvement of dorsolateral frontal cortex[5]. It has been suggested that ^{18}F-FDG PET findings may be useful in predicting short term conversion to AD[5, 6]. Part of the previously mentioned results are obtained by means of computer-assisted quantitative

interpretation of images[7], being the visual rating of functional brain ^{18}F-FDG PET images heavily dependent to the lack of clearly defined cutoffs to distinguish between normal and pathologic findings especially at the early stage of the disease [2]. Several semi-automated tools initially developed for research applications[7] have been developed (i.e. statistical parametric mapping, SPM, Wellcome Department of Cognitive Neurology, London, UK) for clinical interpretations of a large number of neurologic disorders[8]. In our experience, the application of these tools leads to a greater diagnostic accuracy, but the process is a little time consuming and images derived from different scanners and with different acquisition parameters cannot always be compared. ^{11}C labelled PET tracer (Pittsburg Compound B) PiB is the most widely used radiotracer for amyloid imaging in human beings[9]. Due to short ^{11}C half-life, three ^{18}F labelled tracers are being investigated in clinical trials for amyloid imaging. Flutemetamol (GE-067) is the 3´-fluoro-derivative of PiB , whereas florbetaben (BAY-94-9172, AV-1) and florbetapir (AV-45) are stilbene and styrylpyridine derivatives, which exhibit high affinity binding for fibrillary amyloid similar to PiB[9]. The regional retention of ^{11}C-PiB appears to be reliable to the regional density of Amiloid plaques in AD[10]. In MCI patients, follow-up studies have shown that 70% of ^{11}C-PiB positive MCI subjects will progress to dementia due to AD over 3 years[11]. Less than 10% of ^{11}C-PiB negative MCI patients progress to a clinical diagnosis of AD, whereas about 20% of ^{11}C-PiB negative MCI subjects progress to another type of dementia such as dementia with Lewy bodies or frontotemporal dementia[11]. As a result, tracers for amyloid imaging could be helpful in early identification of MCI patients that will convert in AD[11].

In conclusion the high sensitivity and specificity of ^{18}F-FDG PET in the diagnosis of AD is implemented by software programs for the quantitative interpretation of scans especially in the early stage of the disease and when considering MCI patients. Several early reports suggest a strong predictive value of amyloid tracers for progression from MCI to AD, and this tracer could represent a useful tool in the diagnosis of AD and its differential diagnosis from FTD[2].

It is our opinion that current advances in functional imaging awaits the development of an effective therapy to slow, halt or possibly reverse the amyloid-based disease process.

[1] *Braak H BE (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica **82**, 239-259.*

[2] *Bohnen NI DD, Herholz K, Anzai Y, Minoshima S (2012) in J Nuc Med, pp. 59-71.*

[3] *Juni JE WA, Devous MD Sr, Tikofsky RS, Ichise M, Van Heertum RL, Carretta RF, Chen CC; Society for Nuclear Medicine (2009) Procedure guideline for brain perfusion SPECT using (99m)Tc radiopharmaceuticals 3.0. J Nucl Med Tachnol **37**, 191-195.*

[4] *Haass C SD (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol **8**, 101-112.*

[5] *Anchisi D BB, Franceschi M, Kerrouche N, Kalbe E, Beuthien-Beumann B, Cappa S, Lenz O, Ludecke S, Marcone A, Mielke R, Ortelli P, Padovani A, Pelati O, Pupi A, Scarpini E, Weisenbach S, Herholz K, Salmon E, Holthoff V, Sorbi S, Fazio F, Perani D (2005) Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. Arch Neurol **62**, 1728-1733.*

[6] *Jagust W RB, Mungas D, Ellis W, Decarli C (2007) What does fluorodeoxyglucose PET imaging add to a clinicl diagnosis of dementia? Neurology **69**, 871-877.*
[7] *Friston K HA, Worsley K, Poline J-B, Frith C, Frackowiak R (1995) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp **2**, 189-210.*
[8] *Herholz K SE, Perani D, Baron JC, Holthoff V, Frölich L, Schönknecht P, Ito K, Mielke R, Kalbe E, Zündorf G, Delbeuck X, Pelati O, Anchisi D, Fazio F, Kerrouche N, Desgranges B, Eustache F, Beuthien-Baumann B, Menzel C, Schröder J, Kato T, Arahata Y, Henze M, Heiss WD. (2002) Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage **17**, 302-316.*
[9] *Herholz K EK (2011) Clinical amyloid imaging in Alzheimer's disease. Lancet Neurol **10**, 667-670.*
[10] *Ikonomovic MD KW, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolko S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, DeKosky ST (2008) Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain **131**, 1630-1645.*
[11] *Villemagne VL PK, Chételat G, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szoeke C, Salvado O, Martins R, O'Keefe G, Mathis CA, Klunk WE, Ames D, Masters CL, Rowe CC (2011) Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann Neurol **69**, 181-192.*

7. Molecular Imaging of Parkinson´s disease (Andrea Varrone, Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden) *(35')*

