Nuclear Medicine Review 2012, 15, suppl A: A22–A46

ISSN 1506–9680
VIA MEDICA

ORAL PRESENTATIONS

ADVANCES AT ACSI: HIGH CURRENT TR19 AND THE NEW TR24 CYCLOTRON CAPABILITIES AND OPERATIONAL EXPERIENCE

Alexander Zyuzin, Russell Watt, Bill Gyles, Karl Erdman, Erik J. van Lier

Advanced Cyclotron Systems Inc., Vancouver, BC, Canada

Over the past few years ACSI has successfully automated the TR19 cyclotron operation, has demonstrated the feasibility and reliability of the high current (300 μA) TR19 and completed the development of a new 24 MeV cyclotron — TR24.

High current, fully automated TR19. In January 2009 Advanced Cyclotron Systems Inc. (ACSI) commissioned first fully automated, high current TR19 cyclotron. With over three years in routine operation, this new cyclotron is operating with 100% uptime, no production days were missed. Typical production schedule is 5 day per week, 2–3 production runs production with 2–3 hours irradiation each. Over 30 Ci of F-18 is produced routinely in a single run. Over 100 Ci of F-18 was produced daily for several months of higher demand. Typically, the current on target is 2 x 100 2x100 μA, however, the cyclotron is operated at 2 x 125 μAmp current on targets (limitation by target capacity) when higher production is required, with total extracted current of approximately 300 μAmp.

In factory, the high current TR19 was tested at 1MeV up to 600 μA. Three additional high current TR19 will be installed this year. One of them will be installed at the Institute of Physics and Nuclear Engineering in Bucharest. This machine will be equipped with an external beamline, which will allow it to fully take advantage of the high currents.

Bridging the gap. TR24 cyclotron

Typical Biomedical cyclotrons have energy range from 11 MeV to 19 MeV, while high energy commercial cyclotrons have > 30 MeV. In the recent years many research labs expressed interest in widening spectrum of their research capacity by complementing production of PET radioisotopes with a variety of so-called research isotopes, including classical SPECT isotopes. A number of regional radioisotope suppliers were also exploring business models which included production and supply of not only fluorine-18 based compound, but also of a variety of other isotopes, included, but not limited to I-123, Ge-68, In-111, Ga67.

In the last two years the nuclear medicine community started researching alternatives to the existing reactor based supply of Tc-99m. In 2009 ACSI, in collaboration with a number of Canadian Universities and Research Centers started exploratory work directed at the development of commercially viable technology for the production of Tc-99m using a medium

Automated high current TR19 features:	Cyclotron and Targetry Capacity:
Preset machine wake-up	Extracted current > 300 μAmp
One-button fully automated operation	Variable energy 14 MeV to 19 MeV
4-jaw collimation with operator predetermined collimator spill ratio	Beam on target 2 x 150 μAmp (> 300 μAmp in external beam line)
Real time “Beam-Target” alignment	F18 over 30 Ci in production run
Dual beam split ratio adjustment	
from 1:100 to 50:50	N13 in target ammonia > 1 Ci
Current stability ± 5%	C11 > 4 Ci, 20–40 Ci/nmol
Automated magnetic field compensation	Solid targetry

energy cyclotron. This coincided with the design completion of new medium energy, high current cyclotron. TR24, is based on the TR19 platform and utilizes main components and sub-systems of TR19 and TR30 cyclotrons. In 2010, the first TR24 was manufactured and 400 μA were achieved during factory testing. This cyclotron has rapidly become our best seller, with 10 TR24 orders received in the last two years. In 2010, ACSI was awarded $11 M through the Non-reactor-based Isotope Supply Contribution Program (NISP) to commercialize cyclotron production of Tc-99m using high current TR24 cyclotrons. The high current TR24 cyclotrons will be operational in 2012 at two pilot sites: University of Sherbrooke and University of Alberta, Edmonton. Both sites will supply copious amounts of FDG and demonstrate the feasibility of cyclotron production of Tc-99m.The Sherbrooke cyclotron was installed in February and is now being commissioned. This cyclotron is equipped with two external beam lines and a high current, 500 uAmp, solid target station. Test results and first operational experiences will be reported.

TR24 Cyclotron specifications:

Extracted current:	$>$ 500 μAmp
Energy:	16 MeV to 24 MeV (variable)
Magnet orientation:	Horizontal
Extraction:	Dual, single or multiple extraction foils
Beam lines:	Up to 6 and/or 4-position target selectors mounted on the cyclotron
Targetry:	Full range of liquid, gas and solid targetry for PET and SPECT radioisotope productio

Nuclear Medicine Review 2012, Vol. 15, supplement A

FULLY AUTOMATED PROCESSES AND INNOVATIVE μ-PET APPLICATIONS OF NOVEL LABELLED SUBSTRATES

G Brini, A Caracci, S Caria, M Fulvi

Nuclear Specialists Associated S.r.l Via Pontina vecchia Km 33,800, 00040 Ardea (Rm) Italy

[^{18}F]-Fluorodeoxyglucose ([^{18}F]-FDG) is the most common radiotracer used in PET studies in oncology. In recent years the synthesis of new and long-lived beta emitters compounds has demonstrate the usefulness of PET imaging as non-invasive diagnostic tool also in non oncologic field.

The production of radionuclides is based on a low-energy (p, n) reaction at a small-sized (16.5 MeV) GE PETtrace 10 Ci cyclotron, while the radiotracers production is performed using different automatic modules and different hot cells. Due to the fully automated process, from the radioisotopes production to the synthesis and purification of the final products, the operators are completely shielded from radiation.

In this work we describe the μ-PET preclinical applications of the fully automated synthesis of [^{64}Cu]-Copper ($t_{1/2}$ = 12.7 hours) and [^{124}I]-Iodine ($t_{1/2}$ = 4.18 days) labelled substrates and of [^{18}F]-Fluorine ($t_{1/2}$ = 110 min) based tracers, such as [^{18}F]-Fluorothymidine, [^{18}F]-FluoroDOPA, [^{18}F]-Sodium Fluoride and [^{18}F]-Fluorocholine.

A wide variety of substrates, such as functionalized chelators, peptides, antibodies and other biologically relevant small molecules, can be radiolabeled due to the well-established chemistry of [^{64}Cu]-Copper and [^{124}I]-Iodine. Moreover decay properties and long half-life of [^{64}Cu]-Copper and [^{124}I]-Iodine permits the labeled molecules to be imaged and studied over a longer time period.

The radiopharmaceutical 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine ([^{18}F]-FDOPA) has great interest in neuro-oncology because it is an aminoacid-analogue used to evaluate presynaptic dopaminergic activity. The bone imaging probe with [^{18}F]-Sodium Fluoride has been used to evaluate both benign and malignant skeletal disorders. The radiotracers [^{18}F]-Fluorocholine and [^{18}F]-Fluorothymidine have been developed as PET tracers to image proliferation *in vivo* with two different molecular pathways.

In several preclinical studies we evaluate that the μ-PET applications give the possibility to monitor different experimental situations thanks to the wide variety of radiotracers available. Due to their long half-life, [^{64}Cu]-Copper and [^{124}I]-Iodine are used to radiolabelled molecules and monitor their biodistribution at different time points. Radiolabelling of antibodies with [^{124}I]-Iodine and [^{64}Cu]-Copper was performed to evaluate the capability of radiotracers to bind and accumulate into a district of interest from 4 to 120 hours (in case of radio-iodination) and from 1 to 22 hours (in case of Copper coordination) after the injection. Data obtained from μ-PET analysis allows us to visualize the binding between molecules, while data elaboration permits the rate quantification of radiotracer uptake in the district of interest.

