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Radioisotopes in Drug Research and Development: Focus on Positron Emission Tomography

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1. Introduction

The use of radioisotopes is important in pharmaceutical research and development (R&D). They are frequently used in non-clinical and clinical studies for the development of compounds for different therapeutic areas, such as central nervous system (CNS) diseases (e.g. Dementia, Alzheimer's disease (AD), and Parkinson's disease), oncology, and metabolic diseases (e.g. diabetes mellitus).
Pharmaceutical companies invest a lot of time and money in research on new treatment strategies for diseases with a high medical need, such as oncology and metabolic diseases. A large amount of drugs fails during development due to toxicity and/or the lack of efficacy (Kola, I, 2008). Several attempts are being made to improve this, such as obtaining a better understanding of the pathophysiology of diseases, development of robust animal models, the application of biomarkers, development of pharmacokinetic (PK) - pharmacodynamic (PD) models, and the application of non-invasive techniques such as positron emission tomography (PET) in an early stage of development.

2. Application of radiolabeled compounds

A variety of radioisotopes is used in the R&D of drugs, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S and ^{131}I (Penner et al, 2009). Carbon-14 is the isotope of choice in most of the ADME studies. The labeled part of the drug molecule should not be lost in metabolite formation. Tritium-labeled drugs are also used commonly, but have the risk of tritium exchange. Data from non-clinical studies performed with radiolabeled drugs can provide information to make the choice of the radioisotope and its position in the drug molecule. The tritium- or carbon-14-labeled drug at the metabolically stable position should have a radiochemical purity of ≥98%, and in special cases ≥95% may be acceptable. stability of the radiolabeled drug under dosing conditions should be checked at predose and postdose.

The advantage of using radiolabeled drugs is that the radioactivity can easily be detected and quantified using liquid scintillation techniques and disposition of drugs can be assessed. The choice of the radioisotope, the position of the radiolabel in the drug compound, radiochemical purity, and the specific activity are important parameters. These parameters can have an effect on the metabolic, chemical, and radiochemical stability of the drug, metabolite formation and detection, and the recovery of radioactivity.

2.1 Non-clinical studies

Radioactive labeled compounds are used in non-clinical studies to assess drug absorption, distribution, metabolism, and excretion (ADME). They can provide information on a) drug absorption in cell lines, b) P-glycoprotein (P-gp) transport or inhibition, c) metabolite profiling, d) drug transport (uptake, efflux), and e) drug binding to receptors (Marathe et al., 2004).
Other applications of radiolabeled compounds are to investigate apoptosis (Glaser et al., 2003), DNA replication and cell cycle progression (Hoy et al., 1990) in oncology. In the development of gemcitabine, a pyrimidine nucleoside anticancer drug, radiotracers were used to better understand the pharmacology and toxicology of this compound (Heinemann et al., 1988; Mackey et al., 1988). With the use of radiolabeled [^{3}H]-gemcitabine, its synthesized metabolite [^{3}H]-dFdU, and [^{3}H]-thymidine, novel active metabolites of gemcitabine were revealed, which turned out to be incorporated into DNA, formed *in vivo* in mice and accumulated into the liver following multiple oral dosing (Veltkamp et al.,2008a, 2008b). These findings gave new insights in the metabolism, pharmacology and toxicology of the drug.

2.2 Clinical studies

Administration of radiolabeled compounds to humans is not generally done in the first-in-man study. Considering the amount and type of information that human ADME studies can provide, it should be considered to conduct these studies early during clinical development. Possibilities are just after or in parallel with the multiple ascending dose (MAD) study. Radiolabeled drugs are used in a variety of clinical studies, such as in mass balance (MB), regional drug absorption, and microdose studies.
Mass balance studies provide valuable information on the absorption, metabolism, and elimination of a drug. Identification and quantification of metabolites is important in MB studies (Penner et al., 2009).
Regional drug absorption studies can be performed to determine the PK of a drug from a new modified release (MR) compared to a more conventional immediate release (IR) formulation and to measure absorption from specific areas of the gastrointestinal (GI) tract, such as the distal small bowel, ascending colon, and transverse colon. In this way, it can be determined whether the drug is sufficiently absorbed from the GI tract and together with other PK and its safety it can be determined whether development of a MR formulation would be beneficial.
Microdose studies can give important information on the distribution and metabolism of a new drug. It can also help to reduce the number of animals used in non-clinical studies (Combesa et al., 2003). There has been a growing interest in the safety of drug metabolites, particularly those not produced in experimental animals. In order to avoid unpredictable toxicity caused by such metabolites, the US Food and Drug Administration (FDA) issued the Guidance for Safety Testing of Drug Metabolites (MIST) in 2008 (FDA, 2008). It recommends that, before commencing phase III trials of a drug, a safety report must be prepared relating to drug metabolites that have a systemic exposure >10% of the parent drug and those that occur in significantly greater quantities in humans than in experimental animals.

Subsequently, the International Conference on Harmonisation, ICHM3 guidance, recommends safety assessment of metabolites whose exposure is >10% of the total exposure, not of the parent compound (ICHM3, 2009). This new guideline prompted the pharmaceutical industry to identify and quantify drug metabolites in humans in the early phases of drug development.

In microdose studies PK data are obtained after administration of a trace subpharmacologic quantity to human subjects (Lappin et al., 2006). The ultrasensitive analytic technique of accelerator mass spectrometry (AMS) has been used to quantify the low plasma concentrations anticipated after microdose administration. These studies do not provide information about the safety and tolerability of the drug. Requirements for microdose studies have been summarized by the EMEA, FDA and others (EMEA, 2003; FDA, 2006; Bergstrom et al., 2003; Marchetti et al., 2007).

3. PET imaging

3.1 Principles of PET

PET is a nuclear imaging technique used to map biological and physiological processes in living subjects following the administration of positron emitting radiopharmaceuticals. The technique is based on the detection of photons released by annihilation of positrons emitted by radioisotopes. Positron-emitting radionuclides are produced in a cyclotron by bombarding target material with accelerated protons. In the body, these radionuclides emit positrons that undergo annihilation with nearby electrons, resulting in the release of two photons. These so-called annihilation photons are detected by imaging and the resulting data can be used to reveal the distribution of the radiotracer in the body.

Unlike conventional imaging modalities, such as magnetic resonance imaging (MRI) or computed tomography (CT), which mainly provide detailed anatomical images, PET can measure biochemical and physiological aberrations that occur prior to macroscopic anatomical signs of a disease, such as cancer (Chen et al., 2011). Currently, many positron emitting isotopes are available with different characteristics (see Table 1). Fluorine-18 has the advantage of having a long half-life ($t_{1/2}$), which enables time-consuming radiosyntheses and imaging procedures.

