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INVITED TALKS

CHAIRMEN'S FOREWORD

Jerzy Jastrzębski and Leszek Królicki

On behalf of the Polish scientific community we have the privilege and pleasure to welcome you to Warsaw for the PETRAD2012 Conference. The Conference follows the opening of the University of Warsaw Radiopharmaceuticals Production and Research Centre. The main goal of this centre is the production of radioisotopes and radiopharmaceuticals for Positron Emission Tomography (PET) laboratories in Poland as well as research into new, innovative radiopharmaceuticals.

Poland was *terra incognita* on the PET map of Europe for many years. This was due to a number of political and financial problems. The first PET Laboratory in Poland was opened at the Oncological Centre in Bydgoszcz in 2003. The PET programme of the Ministry of Health, launched in 2006 was the second milestone. At present there are 15 operational PET-CT cameras in Poland and some new ones will be installed shortly. These data firmly indicate that the method is accepted by doctors, scientific societies and the Polish national health service. The PETRAD2012 Conference is certainly a good opportunity to celebrate our story; a story of a multidisciplinary approach to a challenging scientific and social activity.

Every year new fields for PET in clinical and scientific applications are being opened. PETRAD2012 aims to summarize some of these possibilities. This is the first international PET conference to be held in Poland and its success will depend — above all — on the effort of our guests: invited speakers and authors of the oral and poster presentations Their knowledge and experience will certainly contribute to new ideas for all conference participants. In this Book of Abstracts this effort is only highlighted, you will learn more by participating in the Conference sessions and attending the Poster presentation. We hope that the publication of the Conference Proceedings at the end of this year will provide a permanent record and a good summary of this scientific event.

We thank all participants for visiting our Centre and selecting our Conference among so many other meetings all around the world. We do hope that your visit to Warsaw this time will not be your last and that our contacts, with the accompanying exchange of ideas and experience, will continue.

Last but not least, we address our deep thanks to the Sponsors of this Conference. Without their generous support the organization of this scientific event — unique in our region — would certainly not have been possible.

Have a good time in Warsaw!

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THE RADIOPHARMACEUTICALS PRODUCTION AND RESEARCH CENTRE AT HIL UW

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The Heavy Ion Laboratory (HIL), University of Warsaw has recently gained a new capability, the Radiopharmaceuticals Production and Research Centre (RPRC). Opening in 1993, the HIL is an accelerator laboratory operating a Kmax = 160 heavy ion cyclotron currently equipped with two ECR ion sources: a homemade 10 GHz source with a classical magnetic trap, and a commercial Pantechnik 14 GHz Supernanogan source. Our main activity is focused on research in nuclear physics, materials and solid state physics, atomic physics and the life sciences. Our newly finished large project extends our interests to the production of classic PET radiopharmaceuticals and research into innovative radiopharmaceuticals, also including metallic targets. The aim is to establish a radiopharmaceutical production centre for Positron Emission Tomography in the Central part of Poland, mainly in Warsaw and the surrounding region. The one of the crucial conditions of the tender was that the project had to fulfill Good Manufacturing Practice requirements. In this presentation the author will give a short description of the history of the whole project, including of course the sponsoring Authorities and the close collaboration with the International Atomic Energy Agency under the contract "The provision of a cyclotron system, targets and equipment for the manufacture of 18F — Fluorodeoxyglucose and other radiopharmaceuticals for operation at the Heavy Ion Laboratory of the Warsaw University". Finally, the remaining conditions and expectations included in the tender will be presented. Participants will become acquainted with the main equipment destined for the production of FDG, for R&D and QC activity.

A LOOK AHEAD: PET/MR VERSUS PET/CT

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Over the past decade, the introduction of PET/CT has catapulted PET and particularly FDG PET from an interesting, but not to well understood imaging — into a diagnostic mainstream technology, which modern oncology considers standard very much as e-mail and the mobile phone have become the mainstay of communication. PET/CT was very much a technology, oncology was waiting for. Application of FDG-PET/CT has taught us many new insights on how to stage and monitor tumors. FDG activity seems to be an excellent predictor of patient survival and a lack of response of a tumor to therapy is almost always reflected in persisting FDG uptake. Some subtleties of PET scan interpretation have only been understood in combination with CT. Brown fat uptake, globular muscle uptake, benign entities showing FDG uptake such as Warthin's tumor, were mostly unknown in the days of PET only. Hence, addition of CT to PET was dearly needed and made PET more sensitive and specific, resulting in a better test, demonstrating impact on management in up to 50% of cases examined. Use of FDG-PET/CT in the diagnosis and follow-up of inflammatory lesions also has been steadily increasing, while PET applications in the brain and heart, originally considered the key indications to perform PET scans, have not nearly seen a comparable surge in utilization.

Over the last several years, various groups have been experimenting with the integration of PET with MR and currently, the three major imaging equipment manufacturers offer three different versions of PET/MR systems. In complete contrast to PET/CT, no compelling clinical indications for PET/MR have been defined. PET/MR thus remains largely a technology looking for an application. Numerous interesting applications of PET/MR have been proposed and there is no question, that PET/MR is an extremely interesting research tool.

In order for a costly technology to establish itself in the clinical environment, at least one key clinical application has to be developed, where the technology is superior to all other technologies. This has been amply demonstrated by the initial success of MR in imaging brain disease and PET and PET/CT in oncology. The task for research groups disposing of PET/MR is thus to find such a "killer" application. However, various obstacles are in the way of a large scale introduction of PET/MR.

Technology

Building a PET system which works in the magnetic field of an MR scanner is costly and the technology necessary is just developing. Solutions seem to be Avalanche Photodiode or Silicon Photomultiplier based detectors which can replace the unsuited standard photomultipliers as PET detector components. The use of MR data for attenuation correction is still far inferior to using CT data and standardized pulse sequences easily integrated in a PET whole body examination workflow are not clearly defined yet.