Due to the short half life of [^{18}F]-Fluorine, the fluorine radiotracers are not used to monitor the biodistribution over a long time period, but are employed in other PET-studies. [^{18}F]--NaF radiopharmaceutical was used to monitor the osseous tissue regeneration induced by stem cells associated to different biomaterials. The bone regeneration induced by the graft, implanted in rat calvarial defects, was monitored from 2 to 12 week after the implant. [^{18}F]-FCh and [^{18}F]-FLT PET was used to observe the cell proliferation in a luciferase transgenic mouse model, previously analyzed through *in vivo* bioluminescence imaging. [^{18}F]--FDOPA-PET was used to evaluate the therapeutic efficacy of a treatment employeed for the F98 rat glioma growth, an anaplastic tumour characterized by unfavourable clinical outcome. Our PET-data showed a linear reduction of the tumour growth in the experimental group.

In conclusion *in vivo* μ-PET analysis performed with short and long half life isotopes labelled compounds represents a safe and innovative diagnostic and non-invasive system that allows the study of several physiologic processes in small animal models reducing the time of experiment and the number of animals.

Key words: fully automated synthesis; [^{64}Cu]-Copper; [^{124}I]-Iodine; [^{18}F]-Fluorine; μ-PET Imaging

POLYMER SCINTILLATOR DETECTORS FOR TOF-PET WITH LARGE LONGITUDINAL FIELD OF VIEW

P Moskal, T Bednarski, A Heczko, M Kajetanowicz, Ł Kapłon, A Kochanowski, G Konopka-Cupiał, G Korcyl, W Krzemień, K Łojek, W Migdał, M Molenda, S Niedźwiecki, P Salabura, M Silarski, A Słomski, J Smyrski, Z Rudy, J Zdebik, M Zieliński

Jagiellonian University, Cracow, Poland

In this contribution we present a concept of the large acceptance detector systems based on the organic scintillators which in the future may allow for simultaneous diagnostic of large fraction of the human body. Novelty of the concept lies in employing predominantly the timing of signals instead of their amplitudes. The time resolution obtainable with plastic scintillators may be better than 100 ps [1] also for large detectors [2], and plastic scintillators can be produced easily in variety of shapes and dimensions.

One of the investigated detector concepts [3, 4] (called strip-PET) is shown schematically in Fig. 1. The strip-PET test chamber may be built from strips of organic scintillator forming a cylinder. Light signals from each strip are converted to electrical signals by two photomultipliers placed at opposite edges of the strip. The time difference between signals from both ends of the strip is used in order to determine the impact position of the gamma quantum and the time of the interaction of the gamma quantum in the strip is calculated as an arithmetic mean of the times measured on both edges of the scintillator. In the thin plastic scintillator strips the light signal propagates at about one-half of the speed of light in vacuum (c/2). Thus for the FWHM (Δt) equal to 70 ps the resolution of the position determination along the scintillator strip would amount to FWHM(Δl) $\approx$ 0.5 cm and the resolution in the determination of the annihilation point along line-of-response would be equal to FWHM(Δx) $\approx$ 0.7 cm. In particular, the last feature makes the solution very promising.

The plastic scintillators were so far not considered as potential sensors for PET detector due to their low density and small atomic number of elements constituting the material. The probability that two annihilation quanta react independently in *e.g.* 2.5 cm thick layer is about 16 times smaller for the plastic detector than in the detector made of LSO crystals. However, the aforementioned detector concept allows to compensate for the low efficiency. Mainly because: i) In the 3D mode the geometric acceptance of *e.g.* one meter long chamber will increase on average by a factor of about five in the comparison to the present PET detectors. This feature in combination with the five times larger longitudinal field of view causes that about 25 times more pairs of annihilation quanta will reach the detectors. Thus, the signal rate of an individual photomultiplier will be similar as in the currently produced PET scanners, but signals will be more than ten times shorter; ii) Improvement of TOF resolution from ~600 ps to ~70 ps would improve

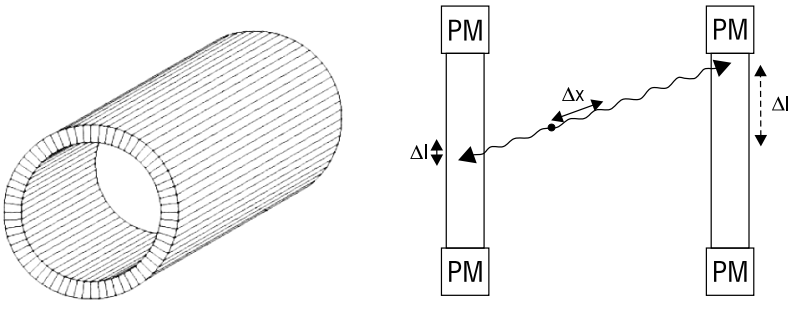


Fig. 1. (left) Scheme of the strip-PET diagnostic chamber. This solution permits for extension of the size of the scanner without a significant increase of costs. (right) Pictorial description of strip-PET concept. The hit position versus the center of the scintillator (Dl) is determined based on time difference measured on both sides of the scintillator strip, and the position (Dx) along the line-of-response is determined from time difference measured between two modules

Nuclear Medicine Review 2012, Vol. 15, supplement A

the signal to noise ratio by a factor of about eight [5]. These two effects would compensate the smaller efficiency, which in addition can also be increased by using several layers of the cylinder. Additionally: a longitudinal field of view would be more than five times larger with respect to present PET detectors allowing for imaging of the head and whole torso simultaneously. In the case of current PET scanners such image requires performance of ten independent measurements. Thus, for the whole body examination with such large detector, while leaving the current dose of radio-pharmaceutical unchanged, one can gain another factor of ten on statistics of registered events. More detailed description of the strip-PET concept and its comparison with the present state-of-art solutions, as well as the second new detector concept [3, 4] which gives a possibility for measuring the depth of interaction (DOI), will be presented and discussed.

References

1. Nishimura S et al. Nucl Instr & Meth 2003; 377: A510.
2. Sugitate T et al. Nucl Instr & Meth 1986; 354: A249.
3. Moskal P. Patent applications: PCT/PL2010/00062 (2010); PCT/PL2010/00061. 2010.
4. Moskal P et al. Bio-Algorithms and Med-Systems 2011; 7: 73.
5. Karp JS et al. J Nucl Med 2008; 49: 462.

SIMPLE PROCEDURE OF DOTATATE LABELLING WITH CYCLOTRON PRODUCED ^{44}SC AND ^{43}SC

Seweryn Krajewski[1], Izabela Cydzik[2], Kamel Abbas[2], Antonio Bulgheroni[2], Federica Simonell[2], Agnieszka Majkowska-Pilip[1], Aleksander Bilewicz[1]

[1]Institute of Nuclear Chemistry and Technology, Warsaw, Poland
[2]European Commission's Joint Research Centre, Institute for Health and Consumer Protection, Ispra Italy