Abstract. *The development of radioligands for the dopaminergic system has provided suitable imaging biomarkers for clinical research in Parkinson´s disease and related movement disorders. Single photon emission tomography (SPECT) has played an important role as main molecular imaging modality because of the availability of imaging tools such as dopamine transporter (DAT) radioligands for wide clinical use. At present, SPECT imaging of the DAT is the main diagnostic imaging procedure for the assessment of patients with suspected degenerative parkinsonism, providing also reliable quantitative outcome measures that correlate with the severity of the disease. Therefore, DAT SPECT has been also used as an imaging biomarker in clinical trials aimed at evaluating putative disease-modifying effects of different drugs for the treatment of Parkinson´s disease.*

Although imaging of the DAT in the striatum is possible with SPECT, visualization and quantification of the DAT in the substantia nigra, the primary site of Parkinson´s disease pathology, is hampered by its limited resolution. Recently, positron emission tomography (PET) has become a more widely available Nuclear Medicine technique. Because of the improved resolution and sensitivity of the most recent PET/CT systems, more widespread application of brain PET as a diagnostic imaging modality could be envisaged in the future. For many years, [^{18}F]fluorodopa has been the most widely acknowledged ^{18}F-labelled PET radioligand for the assessment of the integrity of the dopaminergic terminals and for the evaluation of the progression of the dopaminergic deficit in Parkinson´s disease. Other suitable imaging targets for the assessment of the integrity of the dopaminergic terminals include the DAT and the

vescicular monoamine transporter type 2 (VMAT2). This presentation will summarize the main applications of molecular imaging in Parkinson´s disease. The status of the development of ^{18}F-radioligands for the pre-synaptic dopaminergic system will also be discussed, together with the potential advantages of PET imaging biomarkers for clinical research in parkinsonian disorders.

8. Neurodegeneration markers from structural MRI and FDG-PET brain images: the Alzheimer's disease case study (A. Chincarini, INFN Genova) ***(25')***

Abstract. *In the framework of neurodegenerative diseases, and in particular the Alzheimer's disease (AD), we are witnessing an increasing presence of neuroimaging data, magnetic resonant images (MRI) and positron emission tomography (PET) above all. Despite the fact that clinical scanners have been around for some decades, MRI and PET images have only recently become a dependable support in diagnosing early and prodromal AD. The purpose of image analysis is to find supporting evidence to help in early clinical assessment. In the case of neurodegenration leading to AD, we would ideally look for a measure (marker) able to discriminate between normalcy versus pathology at a pre-clinical stage, easy to implement in clinical practice and possibly based on quick, low- cost, and widely available procedures. In addition, a "good" marker should have predictive value as to whether a subject with current unknown or unclear clinical assessment will or will not develop the pathological condition in a given timeframe. Research supported by INFN experiment MIND (Medical Imaging for Neurodegenerative Diseases) is targeted at developing physical and statistical methods to find reliable and accurate image-based markers, with potential applications in the clinical practice. From a data analysis point of view, the problem can be restated as a measure of a "signal" (the pathology marker) on a "background" of normalcy. Whether a marker can have predictive value at all implies that it must be sensitive to some key aspects of the pathology process well before their effects have a clear clinical counterpart. We shall give an overview of some relevant branches in brain image analysis and the requirements to define a suitable signal over the confounding variability (noises) peculiar to life-science studies.*

coffee break (15.05 – 15.30)

Psychiatric/Neurobehavioral disorders (Chairpersons F. Orzi, A. Varrone)

9. Molecular imaging in psychiatry (P. Stenkrona, Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden ***(25')***

Abstract. *The picomolar sensitivity of Positron Emission Tomography (PET) is increasingly recognized in industrial drug development projects aiming for rapid confirmation of new treatment principles in humans. Three major approaches can be identified. Radio-labeling of a new drug to high specific radioactivity allows for a detailed mapping of drug distribution to critical organs in man after administration of a microdose (<1 μg) at which level limited toxicology documentation is required. For CNS-drugs this approach is particularly useful for passage across the BBB and confirmation of brain exposure. A second approach is to develop a suitable radioligand for the targeted protein. The radioligand can then be used to indirectly measure the occupancy of a candidate drug. This approach is widely used for proof of*

*mechanism, for dose finding and to support dose recommendations. A third approach is to develop radioligands that bind to in vivo biomarkers for pathophysiology, such as beta-amyloid in Alzheimer's disease. Research on the pathophysiology of psychiatric disorders has to a significant degree been based on psychopharmacology. For instance, the dopamine hypothesis of schizophrenia is based on the fact that most antipsychotic drugs block D2-dopamine receptors and the serotonin hypothesis of anxiety and depression is based on the effect of antidepressant drugs on serotonin levels. Testing of such hypothesis with PET has demonstrated changes in dopamine transmission among patients with schizophrenia. New radioligands that are sensitive to endogenous serotonin levels are currently implemented. Understanding of brain physiology may serve as another lead to understand the pathophysiology of major psychiatric conditions. A general view is that the phenotypic expression of higher brain functions comes from an interplay between physiology and environment. This reciprocal relationship between biochemistry and behavior has recently been confirmed with PET for central dopamine receptor binding in relation to personality traits and working m*emory.