Clinical

The simultaneous data acquisition potentially possible with PET/MR is largely irrelevant clinically. Standard PET tracers used in clinical practice are injected and after a substantial wait time, the examination takes place. In this context it is not even clear, what the meaning of "simultaneous data acquisition" really is.

Oncology: while in principle MR has considerable advantages in head and neck, liver and pelvic imaging, it is not clear whether the combination with PET maintains this advantage, *i.e.* the fact that MR is better than CT does not automatically mean that PET/MR is better than PET/CT in a given application. Oncology requires a head to pelvic floor scan in most situations. Many tumors are prone to result in lung metastases. Hence, good lung imaging in such a partial

body procedure is critical. MR is substantially inferior to CT in lung imaging and this problem has to be solved. Some early data show that PET/MR > PET/CT in liver lesions, but otherwise data are sparse.

Neurology: brain imaging is potentially an interesting area for PET/MR because of the well known inferiority of CT compared to MR. However, current clinical PET indications in the brain are limited, and so clinical use is not foreseen to be dramatically altered by the introduction of PET/MR. This may well change when the PET plaque imaging agents become available in the next 2–3 years. Still, the only compelling reason to use integrated PET/MR is that the patient needs to undergo both examinations. Doing "two for one" thus shortens imaging time. PET/MR will be undoubtedly a very interesting brain imaging research tool.

Cardiology: PET perfusion and viability imaging have established themselves in the clinical environment, but SPECT perfusion and MR viability imaging are excellent alternatives. Again, compelling clinical indications for integrated PET/MR in the heart are not on the horizon. With the advent of PET-based perfusion tracers, potentially interesting combined clinical applications can be thought of and like in the brain, PET/MR is an interesting research tool. *e.g.* for cross-validation of MR- and Nuclear Techniques based perfusion imaging.

In summary, PET/MR — unlike PET/CT — is a technology looking for clinical applications. There is little doubt that some will emerge in the future. At this moment PET/MR is an extremely interesting research tool.

PARTICLE ACCELERATORS FOR PET RADIONUCLIDES

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Radionuclides suitable for use in PET imaging will always be found very close to the line of stability in the chart of nuclides. The requirements of suitable half-life and almost pure positron emission lead to a few dozen widely used isotopes, that can all be made by (p, n) or (p, alpha) reactions by protons in the range of 5 to 11 MeV. Only the production of the short-lived physiological tracer O-15 warrants the use of deuterons as alternative to protons.

Higher energy protons (in the range of 11–19 MeV) can be justified in terms of more robust target windows, thicker targets and higher yields, but the technological evolution of high current, low energy targets has lead to very good performances even at 11 MeV.

Although various types of linear accelerators (electrostatic, Alvarez-type and RFQs) have been developed and successfully used for PET, they have never demonstrated superior performance or lower cost when weighted against the activity outputs of the universally accepted isotope production accelerator: the cyclotron.

The energy range and the intensities needed for PET radionuclide production are extremely well covered by modern compact (also called medical) cyclotrons. Although the basic principle of the cyclotron is now more than 80 years old (Lawrence-1932), many developments during the last 30 years have made the cyclotrons much more reliable instruments. They are powerful in terms of isotope output, they are user friendly and easily serviced and with reasonably small requirements for space, power and cooling.

With this said, there remains little reason to decide for anything else than cyclotron for PET radionuclide production, whether it is for routine clinical use or for research. However, there remain a lot detailed choices, not only on maximum beam energy between handfuls of well established commercial manufacturers, but also between different sizes and installations of the cyclotron: bunker versus self-shield, possible beam lines for solid targets or target multiplexing directly on the cyclotron tank.

The Atomic Energy Agency has recently issued a number of very useful guidelines to assist the right size of cyclotron and the design and operation of a PET radioisotope facility (IAEA, TRS references given below). These texts will guide the reader also to the very important interplay between the accelerator itself and the targets, the radiochemistry, the pharmaceutical and regulatory issues and the operational costs.

The talk will highlight some of the key technical issues when deciding for a facility for PET radionuclide production. From many years of experience with the start up of new PET centres, the most important advice is first to plan the projected use of the cyclotron during the first 10–20 years of operation (a cyclotron may well last for more than 40 years),- and then use this plan to choose the cyclotron. It is indeed possible to buy every feature and all possible targets for a new machine, but this is very rarely justified in terms of any practical use. Instead, it adds much to cost, space requirements and to the complexity of site planning, commissioning and operation. It is my personal experience, than no cyclotron has been too simple to be of any use in practical PET life. On the contrary, some machines have indeed been too sophisticated to make them reliably available for daily life in a PET environment.

The talk will discuss the issues of beam energy, maximum target current, activity outputs and operational costs from the basis of the available technology. But it will also try to embrace some very promising current developments in terms of very compact “bed side” PET tracer delivery systems based on highly integrated small cyclotron systems. The advent of such platforms might once again change the way that we think and operate PET facilities in the future.

The talk will also address the possible impact of the so-called Technetium Crisis on the both the choices and the economics of cyclotrons of higher energies, marginally useful for PET, as well

as the obvious disparity of scale and sophistication between conventional single photon emitter imaging and current PET imaging possibilities.
As before, much of the evolution in nuclear medicine is driven by developments by the community of cyclotron engineers and target wizards. The very small machines that are only made possible by advances in cyclotron technology, target materials, radiochemistry systems and in software control may well make a much wider range of PET tracers clinically available on a broader scale and in larger numbers than previously believed possible.