Objectives: Two scandium isotopes, ^{44}Sc and ^{43}Sc, are prospective radionuclides for diagnostic imaging. ^{44}Sc ($\tau_{1/2} = 3.92$ h) and ^{43}Sc ($\tau_{1/2} = 3.89$ h) are ideal β^+-emitters in PET diagnosis. They can be used as an alternative to ^{68}Ga, because they have got better nuclear properties and form complexes of structure similar to those of ^{90}Y and ^{177}Lu, what is important in planning radionuclide therapy [1]. ^{44}Sc can be obtained from ^{44}Ti/^{44}Sc generator. Unfortunately, prohibited cost of production (c.a. 500 000 $ for 1 GBq) and limited availability of the long-lived ^{44}Ti complicate further development in the ^{44}Sc-radiolabeled compounds [2]. The promising method for ^{44}Sc production is irradiation of ^{44}Ca target in small cyclotrons. The aim of our work was to optimize the parameters of $^{44}CaCO_3$ irradiation. The second aim was to develop a simple procedure of ^{44}Sc separation from the calcium target and labelling of the DOTATATE. These results were transferred on ^{43}Sc production from natural calcium carbonate in reaction ^{40}Ca(α,p)^{43}Sc.
Methods: In the present work, we used highly enriched $^{44}CaCO_3$ (Isoflex, Russia) and super pure $^{nat}CaCO_3$ (Merck). The irradiations were performed with the Scanditronix MC 40 cyclotron of the Joint Research Centre (Ispra, Italy). $^{44}CaCO_3$ targets of 2 mg in form of dry powder were irradiated by protons in the energy range from 5.5 to 23 MeV for cross section calculations. The activity of the samples was measured with high resolution γ-ray spectrometers.
5–10 mg of the $^{44}CaCO_3$ target and 20 mg of the $^{nat}CaCO_3$ target were irradiated for labelling experiments. The target was dissolved in 1 ml of 0.1 M HCl. Then, the solution was passed through a column filled with iminodiacetic resin Chelex 100. After adsorption of ^{44}Sc, the column was washed with 0.01 M HCl and the effluent containing enriched calcium was collected for further irradiations. The ^{44}Sc was eluted with 1 M HCl in 0.5 ml fractions.
^{44}Sc-DOTATATE was synthesised with different amounts of the peptide and in different pH in acetate buffer. The solution was heated for 30 min at 95°C. The same procedure was used for ^{43}Sc-DOTATATE synthesis.
Results: The analysis of the results obtained from optimization studies shows that in the proton energy range of 9-10 MeV on the target, the amount of ^{44}Sc reaches the maximum with a minimum production of ^{44m}Sc impurity that is estimated to (0.16%). The ^{44}Sc activity obtained after irradiation of 5 mg target was around 40 MBq for 1 h irradiation and 10 μA protons current, while ^{43}Sc activity obtained of 20 mg target was 16 MBq for 2 h irradiation and 0.3 μA protons current.
The separation with Chelex 100 resin is very good. More than 60% of ^{44}Sc activity was eluted with 1 M HCl in three initial 0.5 ml fractions. The level of Ca^{2+} in ^{44}Sc reaction vials was less than 1 ppm. First experiments on the recovery of the calcium target showed that up to 50% of ^{44}Ca could be recovered.
We received high yield of labelling DOTATATE with ^{44}Sc and ^{43}Sc, for 15 nmol it is higher than 99%. The target was recovered, irradiated and ^{44}Sc was separated with Chelex 100 resin and DOTATATE was labelled with the yield of 99.5%. We checked the possibility of ^{44}Sc-DOTATATE synthesis without calcium separation and using C18 Sep-Pak column for purification of the labelled bioconjugate.
Conclusions: The low-energy irradiation of ^{44}Ca gives opportunity to produce GBq activity levels of ^{44}Sc. The proposed separation process of ^{44}Sc and ^{43}Sc from calcium target is simple and fast. The obtained ^{44}Sc and ^{43}Sc can be used instead of ^{68}Ga in PET diagnosis and planning radionuclide receptor therapy with ^{177}Lu- and ^{90}Y. The synthesis and purification procedure of ^{44,43}Sc-DOTATATE can be simplified using C18 Sep-Pak columns.
Research Support: This study was supported by Institute of Nuclear Chemistry and Technology in Warsaw, Poland and by European Commission's Joint Research Centre in Ispra, Italy.

References

1. Majkowska-Pilip A, Bilewicz A. J Inorg Biochem 2011; 105: 313–320.
2. Zhernosekov K, Bunka M, Hohn A, Schibli R, Türler A. J Label Compd Radiopharm 2011; 54: S239.

Nuclear Medicine Review 2012, Vol. 15, supplement A

COMPTON IMAGING WITH LIQUID XENON AND ^{44}SC: RECENT PROGRESS TOWARD 3 GAMMA IMAGING

T Oger, WT Chen, JP Cussonneau, J Donnard, S Duval, J Lamblin, O Lemaire, AF Mohamad Hadi, P Le Ray, E Morteau, L Scotto Lavina, J S Stutzmann, D Thers

SUBATECH, UMR 6457, Ecole des Mines de Nantes, CNRS/IN2P3 and Université de Nantes, 44307 Nantes, France

Subatech began a new medical imaging technique by beneficiating from the development of Arronax cyclotron around the Nantes city in France. This new technique is called the 3 gammas imaging. The main idea is to try to locate each decays of Sc44 radionuclide individually with a 3D position resolution beneath the centimeter. This breakthrough in instrumentation technique should be demonstrated by the help of the Xemis 1 prototype which is a high sensitive liquid Xenon Compton telescope. The good properties of ultrapur liquid Xenon as detection medium (high atomic number, high density, high emission light and ionization yield) leads to a construction of a sensitive monolithic and homogeneous volume of detection with an adaptable geometry. Thanks to an ultra low noise front end electronics operating at liquid Xenon temperature (around 100 electrons NEC) and a fast UV sensitive PMT, high spatial resolution and high energy resolution are achievable in 3D. This is particularly important for Compton imaging since all interactions in the medium have to be identified to reconstruct the direction of arrival of the gamma ray.

A small prototype with an active area of 1''x1'' is now in test at Subatech and shows promising results with a 511keV source from ^{22}Na. All the cryogenic system is fully operational with a high purification rate and shows a very good stability. A new geometry Xemis 2 is currently under development to adapt this imaging technique to the small animal size.

PET/MR: THE MOLECULAR IMAGING DREAM TEAM

Piotr Maniawski

Philips Healthcare, Cleveland, Ohio

In the last decade, PET/CT imaging systems have become an essential tool for staging and restaging of various types of malignant tumors and has been shown to have a significant impact on patient management. PET/CT also shows exciting potential in predicting the response to treatment for several types of cancer, including metastatic breast cancer, lung cancer, lymphomas and others.

The clinical and commercial success of combined PET and CT imaging modality was primarily driven by the complementary character of data derived from each of the imaging modalities: anatomical detail of the CT and metabolic, molecular level information delivered by PET imaging. In addition, the clinical workflow improvement and ease of use of the combined system can't be overlooked.

Integration of CT and PET addressed some of the critical questions in diagnosis and staging of the disease: combination of lesions detectability (with FDG PET) and their localization (with CT). It also paved the way to further integration of other imaging modalities. For example, more and more SPECT cameras are being replaced by combined SPECT/CT systems.

With the evolution of MR imaging techniques, MR imaging studies can provide additional diagnostic information regarding soft-tissue analysis, tumor detection, tissue characterization and functional imaging. It is not uncommon today for oncology patients to have both a PET/CT and MR imaging scans providing complementary diagnostic data. In some cases, the diagnostic value of MR for detection and staging of cancers can be superior to CT studies, which limits the value of the diagnostic CT studies that can be performed in combination with the PET/CT study to a simple anatomical localization and attenuation correction scan.

This promise to provide a comprehensive picture of patient anatomy (imaged by MR) combined with multi parameter lesion characterization (imaged by PET and advanced MR imaging techniques) makes an integrated PET/MR system a leading candidate for the molecular imaging 'dream team'.

Nuclear Medicine Review 2012, Vol. 15, supplement A

CORTICAL ACTIVITY IN BILATERAL COCHLEAR IMPLANT USERS

Katarzyna Cieśla[1], Julian Matthews[2], Rohini Aggarwal[3], Kevin Green[4]

[1]MSc, School of Psychological Sciences, University of Manchester, UK; Bioimaging Research Center, Institute of Physiology and Pathology of Hearing, Warsaw, Poland
[2]Senior Lecturer, School of Cancer Enabling Sciences, MAHSC, University of Manchester
[3]Research Fellow, Central Manchester University, NHS Foundation Trust
[4]Consultant ENT Surgeon, University of Manchester, MAHSC, Central Manchester NHS Foundation Trust

Introduction: The study aims to compare cortical changes observed in recipients of bilateral cochlear implants (CI) to normal hearing controls (NH) in response to simultaneous binaural auditory stimulation.