10. Investigating behavioral disorders by neuroimaging (P.Stenkrona, Karolinska) *(25')*

Excursion to Taormina (16.30)
Conference dinner

Special conference presentation: "Archimede - On the equilibrium of the planets (A good exercise for brain)", A. Pagano, INFN CT.

Abstract. *It is well known that the work of Archimedes of Syracuse was characterized by a wide range of scientific subjects. This paper reports about the laws of static created by Archimedes (equilibrium under gravity of planes). The formal interpretation of this work of Archimedes allows us to clarify the epistemological position of the great Syracusan also in comparison with those criticisms advanced on XIX century by Ernest Mach, criticisms that have been the subject of extensive discussions by scientists.*

Sunday September 2

Starting at 8.45 am: Advanced tools and techniques for brain imaging (Chairpersons G.Cuttone, P. Lecoq)

11. Dedicated PET-MRI-fMRI detectors for brain (H. Herzog. Institute of Neuroscience and Medicine – 4, Forschungszentrum Juelich, Germany) ***(25')***

Abstract. *After more than 10 years of experimental developments towards simultaneous PET/MRI especially for small animals, first prototype scanners for PET/MRI of the human brain have been realized. At the Forschungszentrum Juelich, one of four prototypes delivered by Siemens worldwide combines a commercial 3 T MRI with a newly developed BrainPET insert allowing simultaneous data acquisition with PET and MRI. The BrainPET is equipped with LSO crystals of 2.5 mm width and Avalanche photodiodes (APD) as readout electronics. A second BrainPET detector is available at our institute to be operated in a 9.4 T whole-body MRI. Here we describe the technical, methodological and performance characteristics of the BrainPET and report on BrainPET/MRI studies of various patients. As radiotracers [^{18}F]-fluoro-deoxy-glucose (FDG), [^{18}F]-fluoro-ethyl-tyrosine (FET), [^{11}C]-flumazenil, and [^{15}O]-water applied. Comparing the PET data obtained with the BrainPET to those of the HR+ scanner demonstrated the high image quality and the superior resolution capability of the BrainPET. Furthermore, it is shown that various MR images of excellent quality could be acquired simultaneously with BrainPET scans without any relevant artefacts. It is demonstrated that the BrainPET/MRI is a promising basis for obtaining an image derived input function and correcting head motion in simultaneous PET/fMRI studies. Finally, a short reference to comparable MR-compatible BrainPET systems under development by others groups is given.*

12. Molecular Imaging of therapeutic cells: pre-clinical and clinical studies (G. Marfia)(25')

Abstract. *Cell replacement therapy with stem cells holds tremendous therapeutic potential for treating neurodegenerative diseases. Over the last decade, molecular imaging techniques have proven to be of great value in tracking transplanted cells and assessing the therapeutic efficacy. This current study summarizes the role and capabilities of different molecular imaging modalities including optical imaging, nuclear imaging and magnetic resonance imaging in the field of stem cell therapy for neurodegenerative disorders. We discuss current challenges and perspectives of these techniques and encompass updated information. Stem cells and their derivatives show tremendous potential for treating many disorders, including neurodegenerative diseases. We discuss here the challenges and potential for the translation of Adult Neural and Mesenchymal stem-cell-based approaches into treatments for Spinal Cord Injury, Spinal Muscular Atrophy, intervertebral disc degeneration, and Stroke.*

13. Dedicated innovative SPECT detectors for brain (Ben Tsui, Johns Hopkins) ***(25')***

Abstract. *SPECT imaging of the brain has a long history of development. The goal of the development of brain SPECT imaging instrumentation and techniques is to provide the maximum detection efficiency or the lowest image noise level for increasingly improved spatial resolution. Most of the traditional brain SPECT systems utilize the scintillation detector technologies and improve the imaging performance through novel system configurations. Recently radiation detector technologies combined with special system geometries offer unique opportunities for new generations of brain SPECT system. In this presentation, we will provide a review of the development of brain SPECT systems, the radiation detectors they employed, and the special image reconstruction methods required. The progressive improvement of the quality of brain SPECT images will be demonstrated through examples from simulation, phantom and clinical studies. The recent advances in radiation detector technologies that provide great potential to make significant impact of the future of SPECT imaging of the brain will be discussed.*