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FROM TARGET TO SMALL-ANIMALS IMAGING

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Outline

1. Intro How to get PET radiopharmaceuticals into living systems? Main PET radionuclides used are 18F and 11C others much less widely used. Useful chemistry good imaging characteristics why others less useful.
2. Evolution of ^{18}F targetry
   Early $H_2{}^{16}O$ water targets for fluoride leading to present high current $H_2{}^{18}O{}^{18}FDG$ factory targets.
3. Evolution of ^{11}C targetry
   Solid targets of B_2O_3 used in discovery experiments. Can be used with pr tons or deuterons. Recovery of ^{11}C can be problematical several methods developed before theintroduction $^{14}N(p,alpha)^{11}C$ gas targetry. Some significant in-target chemistry will be described.
   How to convert the target output into a radiopharmaceutical?
   Fast synthetic organic Radiochemistry and it's automation.
4. Essentials characteristics include reaction vessels with heating and cooling made of compatible materials, valves and pipes with appropriate qualities for the media and pressures of the gases liquids and vapours, to be transported.
   Control of the process sequence including temperature control, reagent additions, reactants mixing solvent evaporations etc.
   Early systems controlled using manual switches which were replaced by programmable controllers (PLC's).More recently control has been achieved using computers (PC's) with a variety of interface methodologies.
   Purification of the desired product from the crude reaction mixture using ion exchange or more solid phase extraction. Often based on analytical reverse phase HPLC with radioactivity and UV detectors situated at the column outlet.
   Formulation and terminal sterilisation. Often the HPLC solvent must be removed and exchanged for a more biologically appropriate one. Reverse phase cartridges often referred to as C 18 Sep Pak's provide an effective solution.

To autoclave or not to autoclave?

5. Animal PET it's roots and rapid growth
   Early attempts to build instruments from best available BGO block detectors made for human scanners. CTI/Hammersmith collaboration on "RATPET" with low resolution but high sensitivity.
   CERN multiwire proportional counter detector technology re-engineered to provide whole body animal PET scanner Oxford PositronQuad HIDAC. High resolution but low sensitivity.
   LSO breakthrough yielding lots of very fast light allowing much small crystal elements to be made leading to sub millimetre intrinsic resolution.
   Multmodality PET/CT followed on from Human usage and PET/MR developed in various prototype forms examples.
6. Animal PET problems and pitfalls. Examples illustrating some strengths and weaknesses.
7. Conclusion with a look into the future from a personal standpoint.

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PRESENT AND FUTURE OF PET-RADIOPHARMACEUTICALS

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The selection of appropriate animal models, suitable validated tracers and kinetic analysis are key issues for successful application of PET.

Although number of newly discovered biological targets (often of poorly understood function) is increasing rapidly, the repertoire of well-characterized PET radiotracers for in vivo imaging is limited. Therefore radiochemists will play a continuing crucial role in the discovery and development of PET radiopharmaceuticals to enable the study of novel biological targets and evaluate treatment in humans. Several criteria should be considered in the development of novel PET probes for in vivo imaging, such as choice of radionuclide, position of labelling, metabolism, non-specific binding and radiolabelling strategies. The development of new PET imaging probes relies mainly on 2 radionuclides. Carbon-11 is the radionuclide of choice for radiolabelling the investigational drug. Replacement of naturally occurring carbon-12 by carbon-11 does not alter the (bio)chemical properties of a molecule. Since ^{11}C can directly replace stable carbon in the compound of interest it is of the greatest interest to drug discovery and development. Many synthetic routes to ^{11}C-compounds are already available and several others are still under development. Because of the very short radioactive half life of ^{11}C the synthetic procedures should be very efficient. The second radionuclide is fluorine-18, mainly due to its adequate physical and nuclear characteristics. There is still a need to simplify ^{18}F-chemistry to allow better dissemination of PET which may become comparable to conventional SPECT.

Fluorine-18 is the most often used radionuclide for diagnostic PET imaging because physical properties of ^{18}F are very favourable. Among the routinely produced very short-lived positron emitters, the relatively longer half-life of ^{18}F poses less constraints on synthesis time and permits longer imaging protocols to investigate processes of slower tracer kinetics.

Currently, FDG is the most widely used (~90%) radiopharmaceutical in PET often making PET synonymous to a study using FDG. A large number of drugs and biomolecules have been evaluated for labeling with fluorine-18 in order to apply radiopharmaceuticals that target specific biochemical processes. Thanks to the continued efforts of a large number of scientists in several countries, there is now a wide variety of ^{18}F-tracers that can be used for PET studies in the fields of oncology, inflammation, neurology, psychiatry, and cardiology. However, these radiopharmaceuticals are not optimally used. Therefore it is of utmost importance to translate these radiopharmaceuticals into a clinical setting for the better understanding of the disease process in humans.

The relatively longer half-life of ^{18}F also permits the distribution of ^{18}F-labelled radiopharmaceuticals to clinical services approachable within a few hours of transport. The initiatives of several small and medium companies made possible the regular supply of GMP grade ^{18}F-labelled radiopharmaceuticals from a single cyclotron/PET radiopharmaceutical production facility to several clinical PET centers. 'Cyclotron-PET satellite' concept is a successful business venture in many parts of the world and significantly contributed to the growth in the number of PET/CT cameras installed all over the world. The market is still rapidly expanded also due to its exponential growth in developing countries.

Centralized versus non-centralized radiopharmaceutical production holds several issues in relation to cost-effectiveness, regulations and scientific innovations. Besides aspects of regulation there is impact on the design of the facility and the required equipment. As a consequence new synthesis equipment based on microfluidics is under development to produce PET-radiopharmaceutical s on patient basis.