Isotope	$t_{1/2}$
^{18}F	109.8 min
^{11}C	20.4 min
^{15}O	2.04 min
^{13}N	9.97 min
^{64}Cu	12.7 hours
^{68}Ga	68.1 min
^{124}I	4.2 days

Table 1. Positron emitters commonly used in PET studies.

3.2 Application of PET imaging

PET imaging has become an important tool in the process of drug development for a variety of compounds, such as for CNS targeted and anticancer drugs. PET imaging has the

advantage of having high sensitivity and high specificity when using the appropriate PET probes. Therefore, it can be used for examination of the physiology of tissues and for evaluation of the distribution of a drug in specific organs or regions in a quantitive manner. PET imaging is used to examine the PK of drugs in tissues using a positron-labeled drug candidate or the PD (e.g. target expression, occupancy) using the radiolabeled drug itself or a different target-specific tracer. PET radiotracers used in R&D of drugs in the field of CNS, oncology and diabetes mellitus are listed in Table 2.

a. CNS

PET tracer	**Target**	**Purpose**
[^{11}C]-PIB (Rostomian et al., 2011)	Amyloid plaque	Diagnosis of Alzheimer's disease and efficacy on Aβ plaques
[^{18}F]-AV45 (Wong et al., 2010)	Amyloid plaque	Diagnosis of Alzheimer's disease and efficacy measurement of Aβ plaques
[^{18}F]-FK960 (Noda et al., 2003a)	Hippocampus (exact target not identified yet)	Dose setting Dementia
[^{11}C]-SCH442416 (Mihara et al., 2008)	Adenosine A_{2A}R*	Determine receptor binding of a therapeutic drug Parkinson's disease
[^{18}F]-FDG (Asai et al., 2009)	Glucose metabolism (rCMRglu**)	Diagnosis of Alzheimer's disease

*Adenosine A_{2A}R, adenosine A_{2A} receptor; **rCMRglu, regional cerebral metabolic rate of glucose.

b. Oncology

PET tracer	**Target**	**Purpose**
[^{18}F]-FDG	Glucose metabolism	Tumor response/disease staging
[^{18}F]-FLT	Cell proliferation	Tumor response
[^{11}C]-Gly-Sar (Mitsuoka et al., 2008)	Peptide transport	Cancer detection (distinction between cancer and inflammatory tissue)
[^{11}C]-methionine (Narayanan et al., 2002)	Amino acid metabolism	Tumor response (brain tumors)
[^{18}F]-FMISO (Bruehlmeier et al., 2004)	Hypoxia	Diagnosis of hypoxic state of cancer
[^{18}F]-FAZA (Piert et al., 2005)	Hypoxia	Diagnosis of hypoxic state of cancer

FDG; fluorodeoxyglucose; FLT; fluorothymidine; Gly-Sar, glycylsarcosine; FMT, fluoromethyltyrosine; FMISO, fluoromisonidazole; FAZA, fluoroazomycin-arabinofuranoside.

c. Diabetes mellitus (see also sections 3.3.3 and 3.4.3)

PET tracer	Target	Purpose
[^{11}C]-DTBZ	VMAT2 β-cells pancreas	Assessment of β-cell mass
[^{18}F]-FP-(+)-DTBZ (AV133)	VMAT2 β-cells pancreas	Assessment of β-cell mass
[^{18}F]-FP-(+)-epoxy-DTBZ	VMAT2 β-cells pancreas	Assessment of β-cell mass

DTBZ, dihydrotetrabenazine; VMAT2, vesicular monoamine transporter 2; FP-DTBZ, fluoropropyl-dihydrotetrabenazine.

Table 2. PET radiotracers in R&D of drugs in the field of CNS (a), oncology (b) and diabetes mellitus (c).

Amyloid plaque is a major feature of Alzheimer's disease (AD), for which several amyloid-imaging tracers have been developed (Kadir et al., 2010). Among these tracers, [^{11}C]-PIB and [^{18}F]-AV45 were examined as diagnostic agents for *in vivo* imaging of amyloid deposition in humans. According to the National Institute on Aging and Alzheimer's Association Lead Effort to Update Diagnostic Criteria for Alzheimer's Disease, biomarkers for AD have been developed and are being validated. These fall into several categories and include biomarkers for a) beta amyloid pathology, including amyloid PET imaging and levels of beta amyloid in cerebrospinal fluid (CSF), b) neuronal injury, including levels of CSF τ and phospho-τ, c) neuronal dysfunction, including decreased uptake of FDG on PET scans, and d) neurodegeneration, including brain atrophy on structural MRI scans.

PET imaging in oncology is used to assess tracer distribution and extent of uptake to identify the disease, for disease staging, and for monitoring therapeutic response. The most widely used PET tracer in oncology is [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG), a glucose analog that enters the cell after uptake by glucose transporter 1 (GLUT1). FDG is subsequently phosphorylated by hexokinase-II and accumulates in tumor cells, a mechanism also called metabolic trapping. In fact, increased glucose transport is associated with elevated glycolysis of the cancer cell and a corresponding increase in hexokinase activity. Tissues that metabolize gucose faster will accumulate more [^{18}F]-FDG. Therefore, cancer cells can be differentiated from benign tissues by their increased metabolism. Correspondingly, this uptake can be semi-quantified on PET.

However, [^{18}F]-FDG is not a target-specific tracer and it cannot differentiate between cells that have a high metabolic rate associated with neoplasia, and those for which the increased metabolic rate is associated with other etiologies, such as infection or inflammation. In addition, many malignancies do not exhibit high metabolic rates and, thus, are not properly diagnosed by [^{18}F]-FDG (Chen et al., 2011).

A novel PET tracer, [^{11}C]-glycylsarcosine ([^{11}C]-Gly-Sar), targeted to H^+/peptide transporters (PEPTs) was investigated for its specificity as compared to that of FDG in distinguishing between tumor and inflammatory tissues (Mitsuoka et al., 2008; Fig. 1). After i.v. administration of [^{11}C]-Gly-Sar to mice, it was possible to visualize prostate, pancreatic and gastric tumor xenografts all expressing PEPTs. Accumulation of [^{11}C]-Gly-Sar occured in kidneys and bladder, and was low in other tissues (e.g. brain, heart, lung, and liver), which had restricted functional expression of PEPTs. Accumulation of [^{18}F]-FDG occured in brain, heart, kidneys and bladder. The detection of tumors in mice was improved using [^{11}C]-Gly-Sar compared to [^{18}F]-FDG (Fig. 1). Whereas ^{18}F-FDG accumulated also in inflammatory tissue, uptake of [^{11}C]-Gly-Sar was absent in inflammatory tissues. [^{11}C]-Gly-

Sar is a promising tumor-imaging agent and appears superior to FDG for distinguishing between tumor and inflammatory tissue.