Materials and methods: Six adult individuals with post-lingual deafness, experienced bilateral cochlear implant users, and six normally hearing volunteers participated in the study. All subjects had up to twelve PET scans (using $[^{15}O]H_2O$) in two scanning sessions on the same day. During each scan one of three auditory stimuli (randomised), including BKB Sentences, Reversed BKB Sentences and Silence was delivered (Bench et al.1979). Images of the radioactivity concentration during 90 seconds following arrival of $[^{15}O]H_2O$ in the brain were reconstructed (FBP, OSEM, OSEM+PSF); SPM8 software (The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm/ software/spm8) was used to perform data pre-processing and statistical analysis (factorial design). An additional statistical comparison with left-right flipped images served to assess any lateralisation of activations. Region of interest analysis (ROI) using the Automatic Anatomical Labelling Atlas and an in-house programme was carried out to verify the SPM findings. The following contrasts were employed to investigate within- and between-group effects: (1) Sentences vs. Silence, (2) Sentences vs. Reversed Sentences, and (3) Reversed Sentences vs. Silence. The study was approved by the Cumbria and Lancashire Research Ethics Committee B and the Administration of Radioactive Substances Advisory Committee. All participants provided an informed consent.

Results

Sentences *vs.* Silence

In subjects with normal hearing significant activations were found in bilateral superior temporal lobes (Brodmann's areas [BA] 21 and 22), the left middle temporal lobe (BA 21), and the right superior temporal pole (BA 22) ($p < 0.001$, Family-wise error-corrected [FWE]). In cochlear implant-users bilateral middle temporal lobes were recruited (BA 21,22), as well as the left superior temporal pole (BA 21) and the right superior temporal lobe (BA 21) ($p < 0.001$, FWE). ROI analysis showed activations in bilateral superior temporal lobes in both groups, and bilateral middle temporal lobes and superior temporal poles in cochlear implant users ($p < 0.001$, Sidak correction).

Reversed Sentences vs. Silence

Both groups showed activations in bilateral superior temporal lobes (BA 21,22) ($p < 0.001$, FWE); patients additionally recruited bilateral middle temporal lobes (BA 21) ($p < 0.001$, FWE). Regions-of-interest approach revealed recruitment of bilateral superior temporal lobes in both groups and the left Heschl gyrus in normally hearing individuals ($p<0.001$, Sidak correction).

Sentences *vs.* Silence/Reversed Sentences *vs.* Silence

Further voxel-by-voxel analysis revealed larger and more diffuse activations in various temporal regions in CI-subjects when compared to normally hearing individuals in all three contrasts ($p < 0.001$, FWE). There was no hemispheric lateralisation found for either of the groups and comparisons.

Sentences *vs.* Reversed Sentences

Normally hearing subjects had activations in the left-hemisphere superior temporal pole (BA 38) and the superior temporal lobe (BA 21,38) ($p = 0.008$, FWE), whereas cochlear implant recipients recruited bilateral middle temporal lobes (BA 21) ($p = 0.04$ FWE on the left and $p < 0.001$ FWE on the right), middle temporal poles (BA 21) ($p < 0.001$, FWE), and the left

superior temporal pole (BA 38) ($p < 0.001$, FWE). Although visual inspection suggested more diffuse and more significant activations in the left hemisphere in both NH and CI-users, lateralisation analysis did not reach statistical significance. ROI approach revealed no significant activations in this high-level contrast

Conclusions: Users of bilateral cochlear implants with post-lingual deafness showed to process speech stimuli using mechanisms similar to normally hearing individuals, engaging areas in bilateral temporal lobes. Activations found in the study were consistently more diffuse in CI-patients, compared to normally hearing controls. This might imply that recipients of cochlear implants require larger neuronal contribution to process speech. Left-hemispheric lateralisation of supra-phonological features of language (contrast Sentences *vs.* Reversed Sentences) was suggested in both groups but the analysis did not reach statistical significance.

Nuclear Medicine Review 2012, Vol. 15, supplement A

SYNTHESIS AND *IN VITRO* AND *IN VIVO* EVALUATION OF NEW $^{67/68}$GA-SEMICARBAZONE COMPLEX: POTENTIAL PET/SPECT TUMOR IMAGING AGENT

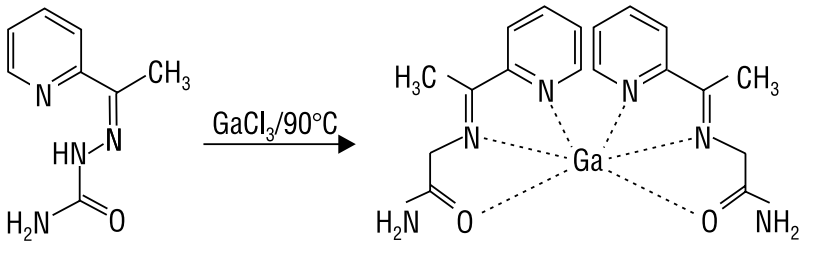
I Al Jammaz, B Al-Otaibi, N AlHokbany, S Okarvi

Cyclotron and Radiopharmaceuticals Department, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Kingdom of Saudi Arabia

Heterocyclic thiosemicarbazones, semicarbazones and their metal complexes have been extensively investigated as potential antitumor agents. Most studied thiosemicarbazones and semicarbazones were the pyridine-based compounds which might be attributed to their resemblance to pyridoxal metabolites that attach to co-enzyme B6-dependent enzymes and cause enzyme inhibition. Varieties of metallic positron emission tomography (PET) and single photon emission computed tomography (SPECT) radionuclides were incorporated into thiosemicarbazones chelates. Among these radionuclides, gallium-67/68 ($^{67/68}$Ga) and copper-62/64 ($^{62/64}$Cu) have shown considerable success for targeting tumor xenografts in athymic mouse models. Recently, radiolabeled ^{67}Ga-thiosemicarbazone complex was synthesized with high radiochemical yield and purity. Biodistribution study in fibrosarcoma bearing mice revealed specific tumor accumulation after 2 h post injection which may suggest that ^{68}Ga is a better candidate for tumor imaging than ^{67}Ga.

Due to the well known coordination chemistry of gallium, high stability of Ga^{III}-semicarbazone complexes as well as their enhanced anti-neoblastic activity and in an attempt to develop new radiotracers with favorable biochemical properties, we here report the synthesis, characterization and preclinical evaluation of new $^{67/68}$Ga-2-acetylpyridine 4,4-dimethylsemicarbazone ($^{67/68}$Ga-APSM) as a potential PET and SPECT tumor imaging agent. The synthetic approaches for the preparation of $^{67/68}$Ga-APSM chelates were simple and straightforward. Acetate buffer solutions of $^{67/68}GaCl_3$ (37–300 MBq, prepared according to well-established procedure) were reacted with 2-acetylpyridine 4,4-dimethylsemicarbazone dissolved in absolute ethanol (pH = 4.5). The reaction mixture was heated at 90°C and monitored by means of TLC and HPLC at different time intervals (15–60 min). Work up of these reactions gave $^{67/68}$Ga-APSM complexes in quantitative radiochemical yields and purities as assessed by TLC and HPLC in less than 60 min. The proteolytic degradation of these complexes were determined in human plasma and revealed that these radiotracers remained sufficiently stable during incubation at 37°C for at least 2 h.

In vivo biological characterizations were carried out in normal Balb/c mice, revealed rapid blood clearance of radioconjugates with equal excretion by the urinary and hepatobialary systems. Biodistribution studies in nude mice bearing tumor are in progress.