Finally metal-based PET-radionuclides such as ^{64}Cu, ^{89}Zr and ^{68}Ga are increasingly used thereby building on the longlasting experience that the community gained with SPECT-radiopharmaceuticals. These radionuclides are mainly being used for radiolabelling of peptides, proteins and antibodies. Since ^{64}Cu and ^{89}Zr have a relatively long half life they may easily be distributed over long distances and can be used to produce a wide range of peptides and antibodies. ^{68}Ga is available through a generator and is very suitable to produce radiolabelled peptides. The metal-based radionuclides have the advantage that they can be available without having the expensive cyclotron infrastructure.

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RECONSTRUCTION IN POSITRON EMISSION TOMOGRAPHY: 2D-4D, RESOLUTION RECOVERY, ARTEFACT REDUCTION

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The basic problem to solve is the solution of the inverse problem **P** = **F.X** where **P** are the acquired data, **F** is the forward or system matrix and **X** are the image(s) to reconstruct and then quantitate. Although direct methods such as Filtered back Projection exist, now iterative methods are almost always used. Both list mode where each line of response is considered individually, and methods where frames of projection images are formed. Associated problems include uniformity correction (or normalisation of sensitivity), decay, scatter and randoms correction, and of course attenuation correction. Reconstruction is normally of volumes including currently semi whole body, and therefore motion correction, and redistribution of activity hence4-d reconstruction *i.e.* of 3-d data in time, as a function of a physiological time activity information. Note that the 3-d itself is a limited angle problem. The iterative solution of the inverse problem is typically using a method such as MLEM (or variants) where a guessed solution $\mathbf{X}^n$ uses **F** to generate a guessed set of projections $\mathbf{P}^{n'}$ which are compared with **P** the original raw data to create modifications to $\mathbf{X}^n$ until a 'satisfactory' solution is found. This can be done in 2-d, 3-d or4-d. However note that problem is in principle quite large. How should **F** be represented? One useful tool is this process is Monte Carlo simulation but reasonable reconstruction times are required although the use Graphic Processor Units (GPUs) are now often used. **F** is often computed dynamically (on the fly), rather than precomputed and then stored. In the 4-d (time) problem a compartmental model can be assumed and the interactive solution includes a search for the coefficients of the model itself.

PET IN NEUROLOGICAL RESEARCH AND DIAGNOSTICS

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From its inception in the mid 70's, PET has been a major tool for basic and clinical neuroscientists. Today, PET continues toplay a critical role in preclinical fundamental research both for the understanding of brain disease pathophysiology and for drug development. But PET is also routinely used for the diagnostic and the theranostic of many neuropathologies, including major social impact brain diseases such as stroke, neurodegenerative disorders, including Alzheimer and Parkinson diseases, and epilepsy.

Tracing neurobiological processes with PET

Because of its intrinsic exquisite sensitivity, and thanks to the wide spectrum of high specificity available radiotracers, PET can indeed assess many neurophysiological and neuropathophysiological processes in vivo. For instance, parameters of regional cerebral energy supply and consumption parameters can be quantitatively estimated, including blood flow (with ^{15}O-water or ^{15}O-butanol), glucose (with ^{18}F-deoxyglucose or FDG) and oxygen metabolism (with $^{15}O_2$, ^{18}F-misonidazole or FMISO) and used to evaluate neural cell degeneration. Similarly, brain protein synthesis and turnover can be locally measured with labeled amino acids (^{11}C-Methionine, ^{11}C-Leucine, ^{18}F-Tyrosine, α^{11}C-Methyl-Tryptophan or AMT) or nucleoside (^{18}F-Thymidine or FLT), allowing the assessment and follow-up of brain cell division. Even more interesting for research purposes, is the unique ability of PET to allow the investigation of brain neurotransmission systems. The regional distribution, kinetic parameters and metabolism of neurotransmitters and membrane receptors can so be quantified for the dopaminergic (^{11}C-Raclopride, ^{18}F-DOPA), serotoninergic (^{18}F-Altanserin, ^{18}F-CWAY), cholinergic, gabaergic-A central (^{11}C-Flumazenil, FMZ), peripheral benzodiazepine (^{11}C-PK1185), and opioid (^{11}C-Carfentanyl) systems, to name the most important of them. For several brain disorders, such PET tracers are extremely useful 1- for the understanding of their pathophysiology at the molecular level, thereby allowing the identification of specific therapeutic targets, and 2- for designing optimal PET diagnostic and theranostic tools. Last but not the least, PET is also the technique of choice for the evaluation of b-amyloid aggregation and neuritic plaque formation (using ^{11}C-PIB, ^{18}F-florbetapir or ^{18}F-flutemetamol), two processes thought to be at the core of the pathophysiology of neurodegenerative disorders, including AD.

PET diagnostic and theranostic of neuropathologies

Alzheimer disease and other neurodegenerative disorders. This is the domain where PET is the most useful in both the research and clinical routine areas, one major pathology being extensively investigated with PET, namely Alzheimer disease (AD). AD, the most common cause of dementia and an important challenge for healthcare systems, is initially characterized by memory complaints, evolving later on towards severe cognitive decline. At the molecular/cellular level, AD is characterized by the presence of amyloid–β (Aβ) plaques, neurofibrillary tangles and activated microglia, resulting in neuronal cell loss. These neuropathological changes are thought to precede cognitive symptoms by many years, which justifies the use of PET using both FDG and Aβ markers (such as ^{11}C-PIB or newly developed ^{18}F-labeled tracers, see above) in order: 1 — to make an early detection of the disease, 2 — to predict whether or not a subject with mild cognitive impairment (MCI) will end up having AD, 3 — to make differential diagnosis with other diseases such as Lewis body dementia or fronto-temporal dementia (FTD), 4 — to assess treatment outcome. Other PET tracers, including for various neurotransmitter systems, are used to progress in the knowledge of AD pathophysiology.

Cerebrovascular disease (CVD). CVD results from an imbalance of the normal relationship between the cerebral vasculature and the brain parenchyma, sometimes resulting in stroke.