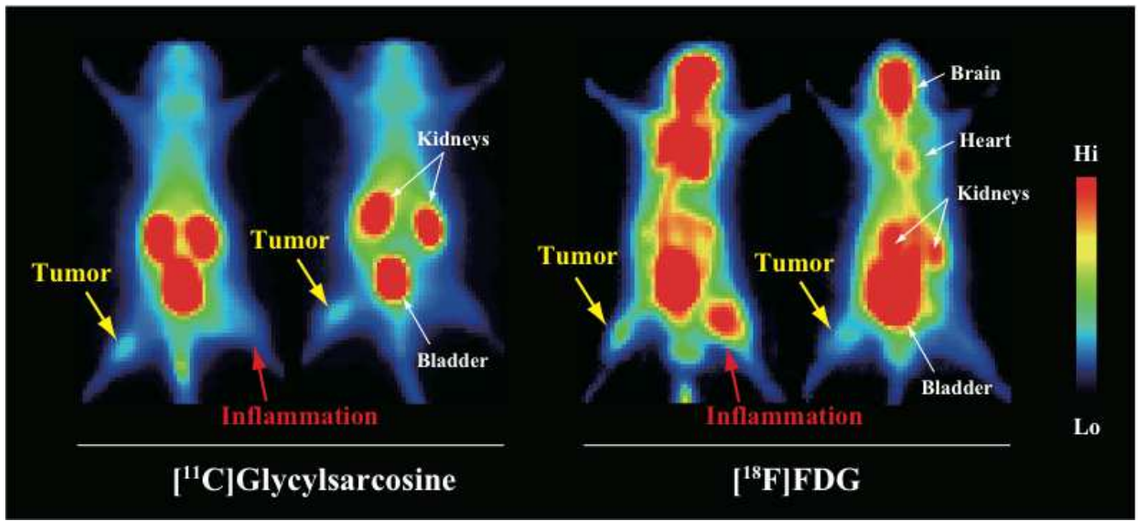


Fig. 1. Planer images of mice bearing human pancreatic tumors after injection of AsPC-1 pancreatic adenocarcinoma cells in their right hind limb. [^{11}C]-Gly-Sar (~ 5 MBq) or [^{18}F]-FDG (~ 5 MBq) were administered i.v. Turpentine oil was administered subcutaneously into the left hind limb of control mice (left mice for [^{11}C]-Gly-Sar and [^{18}F]-FDG) to induce inflammation. Yellow arrowhead, tumor; red arrowhead, inflammation.

Another promising radiopharmaceutical is 3'-deoxy-3'-[^{18}F]-fluoro-L-thymidine (FLT), a marker for cell proliferation. Accumulation of FLT in tumor cells has been shown to be dependent on the activity of cellular thymidine kinase-1 (TK1). TK1 is the key enzyme and limiting step in the pyrimidine salvage pathway of DNA synthesis and is overexpressed in most tumor types. Intracellarly, FLT is phosporylated to FLT-monophosphate, but unlike thymidine, FLT is not incorporated into DNA as it lacks the 3'-hydroxyl group. As TK1 is functional only in the late G_1- and S-phase of the cell cycle, FLT uptake closely correlates with the amount of proliferating cells. L-[methyl-^{11}C]-methionine, or [^{11}C]-methionine, is a PET tracer for amino acid metabolism used in neuro-oncology, which makes it possible to assess the characteristics of lesions in the brain, impossible with FDG-PET or MRI. The uptake of [^{11}C]-methionine provides information on the malignancy of lesions. Sodium-independent amino acid transporters (LATs), which mediate transport of large branched and aromatic amino acids, has attracted special interest, because system L is commonly upregulated in many tumors and correlates with tumor growth and prognosis. Other amino acid tracers have been developed to detect cancers. On the other hand, the prevalence of hypoxic areas is a characteristic feature of locally advanced solid tumours and has been described in a wide range of human malignancies. Evidence from experimental and clinical studies point to a role for tumor hypoxia in tumor propagation, resistance to therapy and malignant progression. To monitor the hypoxia, nitroimidazole compounds such as [^{18}F]-fluoromisonidazole (FMISO)or [^{18}F]-fluoroazomycin-arabinofuranoside (FAZA) have been described. These compounds are degraded into reactive intermediate metabolites by intracellular reductases in a process which is directly related to the level of

oxygenation/hypoxia. This causes a gradient which is favorable for detection of hypoxic cells. Subsequently, these metabolites covalently bind to thiol groups of intracellular proteins and thereby accumulate within viable hypoxic cells.

PET images from orthotopically implanted pulmonary human tumor xenografts in mice are shown in Figure 2. The micro-PET images were coupled to micro-CT images in the lung. By using different radiotracers, these PET images provided information on the tumor condition, such as on glucose metabolism ([^{18}F]-FDG), cell proliferation ([^{18}F]-FLT], and hypoxia [^{18}F]-FMISO]. Micro-PET/CT imaging could be a robust surrogate biomarker for antitumor activity in preclinical studies.

Assessment of treatment response is essential for disease management. Anatomic imaging alone using the Response Evaluation Criteria in Solid Tumors (RECIST) does not reflect physiological changes of the tumors, and therefore still has limitations in response evaluation. Functional imaging is very useful in the evaluation of the efficacy of novel anticancer drugs.