Scheme 1. Synthesis of of Ga-APSM complexes (Ga=$^{nat/67/68}$Ga)

THE EVALUATION OF FLUORESCENT AND F-18 LABELLED PEPTIDE SEQUENCES TARGETING APOPTOTIC CELLS *IN VITRO* AND *IN VIVO*

Janice Kapty[1], Melinda Wuest[1, 2], Frank Wuest[1, 2], John R. Mercer[1, 2]

[1]Department of Oncology, Faculty of Medicine and Dentistry, University of Alberta
[2]Edmonton P.E.T. Center, Cross Cancer Institute, Edmonton, Alberta, Canada

Introduction: Programmed cell death (apoptosis) is both a natural process in organ and tissue development and homeostasis and a contributor to human pathology in a variety of diseases. In addition, the induction of apoptosis is a desired aim in cytotoxic therapies used in the clinical management of cancer. Despite its importance we do not yet have a clinically acceptable, non-invasive imaging modality targeting apoptosis. A variety of PET imaging agents have been investigated for clinical imaging of apoptosis (1) but none has yet achieved the status of a routine agent with the required targeting selectivity and pharmacokinetic properties. Recently a series of hexapeptides was found to possess strong binding affinity for cell surface phosphatidylserine (PS) expression based on phage display analysis (2). The goal of the present study was to evaluate these peptides *in vitro* and *in vivo* as potential PET radiotracers.

Methods: A series of peptides (LIKKPF, PGDLSR, CLIKKPF, CPGDLSR) were modified by N-terminus attachment of fluorescent 5-carboxyfluorescein (5-FAM) and evaluated in *vitro* for binding using an immobilized PS plate assay, a PS liposome cell-mimic assay and normal and apoptotic Jurkat cells. The peptides were labelled with F-18 via prosthetic group chemistry using N-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]-SFB) for peptides LIKKPF and PGDLSR and using N-[6-(4-[^{18}F]fluorobenzylidine)aminohexyl]maleimide ([^{18}F]-FBAM) for the thiol containing peptides CLIKKPF and CPGDLSR (3). The [^{18}F]FBAM labeled peptides were further evaluated for binding on normal and apoptotic Jurkat cells and in small animal PET imaging studies using a murine EL4 lymphoma tumor model in C57BL6 mice with chemotherapy induced apoptosis *in vivo* (100mg/kg cyclophosphamide and 38mg/kg etoposide on two consecutive days) validated with the TUNEL assay.

Results: In the plate-based assay all four fluorescent-labeled peptides bind with some selectivity to PS relative to phosphatidylcholine (PC) with estimated K_D values between 0.4–7.9 μM. Fluorescent labeled annexin-V (FITC) showed an estimated K_D value of 6.6 nM in this assay. Liposomes with 10% PS/90% PC in the membrane bilayer showed fluorescence from bound peptides and annexin-V (FITC) by confocal microscopy while 100% PC liposomes showed no fluorescence. Binding of the fluorescent peptides and annexin-V (FITC) was also observed selectively in apoptotic Jurkat cells. Radiolabelling of the hexapeptides LIKKPF and PGDLSR with the prosthetic group [^{18}F]-SFB led to only low radiochemical yields ($< 20\%$) due to poor reactivity and lack of chemoselective attachment to the terminal amine group. The cysteine modified heptapeptides CLIKKPF and CPGDLSR on the other hand were radiolabelled at high radiochemical yield ($> 95\%$) and chemoselectivity at the thiol group of the terminal cysteine when reacted with [^{18}F]-FBAM. The [^{18}F]-FBAM labelled peptides showed binding to normal Jurkat cells ([^{18}F]-FBAM-CLIKKPF 7.6 ± 2.0 and [^{18}F]-FBAM-CPGDLSR 1.6 ± 0.8 %ID/mg protein ($n = 3$) after 15 min), which increased in apoptotic Jurkat cells (16.7 ± 2.2 ($p < 0.05$) and 3.3 ± 2.4 %ID/mg protein).

Mouse biodistribution studies in tumor mice were unremarkable, exhibiting rapid blood clearance and shared excretion by hepatobiliary and renal routes. Both [^{18}F]-FBAM labelled peptides were analyzed by 60 minute dynamic small animal PET. In untreated EL4 tumors [^{18}F]-FBAM-CLIKKPF showed an initial uptake resulting in a standardized uptake value (SUV_{3min}) of 0.51 ± 0.04 which decreased to 0.13 ± 0.01 ($n = 3$) after 60 min. For muscle tissue SUV_{3min} 0.29 ± 0.04 and SUV_{60min} 0.09 ± 0.01 was determined. [^{18}F]-FBAM-CPGDLSR possessed lower EL4 tumor uptake levels: SUV_{1min} 0.35 ± 0.02, SUV_{3min} 0.17 ± 0.02 to SUV_{60min} 0.06 ± 0.01 ($n = 3$). In apoptotic EL4 tumors no significant difference in radioactivity uptake profile was observed for either [^{18}F]-FBAM-labelled peptides. The poor targeting may in part be due to the relatively rapid metabolism of both radiolabeled peptide sequences *in vivo* as determined in mouse plasma by radio-TLC (1 to 25% intact after 15 min).

Nuclear Medicine Review 2012, Vol. 15, supplement A

Conclusions: These studies have examined the first peptide-based probes designed for PET imaging of apoptosis. While the chosen peptide sequences show promise in *in vitro* studies, retaining their selective binding ability toward PS, they did not accumulate in apoptotic mouse tumors *in vivo*. Future studies to identify PS binding peptides stabilized against enzymatic degradation are warranted.

References

1. Kapty et al. Cancer Biother Radiopharm 2010; 25: 615.
2. Burtea et al. Mol Pharm 2009; 6: 1903.
3. Kapty et al. Appl Radiat Isot 2011; 69: 1218.

DEVELOPMENT OF NEW PET RADIOPHARMACEUTICALS BASED ON ^{68}GA FOR DIAGNOSIS AND MONITORING OF THE THERAPEUTIC RESPONSE

D Niculae, I Esanu, I Ursu, P Albu

Horia Hulubei, National Institute for Physics and Nuclear Engineering (IFIN-HH), Department of Radioisotopes and Radiation Metrology, Magurele, Ilfov, Romania

^{68}Ge/^{68}Ga generators provide cyclotron-independent access to positron emission tomography (PET) radiopharmaceuticals. The 270 days half-life of the parent allows the use of the generator for a long period, potentially up to 1 year or even longer. The 68 min half-life of the ^{68}Ga matches the pharmacokinetics of many peptides and other small molecules owing to rapid diffusion, localization at the target and fast blood clearance. The ^{68}Ga solutions eluted from a tin dioxide based generator are usually containing small amounts of other cations (metallic impurities such as Fe, Zn, Ge, Sn) and should be purified prior the radiolabelling of peptides but fractionated elution could also be used for synthesis, when short reaction time is needed and further purification is envisaged. The elution profile and yield was followed over 1 year. The elution yield is highly dependent on HCl concentration; 0.6 M HCl was used for elution (yield > 75%) followed by 5–7 mL 1M HCl washing. Ge-68 content in the eluate was less than 0.002% over 1 yr. The solution of Ga-68 coming from generators is in stable chemical form, cation Ga(III), which can precipitate and hydrolysis at pH 4–7 in the insoluble form, trihydroxide, if the concentration exceeds the nanomolar level. Ga(III) is suitable for the complexation with chelates conjugated with peptides. The purified eluate was used for radiolabelling of DOTA-VIP. The radiolabelling parameter were establish, the most critical being pH (3.8–4), temperature (95–100°C) and the buffer (only non-ionic buffers should be used).

