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Review

Establishing a PET research centre in Zagreb, Croatia (status and progress report)

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Abstract

The completion and opening of a commercial FDG production facility at the Rudjer Boskovic Institute, Zagreb, Croatia ensured a continuous, reliable daily supply of radioactive compound on site. This has laid the foundations for establishing a centre for nuclear molecular diagnostics which initially uses already available FDG, but later we also plan to synthesise 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 the facility, we show the first preliminary results, and offer our projections for further development in the scientific and organisational sense. The final aim of this facility is to grow into a strong research centre with good scientific collaboration with other R&D organisations in the region.
Key words: ***small-animal PET diagnostics,*** ^{18} ***F - FDG***

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Existing infrastructural advantages

Availability of radioisotopes and FDG radiopharmaceutical

Commissioning the new 18 MeV Cyclone 18/9 HC proton cyclotron, located at the site of the Institute, and setting up the whole chain of GMP production of fludeoxyglocose (FDG) for supplying the daily needs of Croatian hospitals in the form of the Rudjer Medikol Cyclotron (RMC) company, the RBI has gained the opportunity of preferred, regular and daily use of the radioisotopes produced, but also the use of the cyclotron in time not intended for commercial production. The scheme of the existing facility and the planned extension are shown in Figure 1.

As the availability of radiopharmaceuticals is a conditio sine qua non of each PET diagnostic procedure, this has opened the possibility to enter new areas of scientific research in physics, chemistry and bio-medicine based on using nuclear molecular diagnostics techniques in small animals. Because of daily medical routines in Croatian hospitals the FDG is reliably produced each morning, and the small quantity needed for experimental PET can be spared with almost no extra costs. The continuity of the radio-production procedures, qualified operating personnel and above all regular maintenance of the nuclear and radio-chemical part is guaranteed by the commercial aspect of the undertaking.

Animal facility

A second conditio sine qua non of PET diagnostics is the availability of experimental animals and the legal permission to perform in vivo experiments. The Rudjer Boskovic Institute has a well established animal facility which breeds inbred strains of mice [BALB/cBkl, CBA/H, C3Hf/Bu, C57BL/Go, C57BL/6-Ly5, NOD, Hsd:ICR (CD-1)] for research projects conducted mainly at the Rudjer Boskovic Institute. In our animal unit two colonies of rats have been developed from the Wistar stock, i.e. “Hyperserotoninemic rat” and “Wistar-Zagreb 5HT rat”. Both types are used in neuroscience research as rodent models for selected neuropsychiatric disorders as well as in related neuro-psycho-pharmacological research.

Scientific interest

As the RBI is a multidisciplinary institute a number of bio-medical research projects are in progress, so the main task of the future PET centre is not only to develop and accept PET research techniques, but above all to make them known to an environment where there is no active knowledge about their comprehensiveness and potential. Therefore, one of our

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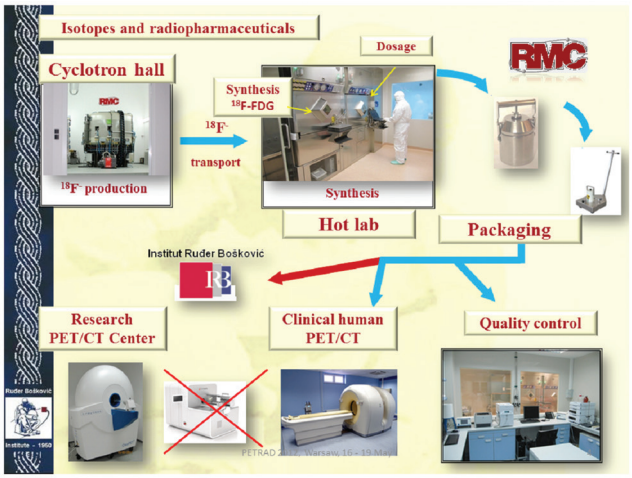