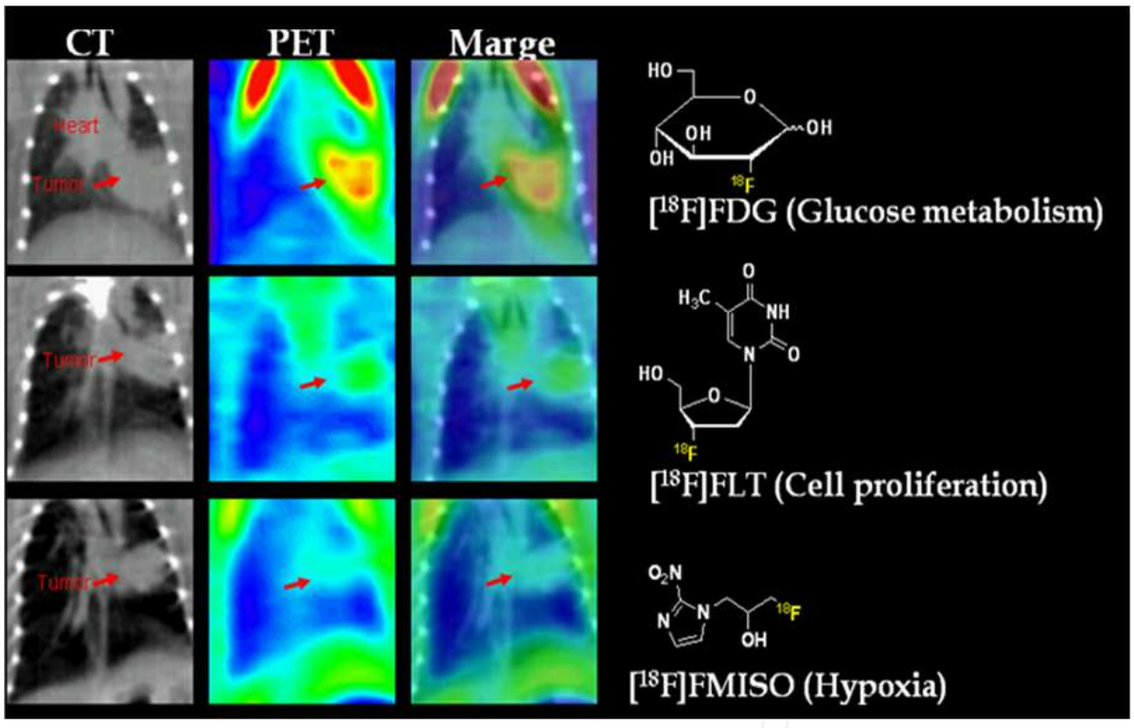


Fig. 2. PET, CT, and combined PET/CT-images of orthotopic human lung tumor xenografts in mice. Mice were administrated via the tail vein 15 MBq of [^{18}F]-FDG for detection of glucose metabolism (top row), [^{18}F]-FLT for detection of cell proliferation (middle row) and [^{18}F]-FMISO for detection of hypoxia (bottom row). PET images were acquired for 50 to 60 min after tracer administration using three-dimensional ordered subset expectation maximization (3D-OSEM) reconstruction.

3.3 Examples of PET in non-clinical studies

Several examples of the application of PET in non-clinical studies for the development of CNS drugs, anticancer drugs and antidiabetic drugs is described in this Section.

3.3.1 Determination of the PK and PD of CNS drugs

The brain anatomy and function can be visualized using PET scanning in conjunction with a very small amount of a radiolabeled compound. It is also a useful technique to assess the PK of radioactive labeled therapeutic agents, and is commonly used in the development of CNS targeted drugs to determine the extent of brain penetration of the drug. After administration of the radioactive labeled therapeutic drug, the drug exposure in different areas of the brain can easily be determined noninvasively by measurement of the radioactivity with PET. In preclinical PET studies, the radioactive labeled drug is often evaluated in well-trained rhesus macaques in conscious condition without anxiety and stress. PET results in conscious monkeys are considered preferable above sedated monkeys for predicting brain penetration of a CNS drug in human, since anesthesia does depress the neuronal activity, regional cerebral blood flow (rCBF), and regional cerebral metabolic rate for glucose (rCMRGlu) in animal experiments.

For successful drug development, optimal dose setting in clinical trials is important. Because each drug has its corresponding target site, achievement of the most suitable drug concentration in the target organ or tissue becomes critical to allow the drug to exhibit its maximal effect. Although PK data in animal experiments are usually used to estimate the clinical dose, discrepancies in absorption, distribution, and metabolism of drugs between experimental animals and humans still remains in most cases, and these make the dose estimation difficult. Especially when a drug acts in the brain, further difficulty is caused by the presence of the blood-brain barrier.

FK960, (*N*-(4-acetyl-1-piperazinyl)-*p*-fluorobenzamide monohydrate) is a novel drug in development for Dementia. Its proposed mechanism of action is enhancement of somatostatin release in the hippocampus. Since somatostatin also enhances the release of acetylcholine, FK960, could indirectly activate the release of acetylcholine. FK960 improved memory impairment in several kinds of rodent and non human primate animal models. However, the dose-response relationships of FK960 in memory improvement in animal models of amnesia and in the enhancement of long-term potentiation (LTP) in hippocampal slices were bell shaped. Therefore, the optimal dose setting to exhibit efficacy in patients remains to be exactly determined. Because PET can measure radioactivity concentrations dynamically in a target organ in a living subject with minimal invasion, the acquisition of bridging data between animals and humans may be expected.

[^{18}F]-FK960 was synthesized and administered orally in combination with non radioactive labeled drug to conscious rhesus monkeys. Drug concentration versus time profiles in plasma and the brain were obtained using PET imaging (Noda et al., 2003a; Fig. 3). Dynamic PET images were acquired for 4 hours from 5 min after drug administration. Arterial blood samples were drawn during the PET scan and analyzed by an auto well γ-counter and thin layer chromatography to determine [^{18}F]-FK960 activity in plasma. FK960 concentrations (mol/L) were calculated using the specific activity of FK960.

The study demonstrated that [^{18}F]-FK960 penetrated the blood-brain barrier and distributed dose-dependently into the entire brain. Maximal FK960 brain concentrations were comparable with the levels showing enhancement of LTP in hippocampal slices. The results suggested that this PET imaging method could be used to measure FK960 brain concentrations in humans. A different study showed that FK960 significantly improved regional cerebral blood flow and regional cerebral metabolic rate of glucose in conscious aged macaques (Noda et al., 2003b).

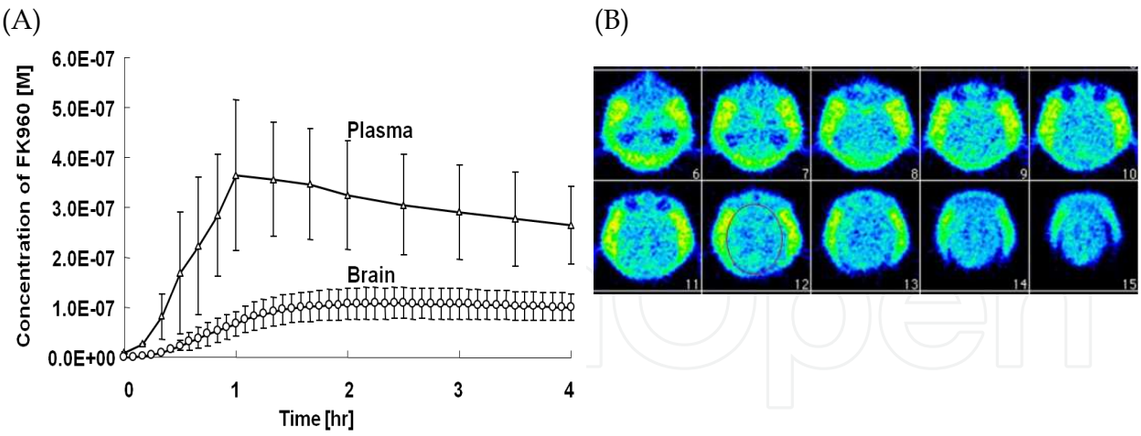


Fig. 3. (A) Brain and plasma concentrations of FK960 versus time in conscious male monkeys (n=3) after oral administration of a mixture of 0.1 mg/kg of FK960 and 370 MBq tracer of [^{18}F]-]FK960 in saline. Concentrations of the drug into the entire brain were obtained from PET data. (B) Transverse PET images showing distribution of [^{18}F]-FK960 into the brain. PET images were taken 90-120 min after drug administration as 3.6 mm transverse slices from the lower brain (top left) to the upper brain (bottom right). FK960 reached higher concentrations in the lower brain compared to the upper brain. The circle as presented in image 12 indicates the brain area in the skull.