The results obtained after fractioned elution and the purification of eluates on a cation exchange column, anion exchange column or combining a cation and an anion exchanger of a tin dioxide based ^{68}Ge/^{68}Ga generator are presented. All this methods for concentration and purification are feasible, but each of them is presenting some advantages over the others. Fractionated elution leads to the concentration of the most the activity (80–95%) in a small volume, 1.5–2 mL but no purification is done. The purification using a cation exchanger leads to 60–80% recovery percentage of ^{68}Ga and the process took 35 minutes but this process involves the use of acetone. The recovery of gallium-68 from the anion exchanger column in 1 mL water was 84–90%, the process is taking less than 30 min but the iron separation remains an issue. By combining the cation and anion exchange processes, 90–94% of the uploaded activity was recovered but the process took 40 min. Depending of the eluate postprocessing method the radiolabelling of DOTA-VIP yield was 60–80% (A), 10–40% (C) 50–70% (C+A) while the radiochemical purity of ^{68}Ga-DOTA-VIP, after SPE purification was 96, 92% and 95% respectively.

We also present the preliminary evaluation of an organic matrix based ^{68}Ge/^{68}Ga generator, its elution profile and yield. The generator was eluted daily, eluent 0.05 M HCl, 1 mL/min; the yield was ranged between 66–93% (10 elutions), average 78%. The elution profile show about 70% of the activity was found in 2 mL eluate and up to 90% in 3 mL.

Nuclear Medicine Review 2012, Vol. 15, supplement A

THE ENVISION PROJECT

Manuela Cirilli, Manjit Dosanjh (on behalf of the ENVISION collaboration)

CERN, 1211 Geneva 23, Switzerland

Hadron therapy is a highly advanced technique of cancer radiotherapy that uses beams of charged particles (ions) to destroy tumour cells. While conventional X-rays traverse the human body depositing radiation as they pass through, ions deliver most of their energy at one point. Although hadron-therapy with protons and light ion beams was proposed for the treatment of cancer sixty years ago, its clinical implementation has been slow, and only since the 1990's have hospital-centred multi-room treatment facilities existed with vertical beam lines and rotating gantries suitable for clinical therapy.

To date, protons and carbon ions have been used to treat about 80.000 and 8.000 patients respectively and the number of hospital-based multi-room centres either running or in construction is almost thirty centres worldwide. Moreover, seven companies offer turn-key solutions featuring either proton or carbon ion accelerators, the associated beam transport lines and treatment rooms - equipped with moving beds and precise alignment systems, and sophisticated treatment planning systems (TPSs).

The conventional methods for the assessment of patient positioning used in X-ray based radiation therapy rely on the transmission of a non-negligible fraction of the treatment beam through the patient. This allows for the simple reconstruction of patient position based on bony anatomy or fiducial markers. Such techniques are not applicable in hadron-therapy, whose remarkable advantage is that the energy deposited by a pencil hadron beam increases in front of the target and, after the "Bragg peak", sharply decreases behind the target, where almost no exit dose (for protons) or a small dose (for carbon ions) is deposited.

Hadron therapy is most advantageous once the position of the tumour is accurately known, so that healthy tissues can be protected. In addition, accurate positioning is a crucial challenge for targeting moving organs and for adapting the irradiation as the tumour shrinks with treatment. Therefore, quality assurance becomes one of the most relevant issues for an effective outcome of the cancer treatment.

In order to improve the quality assurance tools for hadron therapy, ENVISION is developing solutions for:

— real-time non invasive monitoring;
— quantitative imaging;
— precise determination of delivered dose;
— fast feedback for optimal treatment planning;
— real-time response to moving organs;
— simulation studies.

Striving for precision

Positron Emission Tomography (PET) is the only physiological real-time non-invasive monitoring tool available. During charged particle therapy, radioactive isotopes do not have to be injected, as is the case for normal PET imaging, since they are naturally generated in the irradiated tissues. The radioactive isotopes emit positrons that interact with tissues producing a pair of photons. The PET detector looks for two almost simultaneous photons to identify the origin of the positron. Each photon needs a certain time, called Time-Of-Flight, to travel from the emission point to the detector. A fast and accurate measurement of the TOF difference between the two photons allows to better pinpoint the origin of the initial radiation, and therefore to improve the quality of the image.

A second promising way to better monitor the dose in real time is the detection of single photons and charged particles emitted almost instantaneously in the irradiated tumour.

These methods require the development of innovative detectors and dedicated recording electronics, both tackled by ENVISION.

Moving targets

In the field of cancer diagnostics, a major advance over still imaging is represented by PET coupled with a new technique called Four- Dimensional Computer Tomography (4DCT): this cutting

edge technology allows to capture the movement of organs as well as the changes in position and shape of the tumour. 4D PET/CT has a huge potential to improve the current tools used to compensate for organ motion during irradiation. ENVISION explores the feasibility and the clinical relevance of 4D PET/CT application for hadron therapy, and develops innovative technologies and methods for optimizing the quality of the images acquired.

Towards a global treatment planning

ENVISION's ultimate goal is to use the wealth of information provided by these novel imaging techniques to optimise treatment planning. This is an essential step to bring the technology out of the research environment and into the clinical world. ENVISION will develop tools to automatically analyse real-time monitoring images and use the information gathered to give feedback on how to continue the treatment. Since different treatment sites have different set-ups, ENVISION is aiming to develop and build portable devices to measure the specific characteristics of each site and use them to fine-tune the therapy.

Models needed

Accurate numerical simulations are needed by all ENVISION tasks to optimise the design of the detectors, to develop software that can reconstruct the dose map from the images collected, and to assess the accuracy of real-time dose monitoring. ENVISION will implement full simulations of the detailed physics processes that lead from the dose deposition to the recorded image. A fast dedicated simulation tool suitable for use in treatment planning is also being implemented.
The ENVISION project just entered the second half of its 4-year funding, and all the R & D activities produced first encouraging results which will be discussed in this talk.

Acknowledgement: The abstract is submitted on the behalf of the ENVISION project, which is co-funded by the European Commission under FP7 Grant Agreement No 241851.

Nuclear Medicine Review 2012, Vol. 15, supplement A

[18F]FDG PRODUCTION FACILITY AT THE JOINT RESEARCH CENTRE CYCLOTRON (ISPRA SITE — ITALY)

K Abbas[1], F Simonelli[1], N Gibson[1], U Holzwarth[1], A Pecorale[2], F Barberis Negra[2]

[1]European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Via E. Fermi 2479, T.P. 500, 21027 Ispra (VA), Italy
[2]GE Healthcare, Via Galeno 36, 20126 Milano, Italy

Abstract

Nuclear Medicine has been a fundamental tool for many years for cancer treatment. In recent times, Positron Emission Tomography based on the cyclotron-produced radiotracer 18F has significantly contributed to the development of medical imaging in oncology, and combined with CT scanning (PET- CT) has become one of the more widely used medical technologies. The Joint Research Centre (JRC) Cyclotron of the European Commission (Ispra site) is one of a very limited number of such research facilities in the EU. Its characteristics allow the production of a wide range of radioisotopes and its seven beam-lines make possible the setting up of many different experiments. This allows it to support research in many different areas, the most important of which at the present time is research for policy development regarding the new field of nanotechnology.

The JRC Cyclotron is a Scanditronix MC40 model with variable energy. It accelerates protons, deuterons, alphas and Helium-3 ion particles. For protons, the maximum energy is 40 MeV and the maximum extracted current is 60 μA.

The JRC Cyclotron is successfully used for routine [18F]FDG production in compliance with the Marketing Authorization under a commercial partnership between JRC and General Electric Healthcare (GE HC). The commercial production has been operational since April 2004 without any significant interruption. This radiopharmaceutical site has been the first producing centre authorised in Italy. About 18F production, the cyclotron is running every night for about 6 hours. The [18F]FDG radiopharmaceutical is distributed to hospitals and diagnostic centres in the north and central regions of Italy. The radiopharmaceutical is commercially recorded under the brand name SteriPET. This commercial activity does not interfere with other research projects that normally take place during daytime working hours.