Figure 1. The existing facility and planned extension of RBI PET Center

main tasks is not only technical development; we have to devote a significant part of our time to teaching our colleagues and spreading knowledge about PET methods. Up to now we have developed notable interest of our colleagues in research on diabetes, research on tumour diseases and oxidative stress. We have also attracted the attention of our colleagues from the Croatian Institute for Brain Research (CIBR) and the University of Zagreb School of Medicine (SM). With CIBR we have started research on FDG distribution of ischemic brain insult in mice, and with SM we have initiated the study of FGD distribution of ischemic heart insult in rats.

Mission

The mission of the new PET centre is to perform basic research in biomedicine, radiochemistry and physics: 1. investigating metabolic spread of bioactive substances in vivo; 2. the dynamics of the interaction of bioactive substances with healthy and tumorous tissue; 3. the follow up of tumour growth in animal models in vivo; 4. the follow up of normal and pathological metabolic processes in living organisms (diabetes, neurological disorders...); 5. the development of new radiopharmaceuticals based on ^{18}F; 6. the development of new radiopharmaceuticals based on other radioisotopes; 7. offering PET services to external users on a commercial basis.

Vision

To create a regional centre of excellence for basic research based on nuclear molecular diagnostics.

To create a regional centre offering PET services on a commercial basis.

Strategy

1. To purchase the basic equipment for acquiring PET images.
2. To set up (assemble) the whole experimental chain from isotope to image interpretation shown in Figure 2 with minimal additional investments to gain experience.
3. To demonstrate the ability to run the experimental chain.
4. Identify weaknesses.
5. Find financing to improve the weak links.
6. Improve the weak links.
7. Strengthen the research team through local work and international collaborations.

Equipment purchased

We have purchased a ClearPet camera by Raytest, with a minimal configuration of 8 out of 20 possible cassettes, and PMOD software for image analysis. The characteristics of the system and actual photographs are given in Figure 3.

We have performed experiments under minimal biological conditions (Table 1).

Status and results

The experimental system is harmonised, streamlined, tested and standardised.

We have performed over 140 successful in vivo experiments on various inbred strains of mice with the aim of defining the scope, significance and potential of new PET techniques in research on: tumorous diseases, diabetes, metabolic disorders (oxidative stress), neurological disorders (ischemic brain insult) and cardiac disorders (ischemic cardiac insult). Typical results are shown in Figure 4.

Table 1.

Rohbau non-clasified space	Instead of	Class C laboratory
IP anesthesia	Instead of	Isoflourane gasseous anesthesia
IP isotope administration	Instead of	IV isotope administration
Heating with warm air	Instead of	Heating pads with automathic temp. control
Animal tumors	Instead of	Human tumors
Basic vantilation, no temp. and humidity control	Instead of	Full HVAC
Basic radioprotection	Instead of	Full radioprotection
No radiochemistry lab	Instead of	Full radiochemistry lab
Only ^{18}F-FDG	Instead of	^{18}F + different ligands
Only ^{18}F	Instead of	At lest ^{11}C in addition