Besides determination of the PK of a drug, PET imaging is important to assess the PD of drugs and is used in receptor and transporter occupancy studies, e.g. to investigate binding of the PET tracer to the target (receptor/transporter) and inhibition of this PET tracer binding by the drug of interest. These occupancy studies can reveal information on the binding potency and durability of binding *in vivo*, which can be used for dose selection.
In this way, PET imaging can be used to determine both the PK and PD of a drug and to establish the relationships between plasma and brain levels with the extent of receptor occupancy by the drug.
The use of PET to determine PD drug effects were gently shown for ASP5854 (5-[5-amino-3-(4fluorophenyl)pyrazin-2-yl]-1-isopropylpyridine-2(1H)-one), a novel adenosine A_{2A} receptor (A_{2A}R) antagonist, in development for Parkinson's disease. Adenosine A_{2A}Rs are abundantly expressed in the striatum of several species. They are co-expressed with dopamine D_2 receptors in the GABAergic striatopallidal neurons. Stimulation of adenosine A_{2A}Rs decreases the binding affinity of D_2 receptors and elicits effects opposite to the ones shown by D_2 receptor activation. These observations suggested that antagonistic adenosine-dopamine interactions can be important in the regulation of the activity of the basal ganglia and could explain the stimulating effects of adenosine A_{2A}R antagonists on motor behavior. Therefore, ASP5854 was considered of potential interest in the treatment of movement disorders and may reduce the symptoms in Parkinson's disease.
ASP5854 and [^{11}C]-SCH442416, an adenosine A_{2A}R-specific radiotracer, were administered i.v. to conscious rhesus monkeys and adenosine A_{2A}R occupancy in the brain was examined using PET. ASP5854 dose-dependently increased adenosine A_{2A}R occupancy in the striatum (Mihara et al., 2008; Fig. 4) and showed long-lasting occupancy even at decreasing drug concentrations in plasma.

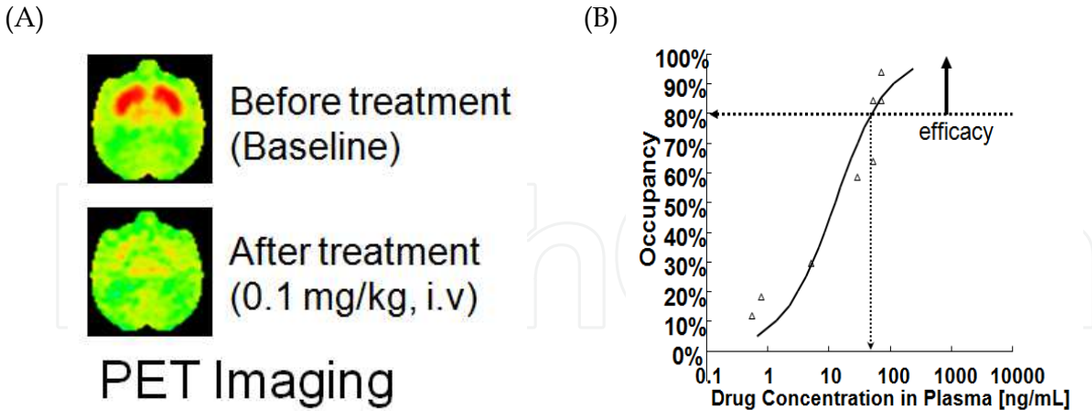


Fig. 4. (A) PET images of [^{11}C]-SCH442416 before and after treatment of adenosine A_{2A} receptor antagonist, ASP5854, in conscious monkeys. At baseline, the tracer accumulated in the striatum, which is rich of A_{2A} receptors (20 mCi, i.v. injection; mean of six animals). At t=1h after drug administration (0.1 mg/kg, i.v.), the accumulation of the tracer in the striatum was lower compared to baseline, due to decreased binding of the PET tracer to the receptor as a result of ASP5854 binding to the receptor. (B) Relationship between the dose and receptor occupancy at 1 h after drug administration. Sigmoidal dose-response curve demonstrating an increase in adenosine A_{2A}R occupancy by ASP5854 with an increase in ASP5854 plasma concentration at t=1 h after drug administration (dose-levels: 0.001 to 0.1 mg/kg, i.v.); 80% receptor occupancy correlated with efficacy (catalepsy) in the monkeys.

Donepezil, an acetylcholine esterase inhibitor (AChEI), has been recommended as a treatment option for patients with AD. [^{18}F]-fluoro-2-deoxyglucose (FDG)-PET was used to measure the regional cerebral metabolic rate of glucose (rCMRglu), an index of neuronal activity, in rhesus monkeys (Asai et al., 2009). The effects on rCMRglu were measured following intramuscular (i.m.) administration of donepezil (500 μg/kg) or the non-selective muscarinic ACh receptor antagonist scopolamine (30 μg/kg, i.m.), or co-administration of both drugs. This FDG-PET study showed that administration of donepezil or scopolamine alone increased rCMRglu in conscious rhesus monkeys. The donepezil-induced increase in rCMRglu was abolished by simultaneous administration of scopolamine, suggesting that muscarinic ACh receptor function plays an important role in the effect of donepezil (Fig. 5).

3.3.2 Determination of early tumor response to anticancer drugs

Oncology is a main therapeutic area of many pharmaceutical companies. PET imaging is helpful to measure early tumor response to anticancer treatment in early phases of research and development.

YM155 is a small molecule survivin suppressant. Survivin is a member of the inhibitor of apoptosis protein family, acting as an inhibitor of caspase activation, and has been implicated in both cell survival and regulation of mitosis in cancer. Although survivin is expressed in a variety of normal fetal tissues, expression is absent in most adult tissues. In contrast, survivin is highly expressed in most tumors. Survivin overexpression in cancer patients is associated with resistance to cytotoxics and is correlated with poor survival. YM155 was shown to have nanomolar antitumor activity in a wide variety of human cancer cell lines. The continuous infusion of YM155 induced tumor regression in mice xenograft