As regards to [18F]FDG commercial production, JRC is responsible for 18F supply and for radioprotection support while GE HC is responsible for the [18F]FDG synthesis and distribution to hospitals. The production facility is located inside the controlled area of the cyclotron building. It comprises the target for 18F-Fluoride production, two automated synthesis modules and an automated dispensing unit, installed in three separate hot-cells. The quality control of the produced [18F]FDG is carried out according to the SteriPET Marketing Authorization. GE HC, after the radiopharmaceutical site of Ispra, has developed other 3 production facilities around Italy in collaboration with national research centres or private companies.

The complete [18F]FDG production facility, being located in the cyclotron controlled area (radioprotection regulations), is in depression with respect to the atmosphere. The Clean Room where the [18F]FDG is synthesised and sterilised is in over pressure with respect to other areas of the facility (pharmaceutical regulations). The two synthesis modules and the [18F]FDG dispenser unit are fully controlled and monitored by computers. In the area dedicated to QC all instruments and equipment are automated.

A synthesis cycle is accomplished in about 35 min. The preparation of the synthesis module does not exceed 15 min. After synthesis, the radiopharmaceutical is transferred to the dispensing unit by helium pressure. The yield of [18F]FDG is around 75% (decay-corrected).

In the dispensing unit, a final sterilisation cycle is performed. Up to 17 vials of [18F]FDG can be dispensed and sterilised in a single production run. The dispensing process is based on dispensing under laminar flow and sterilisation in the final vials with steam at 135°C. The dispensing process lasts a maximum of 30 min depending on the number of vials. After sterilisation, vials are remotely inserted in lead containers inside the hot cell and then transferred through a pass through box into the shipment room. The software of the synthesis module, dispenser and QC equipment are also designed according to GMP guidelines and all relevant parameters are recorded and stored and can be reviewed at any time.

Quality controls on the product is carried out according to the SteriPET Marketing Authorization where the specifications of the product as a radiopharmaceutical are presented. About 30 minutes are necessary for completion of those quality controls required for the release of the radiopharmaceutical. Radionuclide, chemical and radiochemical purity controls are carried out. The [^{18}F]FDG can be released before completion of the biological analysis. As regards to the site production efficiency, the annual production plan for the period March 2011 – March 2012 was defined and approved. Over this period, more than 400 productions were carried out, in which 260 GBq/run of ^{18}F have been produced.

Nuclear Medicine Review 2012, Vol. 15, supplement A

THE PLAN AND DESIGN OF A GMP PET FACILITY: CHALLENGES AND PITFALLS

C Gameiro[1], J M Geets[1], D Blampain[1], F Devillet[1], H Prpic[2], H Amaral[3], A Amaral[3]

[1]Ion Beam Application (IBA), Louvain la Neuve, Belgium
[2]Ruđer Medikol Cyclotron Ltd., Zagreb, Croatia
[3] PositronPharma S.A., Santiago, Chile

Radiopharmaceuticals (RP) are a group of human parenteral medicines that are regulated by a number of directives and regulations. Most of these rules do not consider the special character of RPs such as the short half-life, small scale preparation, parametric release (no guarantee of sterility), low toxicity of the final product besides the radiation issues. In addition, the regulatory environment is still not harmonized at the worldwide level leading to different local interpretations and misunderstandings.

The scope of the facility may range from a dedicated product to a multipurpose site that manufactures various RPs for commercial and/or clinical and/or research applications (categories I-V) [1]. Irrespective to the type of facility crucial factors have to be considered: the current regulatory climate for PET drug production [GMP (*Good Manufacturing Practice*], industrial hygiene and radioprotection); radiation safety issues; effective production flow (*i.e.* optimization between the space, people and material flow); sufficient and qualified personnel [2, 3]. A primary element to be prepared is a complete risk assessment covering the GMP risks as well as the operator and public safety. This evaluation may impact final layout and design as well as the scope and type of equipment and procedures required.

A detailed project design is then compiled for a tender call to local building companies. In this file, complex items such as radiation protection; Heating Ventilation Air-conditioning system (HVAC) system and clean rooms and the utilities (electricity, water, gases, etc) have to be included. Most importantly, besides the cyclotron, other equipment such as shielded cells, synthesizers, dispensing systems, quality and radiation monitoring equipment should be integrated into the pharmaceutical classified environment which is within the radiation controlled area. User Requirement Specifications (URS) are required for all the equipment and installations, and should be agreed upon between project leader and end-user. A set of documentation has to be prepared including radiation protection and pharmaceutical-related protocols and procedures (validation master plan; site master plan; installation, operation, performance qualification; standard operating and working procedures etc...). Staff training and education are essential GMP requirements as well as the qualification and validation work of the facility and of critical equipment before applying for the pharmaceutical certification and market authorization (if applicable).

Due to their complex and multidisciplinary nature such endeavors may fail for several reasons. The first one is the lack of a task force in place where the stakeholders and experts in all related disciplines are put together to evaluate the feasibility and viability of the project at the beginning. Second reason for failure is to select a company without a track record of projects of the same kind or to choose the smallest budget without considering the extent of the work. Another frequent cause of failure is the poor definition of the goals of the PET Center which will create frustration, delays and over cost. Extra space should then be provisioned for future developments rather than adding it later at higher cost. Another point not to be neglected is the need for a centralized project management to coordinate the various suppliers working as an interface in all aspects of the project and dealing with the construction, the delivery and installation schedule.

In conclusion, global support and availability of company experts during the construction, installation and commissioning phases are fundamental elements for a successful project. All the required documentation for the licenses, qualification and validation support as well as the training program must be clearly discussed in the global scope of the project to avoid delays. Having real experts around the table will ensure design with efficient flow of people, material, waste and enough ergonomic for the operation leading to project achievement on budget and on time within the restrictive regulatory environment for PET RPs production.

References

1. IAEA. Technical reports series 471: "Cyclotron produced radionuclides: guidelines for setting-up a facility" 2009.
2. Jacobson MS, Hung JC, Mays TL, Mullan BP. Mol. Imaging & Bio 2002; 4: 119 127.
3. Elsinga P, Todde S, Panuelas I, Meyer G, Farstad B, Faivre-Chauvet A, Mikalojczak R, Westera G, Gmeiner-Stopar T, Descristoforo C. Eur. J. Nucl. Med. Mol Imaging 2010; 37: 1049 1062.

Nuclear Medicine Review 2012, Vol. 15, supplement A

ESTABLISHING A PET RESEARCH CENTER IN ZAGREB, CROATIA. STATUS AND PROGRESS REPORT

Alfred Švarc

Rudjer Boskovic Institute, Zagreb, Croatia

Completion and opening of a commercial FDG production facility at Rudjer Boskovic Institute, Zagreb, Croatia ensured a continuous, reliable daily supply of radioactive compound at site. This has laid foundations for establishing a Centre for nuclear molecular diagnostics which first uses already available FDG, but later we also plan to synthetize other F18 radiopharmaceuticals. In the long run it is anticipated that we shall expand our activities to other positron-emission isotopes like C11. A ClearPet camera has been purchased, delivered, tested and correlated with PMOD image analysis software. We report on the present operational status of facility, we show first preliminary results, and offer our projections for further development in scientific and organizational sense. The final aim of this facility is to grow into a strong research center with good scientific collaboration with other R & D organizations of the region.

PRECLINICAL METABOLIC IMAGING WITH PET TO MONITOR TUMOUR RESPONSE TO THERAPY

Dmitry Soloviev, David Lewis, Kevin Brindle

Cambridge Research Institute, Cancer Research UK, Li KaShing Centre, Robinson Way, CB2 0RE, Cambridge, United Kingdom

Introduction: Preclinical PET imaging can be used in different ways to facilitate translational research. However, there are many challenges in introducing micro PET imaging into practice. In the present work we give examples of how we have used a micro PET/CT imaging facility in a cancer research institute.