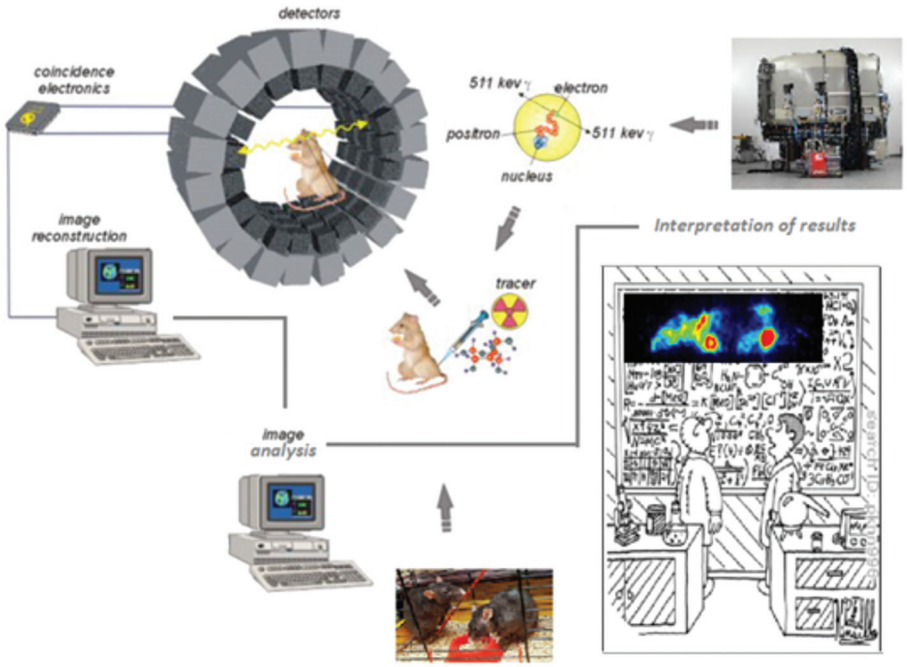

Figure 2. Experimental chain of PET diagnostics

Figure 3. The minimal PET system purchased

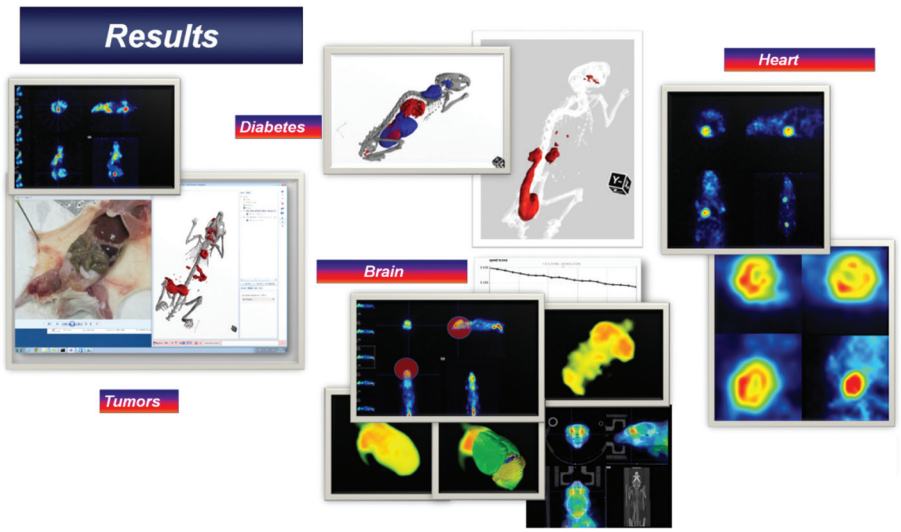

Figure 4. Typical experimental results of the current configuration

At the moment we can with certainty follow qualitative and quantitative distribution of FDG radiopharmaceutical:

- in time intervals of 2 minutes;
- in a grid of 1.15 mm × 1.15 mm × 1.15 mm;
- with an estimated precision of ± 20 %;
- filter, smooth and average the data obtained;
- make a 2D numerical analysis of the images obtained with predefined or manually drawn volumes of interest (VOI);
- make a 3D reconstruction of the images obtained;
- make a corregistration of our images with a given input file from other machines:
  - as a routine we make a corregistration of our images with a CT mouse template obtained from PMOD,
  - as a routine we make a corregistration of our images with MR mouse templates obtained from PMOD,
  - we can use mouse brain VOI templates from the Mirrione mouse atlas and numerically evaluate our results,
  - we can rescale and move in 3D space each individual VOI from the Mirrione mouse atlas and adjust it to fit our particular animal.

However, seemingly identical biological initial conditions give rather different biological uptake.