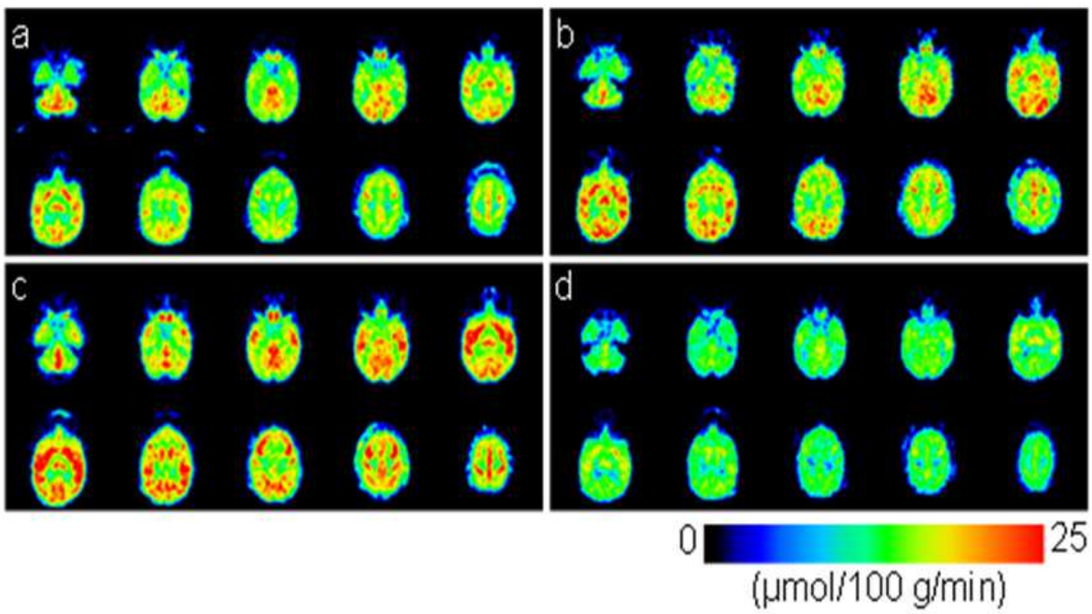


Fig. 5. PET images of the brain of consious monkeys demonstrating rCMRglu using FDG-PET after treatment with empty vehicle (a), donepezil 500 μg/kg (b), scopolamine 30 μg/kg (c), and donepezil+scopolamine (d). Images are orbitomeatal transverse slices (OM) + 0 to OM + 32.4 mm, 3.6 mm thick.

models (Nakahara et al., 2011a). Other results suggested that YM155 sensitized tumor cells to radiation (Iwasa et al., 2008) and platinum compounds both *in vitro* and *in vivo*, and that the effect was likely attributable to the inhibition of DNA repair and consequent enhancement of apoptosis (Iwasa et al., 2010). Non-clinical studies using radioactive ^{14}C-labeled YM155 demonstrated that the organic cation transporter 1 (OCT1) was the predominant transporter for the hepatic uptake of YM155 (Iwai et al., 2009). YM155, administered as 168 hours continuous infusion in 21-day cycles, appeared to be safe and well-tolerated, with a maximum tolerated dose of 8.0 mg/m^2/day in Phase I studies in patients with advanced refractory solid tumors (Satoh et al., 2009), and advanced solid tumors or lymphoma (Tolcher et al., 2008). Multi-center Phase II trials demonstrated the safety and tolerability of YM155 in patients with unresectable stage III or IV melanoma (Lewis et al., 2011) and safety and modest activity in patients with advanced refractory non-small cell lung cancer (NSCLC) (Giaccone et al., 2009).

PET imaging has been used for the development of YM155 in preclinical studies in mice. [^{18}F]-FDG-PET has been used to assess early treatment response in animals with diffuse large B-cell lymphoma (DLBCL) and non-small cell lung cancer (NSCLC) xenografts, and [^{18}F]-FLT-PET was used to determine the effect on cell proliferation. The combined effect of YM155 and docetaxel in human NSCLC xenografts was determined using whole-body imaging. Combination treatment of YM155 and docetaxel for 21 days resulted in increased inhibition of tumor growth (Nakahara et al., 2011b), accompanied by inhibition of tumor uptake of FDG, compared to monotherapy with either YM155 or docetaxel (Fig. 6).

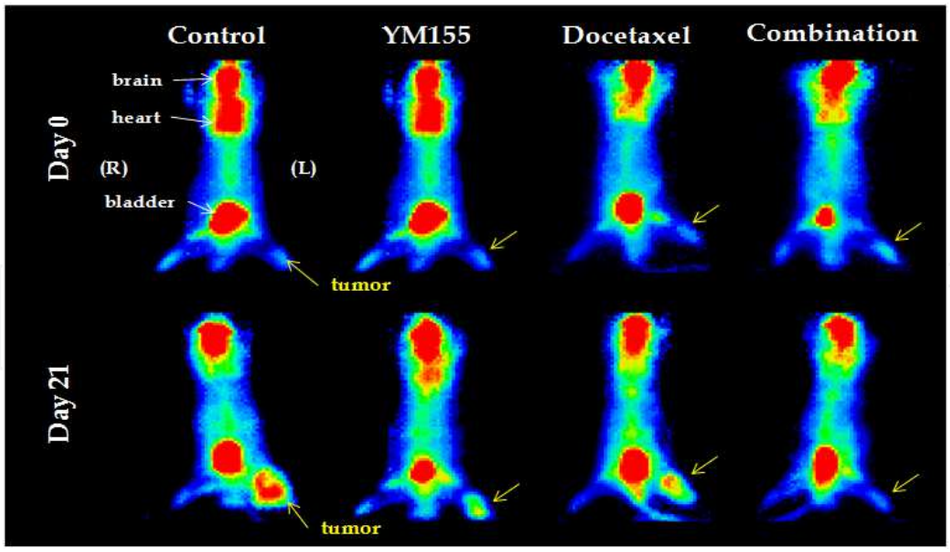


Fig. 6. Whole-body imaging of mice with [^{18}F]-FDG. Human NSCLC xenografts were grown after injection of Calu-6 human tumor cells (3×10^6 cells/100 μL) into the right hind limb of male Balb/c nude mice, aged 6-7 weeks. YM155 (2 mg/kg/day) was administred as s.c. infusion for 7 days. Docetaxel (10 mg/kg) was administered as i.v. bolus injection on days 0, 4 and 8 after the initiation of YM155 treatment. Mice were administerd 5 MBq of [^{18}F]-FDG i.v. via the tail vein. After the appropriate time had elapsed, mice were anesthetized by isoflurane, placed in a prone position, and imaged by using a planar positron imaging system PPIS-4800 (Hamamatsu Photonics) to obtain the whole-body distribution of [^{18}F]-FDG at 50–60 min from tracer injection.

3.3.3 Measurement of pancreatic β-cell mass in the development of antidiabetic drugs

Pancreatic β-cell mass (BCM) is known to decrease as a result of progression of disease in animals with diabetes mellitus. Measurement of BCM *in vivo* is an important tool for early diagnosis of diabetes mellitus and to monitor the efficacy of the treatment. Historically, the pancreas has been a difficult organ to image because of its retroperitoneal location and overlying visceral organs. Over the past 2 decades, the advance of CT and MRI has allowed to correlate disease processes of the pancreas, such as pancreatitis with anatomical structures. Unfortunately, these imaging modalities do not describe organ function or easily separate the endocrine from the exocrine pancreas. The ability to quantify and monitor β-cell mass (BCM) is of particular interest for diabetes mellitus.