Methods: Metabolic substrates available from the clinical PET programmes were used to monitor response to different types of anticancer therapy in genetically modified spontaneous mouse cancer models as well as in tumour xenografts. [^{18}F]FDG and [^{11}C]acetate were injected intravenously and images acquired using a nanoPET/CT (Mediso, Hungary) preclinical scanner. Data were acquired in list mode and reconstruction was performed with proprietary Nucline software using the OSEM algorithm provided by the scanner manufacturer. To process the images we used the InVivoScope software package (Bioscan). Regions of interest were drawn around the tumour based on athresholding method (25, 50 and 75% of the maximum intensity voxel). Standard Uptake Values were calculated for all thresholds, as well as the SUVmax.

Results: Changes in tumour tracer accumulation before and after treatment could be monitored by the nanoPET/CT scanner. Standard Uptake Values calculated for regions of interest incorporating all voxels at the 75% threshold represented the most robust readout to monitor changes in tumour metabolism after anticancer treatment.

Nuclear Medicine Review 2012, Vol. 15, supplement A

PET-CT EVALUATION OF SOLITARY PULMONARY NODULES: WITH OR WITHOUT A RADIOLOGIST?

Andrea d'Amico[1], Cesary Przeorek[1], Jolanta Siewińska[1], Kamil Gorczewski[1], Izabela Szopa[1], Joanna Sczasny[2], Maria Turska-d'Amico[3], Katarzyna Steinhof-Radwańska[2], Barbara Bobek-Billewicz[2], Jarosław Kużdżał[4]

[1]Diagnostic PET Department, Comprehensive Cancer Centre, Maria Sklodowska-Curie, Memorial Institute Branch Gliwice, Gliwice, Poland
[2]Radiodiagnostics Department, Comprehensive Cancer Centre, Maria Sklodowska-Curie, Memorial Institute Branch Gliwice, Gliwice, Poland
[3]Department of Oncological and Reconstructive Surgery, Comprehensive Cancer Centre, Maria Sklodowska-Curie, Memorial Institute Branch Gliwice, Gliwice, Poland
[4]Department of Thoracic Surgery, Jagiellonian University, John Paul II Hospital, Cracow, Poland

Introduction: Detection of radiological changes in the lungs during routinely performed tests is very common.
CT scan provides information about the anatomy and morphology, may confirm whether the change is single or has multifocal character and may suggest the probability of malignancy.
The radiological criteria of benignity are: central location, concentric calcification, round shape, no growth after 2 years of observation in CT; malignant changes are usually characterized by indistinct, blurred boundaries, irregular shape and peripheral location.
Due to increased metabolism, at PET examination malignant tissues usually show a greater uptake of 18F-FDG than benign changes and healthy tissue. A meta-analysis by Gould et al. confirmed that PET with 18F-FDG is an accurate, noninvasive method for diagnosis of SPN, with an overall sensitivity of 96.8% and specificity of 77.8%.
In several cases, PET-CT is described only by a specialist in nuclear medicine without consulting a radiologist.
The aim of this study is to evaluate the accuracy of PET with assessment performed by a single nuclear medicine specialist and shoulder-to-shoulder assessment by both nuclear medicine and radiology specialists.
Materials and methods: PET-CT was performed in 58 consecutive patients referred from Department of Thoracic Surgery from John Paul II Hospital in Cracow because of radiologically diagnosed solitary pulmonary nodule (SPN) with diameter > 1 cm.
An histopatological specimen was obtained in 37 patients, by thoracothomy (36 patients) or transthoracic needle biopsy (1 patient). Seven patients had metastatic lesions at PET and did not undergo further invasive procedures. In the remaining 21 patients a histopathological specimen was not obtained for other reasons.
PET-CT tests were performed by using hybrid tomographs: Philips Gemini GXL (20 patients) or Siemens mCT (17 patients).
In 17 cases PET-CT images were evaluated by a single nuclear medicine specialist (group A), while for the remaining 20 cases, the image evaluation was performed shoulder-to-shoulder by a nuclear medicine specialist and a radiologist (group B).
Analysis of data: Overall PET sensitivity, specificity, positive and negative predictive value and accuracy were calculated on the basis of anatomopathologic results. These data were also calculated separately for groups A and B.
Results: The histopatologic examination demonstrated the non neoplastic character of 7/37 lesions (1 fibrotic nodule, 1 sarcoidosis, 2 hamartomas and 3 inflammatory nodules), while other lesions had neoplastic nature.
Group A, group B and overall values of sensitivity, specificity, accuracy, positive and negative predictive values are shown in Table 1.
Discussion: Our data are consistent with the data reported in the literature. The value of the diagnostic accuracy was approximately 90% for all the groups, without statistically significant differences.

Table 1

	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall	90%	85.7%	96.6%	66.6%	89.1%
Group A	85.7%	100%	100%	33.3%	88%
Group B	92.8%	83.3%	92.8%	83.3%	90%

The lowest sensitivity and negative predictive values were found in group A (study described only by a specialist in nuclear medicine), while in this group the highest specificity was observed. This fact is probably due to the reluctance of nuclear medicine specialist to refer "cold" lesions as positive, even in presence of radiological findings of malignancy. On the other hand, the accuracy was similar in both A and B groups.
It is worth signalizing that several radiological changes caused by inflammation, emphysema, atelectasia or tuberculosis do not necessarily affect the metabolic image, but may be important for the referring doctor. An accurate radiological report gives a large amount of important information to the referring doctor, which will not be necessarily reported by the nuclear medicine specialist.
Conclusion: PET-CT is an accurate diagnostic method to assess the nature of solitary pulmonary nodules. The consultation with radiologist does not substantially affect the PET-CT diagnostic accuracy, but can lead to a higher negative predictive value.

Nuclear Medicine Review 2012, Vol. 15, supplement A

PROGNOSTIC IMPORTANCE OF 18F-FDG UPTAKE PATTERN OF HEPATOCELLULAR CANCER PATIENTS WHO RECEIVED SIRT

Ozlem N Kucuk[1], Cigdem Soydal[1], Mine Araz, Sadik Bilgic[2], Erkan Ibis[1]

[1]Ankara University, Medical School, Department of Nuclear Medicine
[2]Ankara University, Medical School, Department of Radiology

Aim: Aim of the study is to evaluate the effect of 18F-FDG uptake pattern of liver lesions to treatment response of patients who received Y-90 selective internal radiation therapy (SIRT) for Hepatocellular Cancer (HCC).

Material and method: Nineteen patients (5F, 14M, mean age: 64.5 ± 14.7 years old, range: 57–73 years) who received SIRT treatment in our department for HCC between 2008 June and 2011 May were included in the study. All the patients have undergone 18F-FDG PET/CT before SIRT because the evaluation of disease stage and metabolic activities of liver lesions. Patients were divided into three groups according to FDG uptake patterns of primary liver lesions (hypoactive, nonhomogeneous, intense). Progression free survival times (PFS) of each group were analyzed. Disease progression criteria were accepted as increase in tumor volume, progressive elevation of serum AFP levels and detection of extent metastases. Kaplan-Meier analysis was used for comparison of PFS times.

Results: Treatment has been given right and left lobes of liver in 18 and 1 patient respectively. The mean treatment dose was estimated as 1.4 ± 1.0 GBq. While liver lesions of 4 patients were hypoactive in pretreatment 18F-FDG PET/CT, liver lesions of 6 and 9 patients had nonhomogeneous and intense FDG uptake, respectively. Mean PFS time of patients who had hypoactive liver lesions was 5.25 ± 1.52 months. In patients who had liver lesions with nonhomogeneous uptake, mean PFS time was 12.3 ± 2.6 months. Lastly, in patients with intense uptake in liver lesions, PFS time was calculated as 19.8 ± 5.0 months. Difference between each group was statistically significant (p: 0.017).

Conclusion: 18F-FDG uptake pattern of liver lesions is an important prognostic factor in the prediction of PFS of patients who received SIRT for primary HCC.