14. Dedicated innovative PET detectors for brain (Stan Majewski, WV University) ***(25')***

Abstract. *Brain is the most interesting organ to image and there is lately a high level of fascination in the society about imaging brain, due to the increasing hope that many severe debilitating disease conditions such as dementia (Alzheimer's, other), mental diseases and severe depression can be diagnosed early and treated under imaging guidance. The very recently introduced hybrid PET/MRI scanners are already demonstrating the power of this hybrid dual-modality system in diagnosing and staging the abnormal brain biology. In this tandem PET plays the role of a molecular imaging modality. However, these formidable PET/MRI imagers, starting with the Siemens mMR machine, are very expensive and one can predict that their availability to millions of people who are concerned about the deteriorating conditions of their brains (memory loss, loss of cognitive function, deteriorating mental disease conditions) will be limited for quite a long time, and many medical centers will not be even able to acquire these systems. Nevertheless, one can have a vision that high performance and economical dedicated imaging instruments presently under development around the world can provide sufficient dual-modality functionality and can be available much sooner to much larger populations of patients. In this presentation we will review the development efforts primarily in dedicated sequential and simultaneous PET/MRI imagers. This latest relevant technical "revolution" in nuclear medicine imaging is spearheaded by the enabling Silicon Photomultiplier technology. This very compact and robust solid state technology with high intrinsic signal gain is highly immune to strong multi-Tesla magnetic fields and is making possible construction of compact insert-type PET (and single gamma) imagers that can be used in conjunction with MRI scans. In principle "any" MRI scanner could be converted into a PET/MRI brain imager. The efforts in making the two modalities, PET and MRI, compatible with each other are mostly focused on preventing that the insertion of the PET imager deteriorates the signal to noise (S/N) in the MRI scans. Majority of the on-going projects focus on development of special MRI coils that are inside the PET (or gamma) insert, and/or on combining these inserts with the RF coils. There are also development projects that are assuming minimal modification to the MRI modality and application of the standard RF coils. While this solution presents the main challenge of high potential interference on the*

MRI performance, it also offers maximum potential benefit of practically "converting" any standard MRI scanner into a PET/MRI machine to image a particular organ, such as brain, (but also breast, head/neck, extremities, etc). A next level combination of PET/MRI/EEG was already proposed to study epileptic and mental patients. PET/CT is still the most available hybrid imager and there are new developments in mobile PET/CT imagers, also benefiting from the SiPM technology, with applications to imaging of brains of stroke patients or monitoring radiation treatment in case of brain cancer. An important feature of these dedicated PET brain imagers is that they can be made highly efficient and therefore can permit low-dose PET scans. In principle, this will open possibility to longitudinal studies requiring multiple PET scans and multiple injections, for example in short and long term monitoring of the disease treatment effects.

Coffee break (10.25 – 10.55)

15. High Resolution Brain SPECT Imaging Technologies and Clinical Performances (B. Kari, Semmelweis University, Budapest, Hungary) ***(25')***

Abstract*. High resolution SPECT imaging has great impact in the diagnosis of functional abnormalities in deep brain structures and always appeared as a high priority demand. Short summary and overview will be presented about the various functional imaging technologies with their physical and clinical performances including the available methods to improve the image quality on the particular imaging system. It is well known, till nowadays the vast majority of the applied imaging systems are conventional general purpose* ***l****arge* ***f****ield* ***o****f* ***v****iew (LFOV) systems using parallel projection. The main problem of these systems is the high level image blur and the low sensitivity i.e. there is a contradiction between the system resolution and the sensitivity. One way to improve simultaneously the resolution and the sensitivity is to create imaging geometry to adapt suitably to the size, location and the shape of the investigated organ, especially to the brain. XRing/4R four head (cylinder symmetric appr.) dedicated brain SPECT system (Mediso Ltd.) with extra high intrinsic resolution (<2.2mm in 230*220mm UFOV) NaI(Tl) based detectors as well as LEHR/UHR collimator set deliver a feasible solution with Tc-99m/I-123 isotopes for brain SPECT. 2mm isotropic voxel-size is used for both phantom and clinical studies by MTF[-1] based 2D pre-filtering on the projection data and FBP reconstruction method. The system produced morphologically highly detailed images reflecting the brain anatomy by the patient studies. The gyruses and the grey matter along the gyruses are well delineated. 3D* ***o****rdered* ***s****ubset* ***e****xpected* ***m****aximization (OSEM) iterative reconstruction method has been developed for general purpose LFOV parallel projection based imaging systems in order to reduce the image blur effect and simultaneously compensate the photon absorption. The non-linear image blur distortion is originating from the* ***d****istance* ***d****ependent* ***s****patial* ***r****esolution (DDSR) of the parallel projection. Dedicated calibration procedure has been worked out for the* ***p****oint* ***s****pread* ***f****unction (PSF) modeling of DDSR and the photon attenuation map is determined by co-registered and resampled CT imaging. Forward projection step of the 3D reconstruction method includes both the PSF modeling and the photon absorption effect. High performance computing method has been also developed due to the intensive computation demand algorithm. The implementation has been carried out by novel nVidia based GPU's being much faster than the conventional multi-core CPU's (Central Process Unit). AnyScan™ SC (SPECT/CT, Mediso Ltd.) was considered for physical phantom and patient studies. The 3D iterative reconstruction*

method also was possible to apply on the retrospective studies of XRing/4R dedicated brain SPECT systems without CT based attenuation correction (only the conventional Chang method was applicable in this particular case). The 3D iterative reconstruction method was a part of the research project to be supported by TECH_08_A2-TeraTomo (NKTH) and TÁMOP-4.2.1/B-09/1/KMR-2010-0002 grants. The novel 3D GPU based reconstruction algorithm resulted significant improvement in the image contrast and spatial resolution. The reconstructed images showed clear-cut better spatial activity distribution. Considering the speed of the implemented reconstruction method is suitable for daily clinical application too (running time is less than 10min. with nVidia 480GTX GPU in case of 128x128x128 volume sampling rate, and less than 23min. in case of 256x256x128 volume sampling). The processed brain SPECT studies showed surprisingly good and artifact free result for both modalities (AnyScan™ SC and XRing/4R) with significant improvement of the image contrast and signal/noise ratio both by ~2mm and ~1mm voxel size samplings.