Recently, it was reported that vesicular monoamine transporter 2 (VMAT2) is expressed mainly on the pancreatic β-cells as well as on dopaminergic neurons. A VMAT2 ligand, dihydrotetrabenazine (DTBZ), was developed previously for dopaminergic neuron imaging in the striatum and it has been successfully applied for PET studies of Parkinson's disease. DTBZ can also be used to monitor BCM quantitatively for diabetes. PET tracers that have been used to quantify VMAT2 are [^{11}C]-dihydrotetrabenazine ([^{11}C]-DTBZ) (Souza et al., 2006(a); Simpson et al., 2006; Murthy et al., 2008; Goland et al., 2009), [^{18}F]-fluoropropyl-DTBZ ([^{18}F]-FP-DTBZ or [^{18}F]-AV-133) (Kung et al., 2007; Kung et al., 2008(a); Tsao et al., 2010) and [^{18}F]-fluoropropyl-DTBZ epoxide ([^{18}F]-FP-epoxy-DTBZ) (Kung et al., 2008(b)), which were shown to have high potency and selectivity for binding to VMAT2 in rats.

Longitudinal preclinical studies have been performed in induced T1DM and obese rat models (Freeby et al., 2008) and in a spontaneous T2DM diabetic rat model showing a decrease in [^{11}C]-DTBZ uptake that anticipated loss of glycemic control (Souza et al., 2006(a)). These preclinical *in vivo* PET studies in non-human primates are used to evaluate the between-species differences in PK of the tracer, and to establish the most likely optimal tracer for PET studies to establish BCM in humans.

3.4 Examples of PET in clinical studies

Several examples of the application of PET in clinical studies for the development of CNS drugs, anticancer drugs and antidiabetic drugs is described in this Section.

3.4.1 Biodistribution of CNS drugs in humans

Establishing the therapeutic dose and dose regimen of a new drug is challenging, especially for drugs with CNS activity. The major challenge is the blood-brain barrier (BBB), which limits the access of drugs to the brain tissue. It is important to select the right dose range of a drug in early phase clinical trials to establish the PK, PD and safety of a drug. PET is used to determine biodistribution and concentration of a drug in the brain non-invasively, *in vivo*. In such clinical investigation, Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) regulations are required. As described earlier in this Chapter, PET was used in non-clinical studies to predict the optimal clinical dose for FK960, a novel drug in development for the treatment of patients with Dementia. Subsequently, the drug was investigated in humans. FK960 has a bell-shaped dose–response relationship. Determining the proper clinical starting dose and dose range is difficult because of species differences between animals and humans. For example, differences in brain concentrations of the drug at comparable doses may be expected as a result of discrepancies in absorption, distribution, metabolism, and permeability of the drug through the BBB between animals and humans. This may lead to incorrect estimations of the therapeutic dose in humans from the animal data. Therefore it could be useful to determine drug concentrations in the brain, in addition to plasma, by PET in clinical studies.

In a clinical study in healthy male subjects, concentration versus time profiles of FK-960 in plasma and different sections of the brain were determined following oral administration of FK-960 (Fig. 7). A mixture of [^{18}F]-FK960 and FK960 (6 mg/man, male, n=3, p.o.) was administrated to healthy subjects. In addition, whole-body PET imaging was carried out between 120 and 130 min after injection, showing that [^{18}F]-FK960 distributed to liver and kidneys, but not to the stomach and small intestine. The whole body scan suggested hepatic and renal clearance of FK960.

3.4.2 PET imaging in clinical oncology

In clinical oncology PET is used in the diagnosis of cancer, detection of metastasis and disease staging. It is also under investigation for the prediction of patient response to treatment (West et al., 2004). Early evaluation of treatment response can be of value to avoid unnecessary toxicity or ineffective treatment and to terminate development of uneffective drugs at an early stage, thereby saving costs of expensive late phase clinical studies. Currently, only two PET tracers have been described in a guidance by the FDA to assist applicants in preparing New Drug Applications (NDAs) (Guidance PET Drug

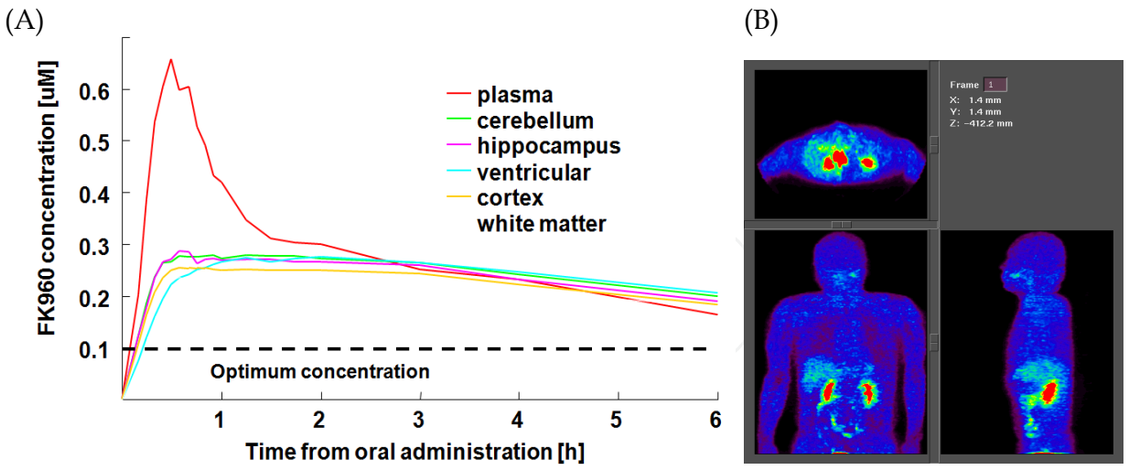


Fig. 7. (A) Concentration versus time curves of FK-960 in plasma and different area's of the brain in healthy subjects following oral administration of a mixture of [^{18}F]-FK960 and FK960 (6mg, n=3). (B) Biodistribution of [^{18}F]-FK960 in human whole-body using PET imaging. Images were acquired 120-130 min after administration.

Applications - Content and Format for NDAs and ANDAs, February 2011). There has been evidence that nuclear medicine imaging techniques could provide unique, biologically relevant, and prognostically important information unavailable through anatomic imaging such as CT or MRI. Multiple quantitative measurements can be performed by PET, which enables to monitor the effects of the treatment at an early stage, before those changes are detectable with conventional imaging modalities. The most important PET tracer in clinical oncology is FDG, which reflects glucose metabolism in the tumor. FDG-PET has shown to be of value in the differentiation of benign and malignant tissues, preoperative staging, detection of recurrent disease, and, more recently, in the identification of early tumor response to therapy. FLT-PET has attracted attention as a biomarker to evaluate tumor cell proliferation. The FDA has approved an investigational new drug (IND) application for [^{18}F]-FLT, sponsored by the Society of Nuclear Medicine (SNM).