PET should be the technique of choice for investigating stroke, being the only technique able to provide quantitative and reliable estimates of cerebral blood flow ($H_2{}^{15}O$), blood volume ($C^{15}O$), and oxygen ($^{15}O_2$) and glucose (FDG) metabolisms. However quantitation and the use of short-lived positron emitters (123 sec for ^{15}O) makes its use restricted to the preclinical or clinical research area. Nevertheless, PET has been found to be invaluable for the understanding of the compensatory responses of the brain to reductions in perfusion pressure and their associated changes in blood flow and metabolism, paving the way for the design of new treatment strategies.

Epilepsy. Epilepsy is a chronic disorder characterized by recurrent and unprovoked seizures. Epilepsy is controlled with drugs in 70% of the cases. When seizures cannot be controlled, surgery is considered and interictal PET with FDG is used to localize the seizure onset zone to be resected. In preclinical research $GABA_A$ opioid, and serotoninergic neurotransmission are being investigated with PET as existing or possible therapeutic targets.

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RADIONUCLIDE-BASED REPORTER GENE IMAGING: CLINICAL IMPLEMENTATION AND APPLICATION

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"Pre-targeting" (delivery) of a reporter gene to the target tissue by transfection or transduction is a requirement for all reporter gene imaging studies. The reporter gene construct usually includes transcriptional control elements that can initiate and regulate reporter gene expression. Two general groups of promoter-enhancer control elements are recognized; one group comprises "constitutive" promoters that result in continuous expression of the reporter gene; the "always on" motif. The other group comprises "inducible" promoters that are activated by endogenous transcription factors that function as a specific cellular "switch".

"Constitutive" driven reporters can be used to identify the site, extent and duration of vector delivery, and can be used to monitor the efficiency of tissue and cell transduction (the normalizing term) for subsequent image and data analysis. "Constitutive" driven reporters can also be used to "label" specific cells, and this can be performed *ex vivo* as well as *in vivo*. For example, the long-term monitoring of T cell trafficking and localization is well recognized as an important component in studies of the immune response following adoptive T cell therapy. Similarly, the long-term monitoring of adoptively administered stem cells is recognized as a key component in the assessment of therapeutic efficacy in patients undergoing stem cell-based therapies. *Ex vivo* labeling of T-cells or stem cells with MR contrast or radiotracers does not provide an opportunity to monitor their long-term trafficking and localization, whereas "genetically labeling" these cells with appropriate reporter systems provides this capability. We and others have demonstrated the feasibility of long-term *in vivo* monitoring of adoptively transferred antigen-specific T cells that were transduced (genetically modified) to express a radionuclide-based reporter gene. This provides the opportunity to image and track the T cells repeatedly and sequentially over time following the administration of a reporter-matched radiolabeled probe.

"Inducible" promoters respond to endogenous transcription factors and transcription-regulating complexes, and can be used as "molecular-genetic sensors". For example, inducible reporter systems can monitor T cell activation upon antigen recognition. Since T cell antigen-T cell activation results in their proliferation, cytokine secretion and other cytolytic functions, monitoring activated T cells at specific target sites is important in the assessment of adoptive T cell efficacy. Inducible reporter systems can also be genetically incorporated into stem cells to monitor their differentiation into specific cell types and tissue through the activation of specific signaling pathways during differentiation. In addition, specific reporter systems have been constructed to be sensitive-to and report-on post-transcriptional processing, modulation of reporter protein translation, protein-protein interactions, and reporter protein ubiquitination. Inducible reporter constructs can be used to monitor the functional status and characteristics of transduced cells.

Although the initial radionuclide-based reporter systems were developed using viral reporter genes (*e.g.*, *HSV1-tk*), there has been recent interest in developing human reporter genes that avoid the potential for initiating an immune response against the reporter-expressing cells. Several human genes have been proposed as potential reporter genes for radiotracer-based imaging. These genes can be classified into three categories, based on whether the gene product is a **receptor**, a **transporter** or an **enzyme**. Examples of highly expressed cell membrane receptors include the specific membrane somatostatin receptors (hSSTRs). The transporter group includes the sodium-iodide symporter (hNIS), and the norepinephrine transporter (hNET). The endogenous enzyme classification includes human mitochondrial thymidine kinase 2 (hTK2). One favorable characteristic of this group of genes is the availability of radiolabeled probes that have already been approved for clinical gamma camera (SPECT) and PET imaging studies. This is largely due to the fact that these radiolabeled

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probes were developed specifically to image specific tumors (*e.g.*, neuroendocrine tumors), where the probes accumulate to high levels due to high expression of a particular receptor or transporter. The clinical application of PET-based reporter gene imaging will expand over the next several years. The translation of reporter gene imaging technology to clinical applications is the focus of this presentation, with an emphasis on the development and use of human reporter genes. Human reporter genes will play an increasingly more important role in this development and it is likely that one or more of the reporter systems (human gene and complimentary radiopharmaceutical) will take leading roles.

The initial applications of reporter gene imaging in patients will be developed within two different clinical disciplines: a) gene therapy, and b) adoptive cell-based therapies. These studies will benefit from the availability of efficient human reporter systems that can provide critical monitoring information for adeno-, retro- and lenteviral-based gene therapy, oncolytic bacterial and viral therapy, and adoptive cell-based therapies. The translational applications of noninvasive *in vivo* reporter gene imaging are likely to include: (i) quantitative monitoring of the gene therapy vector and transduction efficacy in clinical protocols by imaging the location, extent and duration of transgene expression; (ii) monitoring cell trafficking, targeting, replication and activation in adoptive T cell and stem/progenitor cell therapies; (iii) assessments of endogenous molecular events using different inducible reporter gene imaging systems.