11.30 – 13.00 Poster Session (Chairperson: S. Majewski)

Lunch break (13.15 – 16.00)

16.00 - 17.30 Summary talks and "Round Table Discussion" on the theme (Chairpersons: P. Jehenson, F. Garibaldi)
"How can we develop and utilize the novel enabling imaging technologies for brain research and also to advance individual patient care at EU and at the international level"

Following the confirmation of the already identified but also of the new potential applications, an attempt will be made to identify the main areas to be developed by the imaging community, where the application-specific focus will most likely result in a positive impact for the brain imaging research area and for clinical patient care.

Adjunct Workshop: The latest enabling technological breakthroughs in compact radiation sensors, electronics and software for PET and SPECT
Giardini di Naxos (Taormina, Sicily) - August 30-31,2012

Registration is open on Wednesday (6 p.m. – 8 p.m.) and continues starting at 8. a.m. on Thursday.

Thursday August 30

8:45 am Welcome address ***(F. Garibaldi) (15')***

9.00 am Morning session. Chairpersons: M. Carpinelli, E. Nappi

Introductory talk: The role of dedicated advanced detectors in modern molecular imaging. What is missing in the standard scanners (A. Del Guerra, Pisa) *(25')*

Scintillators and Cherenkov light detectors:

- New scintillators for SPECT, PET and TOF-PET (W. Moses, Lawrence Berkeley National Laboratory) ***(25')***

Abstract. *Several newly developed scintillators, namely Lu_2SiO_5:Ce, $LuAlO_3$:Ce, and $LaBr_3$:Ce, have attractive properties for nuclear medical imaging. These properties include excellent energy resolution, high light output, short decay lifetime, and reasonably high density and effective atomic number. This presentation compares the properties of these materials and analyzes how well they meet the requirements for TOF PET. The most important criterion is the initial photon intensity, which is the rate at which photons are produced in the first nanosecond (and is equal to the light output divided by the decay time). By this metric, $LaBr_3$:Ce is the most promising material, with a light output of 61,000 photons/MeV (50% higher than NaI:Tl) and a primary decay time of 35 ns, giving it an initial photon rate of 4000 photons/MeV/ns. This is roughly five times higher than LSO (811 photons/MeV/ns) and six times higher than LuAP (629 photons/MeV/ns). An additional benefit of $LaBr_3$ is its outstanding energy resolution - it achieves 2.9% fwhm for 662 keV gamma rays, which is twice as good as that of NaI:Tl (which typically achieves 6% fwhm for this energy). In addition, preliminary work has been done with solid-state scintillator materials (such as PbI_2 and HgI_2), which have nanosecond decay times and light output similar to BGO (~8000 photons/MeV), and so initial photon intensities about twice that of $LaBr_3$. However, these properties are obtained at cryogenic temperatures.*

- Cherenkov radiation in medical imaging (P. Lecoq, CERN – Geneva)

Abstract*: Charged particles traversing a medium at a speed exceeding the speed of light in this medium will emit Cerenkov radiation. In biological soft tissues the contents of water ranges from 70% in the brain to 90% in lungs. With the index of refraction of water (1.33) the Cerenkov energy threshold is 260 KeV. Scintillating crystals used as radiation detectors in SPECT and PET scanners have a much higher index of refraction and therefore a lower Cerenkov energy threshold:*

Crystal	*Refraction index*	*Cerenkov energy threshold (KeV)*
NaI :Tl	*1.85*	*96*
CsI:Tl	*1.80*	*104*
LSO:Ce	*1.82*	*101*
$LaBr_3$:Ce	*1.88*	*92*
LuAP:Ce	*1.95*	*84*

This talk will illustrate how the Cerenkov emission produced by b^+ or b^- radioisotopes in the human body can be used as a new imaging modality. But it will also discuss under which condition the Cerenkov photons emitted by the recoil electrons during the g conversion process in the detecting medium can be exploited to improve the timing resolution of PET scanners.

Photodetectors:

- Progress on the Hamamatsu SIPM (MPPC) (K.K Koei Yamamoto, Hamamatsu Photonics ((25')

Abstract*. MPPS is a family of multi-pixel, self-quenching type Geiger Avalanche Photodiodes. We have been continuously improving the MPPC performances and getting better test results. We introduce some of resent progresses on the MPPC.*

- *Dark current Decreasing*
- *Wider Operating voltage*
- *Metal Quenching resister to replace Poly-Si resister*
- *Improve Time resolution*
- *Decrease Optical cross talk by Tench*
- *Small pixel with larger Fill factor*
- *4-side Buttable with Silicon Through Via*

- STMicroelectronics Photodetectors Technology – From SPAD to Analog SiPMs (G. Fallica) ***(25')***

Abstract. *Single Photon Avalanche Diodes (SPAD) and Silicon Photo Multipliers (SiPM) are high sensibility sensors with a great potential in heterogeneous insertion of optical technologies. They find main application in Healthcare, in particular inside Medical Image Systems for Nuclear Medicine like Single Photon Emission Computer Tomography (SPECT) and Positron Emission Tomography (PET). Among a lot of others application fields, biological diagnostic micro-Total-Analysis-Systems is a very interesting one. The activity of STMicroelectronics about SPAD and SiPM has been planned and executed in three phases. First of all, target specifications for a general purpose SPAD device and a manufacturing process flow (not derived from CMOS process) were fixed. The technology was then consolidated, featured with an innovating optical trench that actually has no competitor equivalent. Special cleaning procedures were developed in order to obtain an internal dark noise below 10 Hz in small diodes. In a second phase the device was tailored to the requirements of the PET equipment. Large area SiPM prototypes were fabricated. To increase the Photon Detection Efficiency, the edge of the diode has been compacted efficiently (fill factor up to 62% with cell pitch of 60 microns), while some further process, device structure and layout optimizations have been simulated and implemented. Both technology versions: "p on n substrate" and "n on p substrate" were fabricated and characterized. In the blue/violet wavelength range a PDE of about 40% and a Single Photon Time Resolution (SPTR) below 150 ps were obtained. Reliability tests at wafer level and on packaged devices showed that the SiPM has a ruggedness equivalent to the state-of-the-art silicon devices. Moreover: a lot of optical/low-stress package solutions have been exploited: open metal-can or ceramic; Chip-Scale-Package; Surface Mounting Device (SMD) with transparent resin. Finally, a lot of exploitation activity has been started. Some of them are running in the framework of European or Italian funded projects. Inside "CSI" project (European Nano-electronic Initiative Advisory Council ENIAC 2009-2012: Central Nervous-System Imaging) a Small-Animal-PET equipment will be assembled using ST-SiPM. The "High Profile" project (ARTEMIS) has a task for the conceptual design of a Near Infrared Imaging system based on SiPMs photon sensors. The "Muon Portal" project will exploit a muon tracking system for the inspection of cargo containers (to prevent nuclear fissile material contraband).*

11.05 – 11.35 Coffee break

- Strategies to obtain Time of Flight resolution in the 100 psec range (D. Shaart TU Delft) (25')

Abstract. *The use of time-of-flight (TOF) information in positron emission tomography (PET) significantly improves the image quality, in particular the signal-to-noise ratio. Commercially available TOF-PET systems have a CRT in the order of ~500 ps FWHM, which has been shown to significantly improve whole-body PET images. The TOF benefit is inversely proportional to the coincidence resolving time (CRT). Achieving a timing resolution in the order of ~100 ps FWHM would not only benefit whole-body PET, but would also enable dedicated TOF-PET(/MRI) systems for brain imaging. However, such an improvement of the timing resolution only makes sense if it can be achieved without sacrificing other important performance parameters, such as spatial resolution, energy resolution, and system sensitivity. This talk addresses some topics of importance for successful strategies towards these combined objectives. For example, the properties of the scintillator impose inherent limitations on the timing resolution. Research into new and improved materials therefore is ongoing. Furthermore, new photosensors such as silicon photomultipliers (SiPMs) have been shown to enable excellent coincidence resolving times (CRTs), in some cases better than conventional photomultiplier tubes (PMTs). SiPMs furthermore provide MRI-compatibility as well as greatly increased flexibility in the optimization of the detector geometry. We have recently shown how Cramèr-Rao theory can be used to quantitatively predict the best timing resolution achievable as a function of the scintillator and photosensor properties. Both this model and recent experimental results indicate that a 100 ps scanner should in principle be feasible, provided that one minimizes the time spread due to the variation of the position of interaction of the annihilation photons within the scintillation crystals. This requires innovative detector designs as well as new approaches in readout electronics, involving e.g. rapid digitization of a large number of detector channels and real-time signal (pre)processing. These topics will be discussed from a theoretical as well as from a practical point of view, including some examples of recent experimental approaches towards 100 ps PET.*

- Digital SiPMs: Approaching the Cramer-Rao Limit in TOF-PET, Reliably and Robustly (Edoardo Charbon –TU Delft *(25'))*

Abstract*. In this talk we look at digital SiPMs as an alternative to analog SiPMs, analyzing pros and cons of the two architectures, systematically from a theoretical and a practical perspective. The key advantage of digital SiPMs is not higher timing accuracy or better noise but rather higher tolerance to environmental variations and higher long-term robustness. Moreover, thanks to the capability of controlling each SPAD cell individually, trade-offs between dark count rate and photon detection efficiency can be fine tuned depending on the application. For these reasons, digital SiPMs are particularly indicated for Brain PET scanners, where flexibility, reliability, and portability are key.*

Electronics (Chairpersons G. Loudos, J.M. Benlloch) :