CARDIAC PET-CT

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Abstract

Cardiac PET-CT imaging combines different modalities in order to obtain complementary anatomical and functional information in a single imaging study. Coronary CT angiography (CTA) and myocardial perfusion imaging with positron emission tomography (PET) are established non-invasive modalities for the diagnosis of coronary artery disease (CAD). Hybrid PET-CT is a promising tool for evaluation of CAD allowing detection of the coronary atherosclerotic plaques and their consequences on myocardial blood flow in a single study. This appears to offer superior diagnostic accuracy for the detection of flow-limiting stenosis in patients with intermediate risk for CAD as compared with stand-alone imaging especially by improving the positive predictive value.

PET has added an important new dimension to the functional characterization of pathophysiological processes by providing regional information not only on perfusion but also metabolism and cell integrity. With the increasing knowledge in molecular biology new imaging targets have been identified. Specific receptor families as well as cell surface proteins have been proposeed as targets for various imaging approaches using radiolabelled peptides or antibodies. The specific non-invasive visualisation of protein expression has become possible for diagnosis and therapy guidance. Using transgenic approaches, specific proteins can be expressed providing reporter gene imaging for the visualization of gene expression. These developments are believed to be the main players for the success of personalised medicine but also help in drug discovery and development.

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PET IN DRUG DEVELOPMENT

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The human genome contains over 23.000 genes determining structural and/or functional proteins. According to recent estimates, ~4.000 of them can be targeted at ~12.000 various target sites. Using advanced molecular imaging techniques and molecular imaging biomarkers, molecular targets including disease biomarkers and/or disease modifiers can be visualized in the living organism. Complemented with animal disease models, with special regard to transgenic models, this approach has significant benefits in the field of both diagnostic biomarker and therapeutic drug development. 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. PET provides a new way to image the function of a target from rodents to human 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. 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 PET in 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 and development now benefits from the fast development of functional imaging techniques such as translational PET-imaging.

PET MONITORING OF HADRONTHERAPY

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The favorable physical properties of ion beam interaction in matter offer the possibility of superior tumour-dose conformality with better sparing of surrounding critical organs and healthy tissue in comparison to conventional radiation in external beam radiotherapy. However, these advantages come at the expense of an increased sensitivity to uncertainties in the dose delivery. In particular, the praised finite range of ion beams represents a major source of uncertainty in the patient, hampering full clinical exploitation of the ion ballistic properties in the current clinical practice. Although such uncertainties can be accounted for via the introduction of cautious safety margins and the avoidance of treatment portals directly stopping in front of critical structures, in-vivo and non-invasive validation of the actual dose delivery and, in particular, of the ion beam range during the fractionated course of radiotherapy would be highly beneficial.

Over the last years, an increasing interest has been devoted to in-vivo quality assurance of high precision ion beam therapy. Although very promising novel concepts have recently been proposed and started being investigated, Positron-Emission-Tomography (PET) still offers the only technically feasible method for this purpose. The unconventional application of a well-established nuclear medicine imaging modality to ion therapy monitoring is based on the detection of the transient $\beta+$-activation which is induced in nuclear interactions between the ions and the irradiated tissue. Depending on the primary ion beam species, the mechanism of $\beta+$-activation may include either target fragmentation only or the formation of both target and projectile positron-emitting fragments. The mechanism of production mainly affects the shape of the ion-induced activity and its correlation to the deposited dose. In fact, activated target nuclei stay almost at rest in the place of interaction, while positron-emitting projectile fragments travel further and accumulate at their end of range. Nevertheless, dose deposition and irradiation-induced activation remain different quantitities, due to the underlying electromagnetic and nuclear processes, respectively. Hence, treatment verification can be obtained by comparing the actual PET measurement with an expectation based on the treatment plan and the time course of irradiation and imaging.

Due to the intrinsically delayed radioactive decay according to the half-lives of the typical reaction products (e.g., 10C, 15O, 11C), ranging from few seconds up to several minutes, the PET signal can be measured during or shortly after beam delivery. In particular, three major implementations have been so far clinically explored, which utilize either dedicated limited angle detectors integrated in the beam-delivery ("in-beam"), or commercial full ring scanners located inside ("in-room") or outside ("offline") the treatment room.

In addition to the technological efforts for efficient use of the very weak ($<$ 10 kBq/Gy/ml) activation signal induced by the therapeutic irradiation, further challenges of the PET-based verification approach include the modeling of the expected PET images including the physiological clearance of the produced activity (especially remarkable in offline imaging), the co-registration between the imaging and treatment positions (for in-room and offline implementations) as well as the organ motion (depending on the anatomical location and the duration of the PET scan).

To date, several examples of clinical implementations of PET-based treatment verification have been reported worldwide, exploiting different types of installation to measure the signal induced by actively- or passively-shaped ion treatments during or shortly after irradiation. Moreover, several investigations have been performed to tackle the challenging problems of in-vivo range monitoring and even PET-based dose reconstruction.

This talk will give an overview of the main examples of clinical implementation, with special focus on the own experience in in-beam and offline PET monitoring of carbon ion and proton therapy at the GSI Helmholtzzentrum für Schwerionenforschung in Germany, the Massachusetts General Hospital in USA, and the Heidelberg Ion Beam Therapy Center in Germany. In particular, it will highlight the encouraging clinical results but also the encountered major limitations. Furthermore, it will address the most promising developments which are ongoing in order to achieve optimal exploitation of the surrogate PET signal for *in-vivo* quality assurance of high precision ion beam therapy.

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RADIOTHERAPY TREATMENT PLANNING BASED ON FUNCTIONAL PET/CT DATA

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Purpose: To investigate the potential and limitations of functional imaging using combined positron emission tomography and computed tomography (PET/CT) for individually adapted radiotherapy (RT) treatment planning such as dose painting (DP).

Materials and methods: Functional PET/CT data can be integrated into the RT planning process with different levels of complexity. First, metabolic PET information as measured with [18F]--fluorodesoxyglucose (FDG) can be used for precise target volume delineation. PET-based target volumes may subsequently be used as a basis for intratumoral DP by contours (DPC). Here, different algorithms for automatic target volume delineation are investigated: Absolute, relative and automatic thresholding, a contrast-oriented algorithm that takes into account the signal-to-background ratio (SBR) in the image and finally a gradient based algorithm. In addition to a comparison of the resulting target volumes, imaging characteristics originating from different reconstruction methods that may be limiting factors for target volume delineation are investigated.

Secondly, molecular information as obtained from hypoxia PET imaging with [18F]-fluoromisonidazole (FMISO) may be used as a basis for locally varying dose adaptation in terms of DP by numbers (DP). Here, the requirements for imaging protocols, patient positioning and also PET data interpretation and quantification are extremely high. A simulation of FMISO distribution and accumulation is presented. Furthermore, a compartment model has been developed that allows us to extract local hypoxia and perfusion parameters from dynamic FMISO scans. Subsequently, a strategy for integrating dynamic FMISO PET/CT information into the RT planning process in terms of DPN is presented. In addition, the potential of different treatment techniques (IMRT, Tomotherapy, Protontherapy) is investigated.

Results: Functional PET/CT data can be used as basis for individually adapted RT treatment planning. A comparison of different automatic delineation algorithms for FDG PET show large discrepancies. Additionally, the use of different reconstruction algorithms induces large changes into the PET characteristics, such as image contrast and maximum standardized uptake values (SUV). As a consequence, also PET-based target volume delineation is strongly affected by the choice of the reconstruction algorithm. Furthermore, accurate integration of the target volumes in the RT planning process is absolutely necessary and requires careful — eventually deformable — registration of the functional image data to the planning CT.

To use the local hypoxia information of molecular FMISO PET imaging as a basis for DPN, correct and reliable image interpretation is necessary. Local hypoxia and perfusion values are extracted from dynamic FMISO PET scans and used as input for hypoxia DPN. DPN and also DPC were shown to be technically feasible not only by using dynamic IMRT techniques but also with Tomo- and Protontherapy.

Conclusion: Integrating functional PET/CT information into RT planning is feasible, but requires careful handling of patient positioning and image fusion.

Accurate target volume delineation for DPC can be performed on the basis of FDG PET/CT. Standardized acquisition and also reconstruction protocols are a prerequisite for PET-based PT planning in addition to optimized target volume delineation methods.

Furthermore, DPN based on *e.g.* dynamic FMISO PET imaging was shown to be technically feasible. Nevertheless, clinical usage of DPN remains unclear due to high biological and also geometrical uncertainties.

However, integration of functional PET/CT data into the RT planning process in terms of therapy individualization seems to be highly beneficial and might lead to improved RT outcome in the future.

FDG PET IN CLINICAL ONCOLOGY

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In recent years molecular imaging is acquiring importance for the evaluation of cancer patients, being complementary to conventional imaging methods as CT, MR and US. Among molecular imaging procedures, Positron Emission Tomography (PET) is the most diffuse and rapidly growing, and at present it is routinely used in patients affected by a large variety of malignant neoplastic diseases. Many papers in the literature have already demonstrated the utility of this imaging technique whose capabilities have been furthermore developed by the introduction of hybrid scanners (PET-CT). The combination of functional data (given by PET) and anatomic details (provided by CT) allows to significantly increase diagnostic accuracy, essentially due to a better specificity.

The usefulness of PET relies on its capability of investigating molecular processes by means of specific radiotracers, with the most employed being 18F-FluoroDeoxyGlucose (FDG). FDG PET scans provide important information about tissues glucose consumption, usually very increased in the most frequent malignancies as lymphomas, colon carcinoma, lung cancer, breast cancer, gynecologic malignancies, gastric cancer, head & neck cancer, testis cancer, oesophageal cancer, melanoma and others, covering the great majority of solid malignancies.

Main indications for PET use in clinical oncology are: characterization of uncertain lesions; staging; early evaluation of response to therapy; evaluation of residual disease at therapy completion and identification of relapse during follow-up. A typical example of lesion characterization is pulmonary solitary nodule. As regards tumor staging, PET ensures an accurate evaluation of nodes involvement at disease onset, as the diagnosis of nodes malignancy is based not only on size but also on a metabolic index. Furthermore PET is frequently determinant to identify metastatic lesions. Malignancies usually undergoing FDG PET for staging includes lung cancer, lymphomas, oesophageal cancer, melanoma and others. Evaluation of response to therapy is important in many neoplastic affection, such as malignant lymphoma: PET is often the only method enabling to document the presence of residual disease after therapy. The use of FDG PET to evaluate response to therapy is gaining more and more importance, in order to properly plan the treatment on individual basis. Regarding recurrence, PET is particularly important when conventional imaging is inconclusive. FDG PET has been demonstrated to be accurate in many cancers in case of suspect relapse, for both identifying the site of recurrency and evaluate the extent of disease.

Apart from those well established indications, the use of PET is gaining a relevant role in other clinically relevant situations, such as radiotherapy planning. Also it is increasing the number of disease studied by FDG PET with demonstrated usefulness, as multiple myeloma, bone and soft tissue sarcomas and others.

Despite the rapid growth of FDG scans in last decade, we retain PET holds great promises in the next few years with the application of other tracers beyond FDG, introduction of PET-MR scanners and identification of further clinical application of PET: it is easy to predict that in the future PET will continue to increase its impact on clinical and experimental medical science.