- The Role of FPGAs and Reconfigurable Acquisition in Future PET/SPECT Systems (Chockalingam Veerappan - TU Delft)

Abstract. *The advent of digital SiPMs has brought new opportunities to the field of PET and SPECT but also new challenges. Digital SiPMs deliver more detailed spatial and temporal information of the photon showers originating from Gamma events, but the bandwidth of this data can be very large. On the other hand the structure of the data can be used to perform compression and filtering in situ. The information rich dataset generated by digital SiPMs poses new challenges also at the system level. Thus, in many cases, reconfigurable architectures may be preferable to ASICs in that they enable the evaluation of the readout chain in various feasible variants. In this context, we present a novel sensor-network based architecture that is fully scalable to various system configurations targeting preclinical, clinical and brain PET, all at once. A study of the trade-offs between FPGA and ASIC based readout architectures will also be presented*

12.50-16.00 Lunch break

- High-Speed Electronics for PET Systems (William W. Moses, Lawrence Berkeley National Laboratory)

Abstract. *Positron Emission Tomography (PET) cameras provide a real-time data acquisition challenge. A PET camera typically has several hundred detector modules, each servicing about 150 scintillator crystals. Each detector module must identify 511 keV gamma ray interactions (Singles Events) at sustained rates of up to 1 MHz, and for each interacting gamma ray, measure the interaction position, deposited energy, and time (with ~4 mm, ~100 keV, and ~1 ns accuracy respectively). For a subset of these cameras (time-of-flight PET cameras), the required timing accuracy is ~100 ps. A commonly used approach for processing Singles Events in real time is to send a high-bandwidth version of the analog signal from each detector module to a constant fraction discriminator. A time to digital converter (TDC) then records an arrival time that is referenced to a common, master clock. The amplitudes of these analog signals are also digitized to obtain an estimate of the amount of signal observed in each channel. The deposited energy is obtained by summing the analog signals, and the interaction position is obtained using various sums, differences, and ratios of analog signals. The control of the analog digitization and TDC, computations used to measure the energy and position, and additional tasks (such as calibration corrections, Compton scatter rejection, event word formatting, and diagnostics) are performed by a field-programmable gate array (FPGA), often assisted by look-up tables stored in RAM. While there are hundreds of parallel circuits for processing Singles Events, their outputs are usually multiplexed. This enables Coincident Events to be identified by tens of coincidence detection circuits, which are realized in additional FPGAs. These Coincidence Events, which are positron annihilations (identified by finding pairs of Singles Events in different detector modules that occur within ~10 ns of each other) are identified, formatted, and stored at sustained rates up to 10 MHz.*

16.50- 17.20 Coffeee break

Multimodality systems (Chairpersons J.M. Benlloch, R. Pani):

- MR Basics and PET/MR Interferences (Hans F. Wehrl, Bernd J. Pichler, University of Tuebingen) (30')

Abstract. *In this talk, two topics involved in multimodality imaging are covered: The basics of Magnetic Resonance (MR) Imaging, as well as the possible cross-modality interferences in combined PET/MR systems. MR has evolved in the second half of the 20^{th} century from a purely analytical tool used in chemistry to a powerful medical imaging modality. Its major strengths are the use of non ionizing radiation as well as the multitude of contrasts it offers. However, compared to PET the sensitivity of MR is relatively low, only in the millimolar range. MR utilizes the intrinsic property of certain nuclei to possess an observable spin. The spin itself is a fundamental property of nature like mass or electric charge. Most MR experiments use the ^{1}H (hydrogen) atom, which is due to its high abundance in biological tissue, an excellent candidate for MR imaging. When ^{1}H nuclei are placed in an external magnetic field of the strength B_0 (the main magnetic field of the MR scanner), they can absorb photons of the frequency f. This frequency is called the Larmor Frequency, and depends on the gyromagnetic ratio (γ) of the nuclei used. We can calculate the Larmor Frequency by: $f=\gamma*B_0$, one of the fundamental equations in MRI, in case of ^{1}H $\gamma=42.58$ MHz/T, i.e. a 1 T MR scanner operates at 42 MHz, a 7 T machine at 300 MHz. By using radiofrequency pulses of these frequencies we can transfer energy to the spin system and manipulate it. A 90° radiofrequency (RF)-pulse (B_1-field) flips e.g. the spins (in a classical physics view) by 90° from their equilibrium position. After the RF-pulse is turned off, the spins tend to relax back into their original equilibrium, during this process a small RF-signal is emitted from the nuclei which is collected by RF-coils. This relaxation process has two time constants. The spin-lattice relaxation time, also called the longitudinal relaxation time, or T_1, measures how long it takes till all spins are in their original position parallel to the external B_0-field. The spin-spin relaxation time, also called transverse relaxation time T_2, measures how long it takes till the spins dephase once they have been excited. Both relaxation times are different between different tissue types such as water, fat, or cancer – therefore they can be used to generate the MR image contrast. The MR image itself is formed by the use of gradients, these are small (milli Tesla-range) additional magnetic fields, that can be switched on and off over time, and are overlaid to the strong (Tesla-range) B_0-field. To combine PET and MR in one device, various issues that arise from the operation within a strong magnetic field as well as from the MR RF-field and gradients need to be solved. Interferences from the MR to the PET include: operation of PET detectors in a strong B_0 field, and induction of currents by the gradients as well as by the MR RF-pulses. On the other hand, if we have a PET installed inside a MR we need to be careful about: The B_0-field homogeneity, electromagnetic radiation from the PET electronics, eddy currents and susceptibility artefacts. A clever PET design and the use of dedicated PET detectors can solve most of these problems. Combined PET/MR is therefore a technically challenging but definitely worthwhile goal in multimodality imaging.*

Software (Chairpersons: I. Buvat, N. Clinthorne):

- Introductory talk: "Image quality – The role of software and what is indeed needed from the high performance detector. Resolution or efficiency?" (N. Clinthorne, University of Michigan) ***(25)***

- Algorithms for imaging techniques (accuracy, speed, required computing power, and related challenges) - Spatial resolution/efficiency trade-off (pattern vs small lesions detection) (E. Cisbani) ***(25')***

- Reconstruction Techniques (SPECT) (B. Tsui, Johns Hopkins University*) (25')*
Abstract. *Early image reconstruction techniques for SPECT are based on the analytical image reconstruction methods that assume the experimentally acquired projection data are ideal. That is, they are not contaminated by physical factors such as photon attenuation and scatter, instrumentation factors such as trade-off between resolution and detection efficiency, and the spatially variant collimator-detector response, and patient factors such as the size and configuration of the patients, respiratory and cardiac motions and the limitation of radiation dose to the patient. As a result, SPECT image quality has been suffered by poor spatial resolution and high level of image noise. The development of 3D and 4D quantitative SPECT image reconstruction methods in recent years has provided significant improvement in both the quality and quantitative accuracy of SPECT images. In this presentation, we will present the effects of the various image degrading factors for SPECT, the principles of quantitative SPECT image reconstruction, and examples of the significant improvements in the quality and quantitative accuracy from experimental, phantom and clinical studies.*

Starting at 8.45am *Friday August 31*

- Incorporating anatomical information in PET image reconstruction (Dimitris Visvikis, INSERM UMR1101, LaTIM, Brest, France) ***(25')***
Abstract. *Over the last decade multimodality devices have revolutionized the domain of medical imaging. The first example is PET/CT which has already become a gold standard in oncology imaging. The next chapter in multimodality imaging and associated integration concerns the development of PET/MRI devices, offering clear advantages for brain imaging relative to PET/CT. Despite the obvious advantages, from the medical point of view, in combining anatomical and functional information within a multimodality imaging platform there are also a number of software challenges. The most important one is the availability of anatomical information and its integration within the PET image reconstruction process. Such integration targets an improvement in overall PET image quality in terms of both quantitative and qualitative accuracy. These include the use of anatomical images for the correction of different errors associated with the PET physics detection process such as attenuation, scatter and finite spatial resolution. These issues are particularly challenging considering for example the absence or differences in tissue attenuation characteristics obtained through anatomical imaging. On the other hand in order to be able to incorporate such information in PET image reconstruction one requires to ensure that both acquired datasets are within the same spatial framework, including*

accounting for mismatches as a result of physiological motion such as patient respiration. Current and future solutions in the field of anatomically driven PET image reconstruction will be covered.

- Partial volume effect (PVE) issue: instrumental and biological components (I. Buvat IMNC - UMR 8165 CNRS - Université Paris 7 - Université Paris 11) ***(25')***

Abstract. *In the continuing efforts towards accurate quantification in PET and SPECT, partial volume effect (PVE) remains an extremely challenging issue. PVE is not only caused by the limited spatial resolution in PET and SPECT images, but also by the unavoidable sampling of the images into matrices of voxels. PVE results in biased measurements, with bias depending on many factors related not only to the spatial resolution and sampling of the imaging device, but also to the size, shape and contrast of the tissues of interest and neighboring tissues. As most other factors degrading SPECT and PET quantification are now well compensated for, PVE is now gaining a lot of attention. Many corrections have been proposed to tackle PVE, first for brain imaging, but also for cardiac and tumor imaging. This presentation will explain PVE, and give an overview of the current strategies to cope with PVE. The applicability of these methods to various situations will be discussed, as well as how recent advances in detector technology and software can be taken advantage of to reduce errors caused by PVE.*

9.35 – 10.00 Coffee break

10:00 am "Round Table Discussion" on the theme (Chairperson: F. Garibaldi):
"Image quality and detector performance – what is needed (for different applications)"

The interplay between hardware resolution, efficiency and software. How the relevant clinical information can be best extracted from the measurements using novel high resolution detectors, fast image reconstruction, pattern recognition, TOF, image fusion, kinetic parameters estimation, quantitative calculations, etc. Impact of different task-specific requirements. How to lower the injected radioactive doses to enable longitudinal studies and/or screening for brain diseases and monitor therapy using PET or SPECT.

Excursion to Siracusa