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NON-FDG-PET STUDIES IN CLINICAL ONCOLOGY

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The PET tracer and glucose analogue fluorodeoxyglucose (18F) or FDG has obtained a large acceptance in clinical oncology due to its excellent diagnostic performance in many clinical settings (characterisation, staging, radiotherapy planning, therapy follow-up, restaging, detection of occult recurrence) of many cancers (lung, colorectal, ENT, lymphoma, melanoma, oesophagus, breast, pancreas, ovary, thyroid, testicle…). For a NM department, it is very convenient from the logistical point of view to be able to perform PET/CT imaging in so many indications of oncology with one single tracer. However, FDG has reduced performance in some cancers, in particular the less aggressive and most differentiated ones such as prostate cancer or endocrine tumours, and, in one given cancer for some histological types (*e.g.* pure bronchioloalvear lung cancer or mucine-producing digestive or gynaecological cancers) or some localisations (*e.g.* osteoblastic metastases). Furthermore, FDG uptake do not reflect other metabolic/biologic features which can be important for the management such as hypoxia, presence of hormone or growth factor receptor, induction of apoptosis or damage to DNA.

It is therefore important to validate tracers "beyond FDG"; usually this requires the demonstration of superiority over FDG in a precise indication. A routine use of a PET tracer means in practice labelling with a radionuclide the half life of which is compatible with production of a batch for several patients and delivery, which is possible with 18F but disqualifies 11C. Another possibility is a PET radionuclide available on demand by means of a generator, such as 68Ga.

At this moment, three other 18F labelled tracers are registered in several countries of EU, and therefore commercially available: FDOPA (18F) for endocrine tumours and brain tumours, fluoride (18F) for bone PET/CT, and fluorocholine (18F) or FCH for prostate cancer and hepatocellular carcinoma. Others have been documented in series of a significant size and are in the process of registration, such as FET for brain cancers or FLT to assess efficacy of radiochemotherapy with less dependence to inflammation than FDG. It is to note that those tracers are analogues of small molecules, basic constituents of the tissues: carbohydrates, lipids, aminoacids, DNA bases…

Other tracers are not meant to replace FDG in cancers with inconstant FDG uptake but rather to complement FDG by addressing specific patterns or properties, such as analogues of oestradiol or testosterone for an in vivo detection of the presence of steroid sex hormone receptors in metastatic tissue form breast or prostate cancer, or FMISO and other tracers of the same family to detect hypoxia, fluorinated-RGD analogues to detect angiogenesis or tracers of apoptotic tissue.

The small sized metabolic analogues are not the only tracers to be under evaluation. Peptides labelled with 68Ga are currently under development, in particular radioligands of receptors which are overexpressed in cancer. The most documented example is the family of somatostatin receptors ligands such as DOTATOC (68Ga) to detect neuroendocrine tumours, with better performance than somatostatin receptor scintigraphy. Ligands of other receptor peptides are entering into preclinical or clinical studies. Inhibitors and monoclonal antibodies are developing as therapeutic agents in oncology; they are very expensive, with side effects and effective only in some patients. Thus it may be worthwhile to label them for PET imaging prior to a therapeutic use to confirm that the therapeutic agent concentrates in the target tumours. This paves the way to individually tailored medicine. In another approach, the targeting agent is linked to a molecular cage that can chelate radioactive metals for diagnostic imaging (68Ga or 64Cu if the binding kinetics is slow) and, if positive, for targeted internal radiotherapy with metal radionuclides which are beta — (90Y or 177Lu) or alpha emitters (223Ra or 213Bi): the theranostic sequence.

PET RECEPTOR IMAGING IN CLINICAL ONCOLOGY

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Tumor receptors play an important role in carcinogenesis and tumor growth. The knowledge of receptors overexpression such as somatostatin, bombesin, glucagon-like peptide 1, substance P, vasoactive intestinal peptides, and cholecystokinin is the way for dedicated diagnosis and therapy.

Neuroendocrine tumors (NET) are a heterogeneous group of carcinomas characterized by overexpresion of somatostatin (SSTR) receptors. Indium-111 labeled to the SSTR analogue octreotide (Octeroscan) was the first agent to be used and has demonstrated high sensitivity in the detection of NETs. Unfortunately, the unfavorable physical properties of 111-In make it unsuitable for detecting small tumor lesions leading to false negative results. An attempt has been made to introduce somatostatin analogues labeled with 99m-Tc due to the favorable physical characteristics of 99m-Tc and better imaging quality; however these are not widely available in clinical practice.

The increased utilization of PET/CT in oncology has led to the introduction of positron emitting tracers labeled to SSTR analogues, of these gallium-68-1,4, 7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (gallium-68-DOTA) compounds are the most widely used.

There are three compounds most often used in functional imaging with PET: 68Ga-DOTATATE, 68Ga-DOTATOC and 68Ga-DOTANOC. These ligands have different affinity to particular subtype of somatostatin receptors, and it may affect their efficiency in the detection of NET lesions. 68Ga-DOTATATE is a somatostatin analogue that shows high affinity for somatostatin receptor subtype 2 (SSTR2) which is the most common subtype found on NET from the GI tract. The same analogue could be labeled with the β(–) emitters like 90Y and 177Lu by the same chelators and used in targeted therapy.

In contrast to other NET, insulinomas — neuroendocrine tumours derived from pancreatic beta-cells — characterized by relatively low incidence of somatostatin receptor. The sensitivity of SRS for detecting insulinomas is only 40–60%. This tumors presented high incidence (> 90%) and high density of the glucagon-like peptide 1 receptor (GLP-1R). GLP-1 is rapidly degraded *in vivo*, this is the reason that for clinical use more stable agonist 68 Ga-DOTA-exendin-3 is used. Other receptor tracer like gastrin/cholecystokinin-2, bombesin, folate, HER2, neurotensin are investigated in animal study.