Early response evaluation using FDG and FLT has been used for example for erlotinib (Tarceva©), an inhibitor of the epidermal growth factor receptor (EGFR), used in the treatment of solid tumors, such as non-small cell lung cancer (NSCLC) and pancreatic cancer. [^{18}F]-FDG PET has been recognized as an adequate staging tool in patients with NSCLC, and several studies suggested that the standardized uptake value (SUV) has a prognostic value in NSCLC. Furthermore, it has been reported that at an early stage during erlotinib therapy, [^{18}F]-FDG PET/CT can predict treatment in NSCLC patients (Aukema et al., 2010).

The accuracy of FDG-PET and FLT-PET were evaluated in patients with advanced NSCLC for early prediction of progression after 6 weeks of therapy wit erlotinib (Zander et al., 2011). FDG-PET predicted progression-free survival (PFS), overall survival (OS), and absence of progression after 6 weeks of therapy with erlotinib in treatment-naive patients with advanced NSCLC independent from the EGFR mutational status. Moreover, it was reported that early FDG-PET response on day 14 after initiation of erlotinib therapy, was associated with improved PFS and OS, even in the absence of subsequent RECIST response (Mileshkin et al., 2011).

PET is also useful to assess the PK of the anticancer drug in tumor tissue. This is of particular interest for anticancer drugs, which have their target in the tumor cell, for example drugs that target mRNA of a specific cancer gene. Tumor cells generally overexpress efflux pumps, such as P-gp, which prevent anticancer drugs that are P-gp substrate, to enter the tumor cell, thereby causing tumor resistance to the treatment. This can lead to continuation of tumor cell proliferation, experience of unncessary adverse events of the chemotherapy, and delay in determination of the effective dose regimen or decision to switch to other potential effective treatment. The delivery of antisense oligonucleotide directed against survivin mRNA in tumor tissue was determined using [^{11}C]-LY2181308 PET imaging in a phase 1 clinical study (Talbot et al., 2010).

3.4.3 PET imaging to determine the effect of antidiabetic drugs on β-cell mass

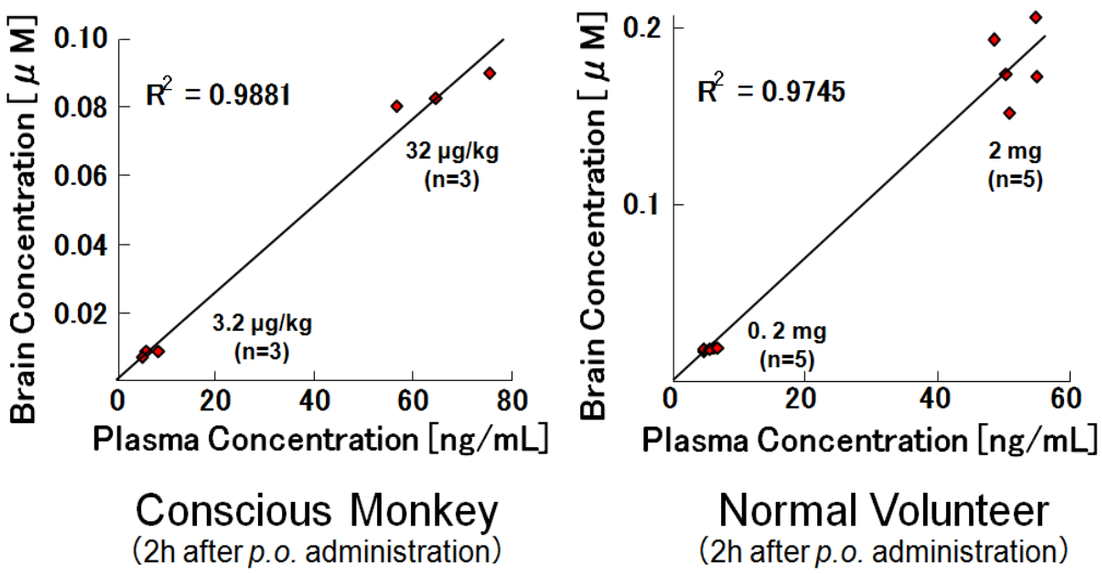
It is considered important to evaluate the effect of glucose lowering drugs on preservation of pancreatic BCM in patients with T2DM, since BCM is affected by the disease. Overall pancreatic BCM reflects the balance between the dynamic processes of β-cell expansion, through proliferation and neogenesis, and β-cell loss via apoptosis. Given that BCM can be modified significantly by altering the rate of any of these mechanisms, therapies that modulate β-cell expansion and loss have garnered recent interest. Therefore, it is also used as a tool to differentiate a novel antidiabetic drug in development from existing/marketed glucose lowering drugs with regard to its pharmacological activity. In fact, pioglitazone treatment preserved pancreatic β-cell morphology and β-cell function in obese diabetic *db/db* mice (Kawasaki et al., 2005). Furthermore, pioglitazone protects human β-cells against apoptosis or loss of function under exposure to interleukin-1β or high-glucose concentrations *in vitro* (Zeender et al., 2004). In obese Zucker rats, rosiglitazone maintained β-cell proliferation and prevented loss of β-cells (Finegood et al., 2001). Recently, treatment with thiazolidinediones was reported to improve β-cell function, which is strongly correlated with glycemic control, in patients with T2DM (Gastaldelli et al., 2007). DPP-IV inhibitors and incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) stimulate not only insulin secretion but also augment BCM via β-cell proliferation and neogenesis. Also, GLP-1 receptor signaling modifies the cellular susceptibility to apoptosis. Unfortunately, most studies measuring BCM have relied on postmortem examination of the pancreas, because until recently it was impossible to prospectively measure BCM *in vivo*.

A PET study with [^{11}C]-DTBZ quantified VMAT2 expression in the pancreas as a non-invasive measurement of pancreatic BCM, and demonstrated differences in BCM between healthy subjects and patients with type 1 diabetes patients (T1DM) (Goland et al., 2009). Others demonstrated that [^{18}F]-FP-DTBZ compared to [^{11}C]-DTBZ substantially improved, both qualitatively and quantitatively, the ability to image pancreatic BCM in T1DM (Normandin et al, 2010). Futhermore, [^{18}F]-FP-DTBZ was suggested to be safe and to be used for biodistribution and radiation dosimetry for imaging in humans and possibly to be used repetitively in longitudinal studies (Lin et al., 2010). Up to date, no PET studies for BCM determination have been published in T2DM patients. Others showed that since there is a significant BCM reserve, T2DM symptoms related to unstable glucose homeostasis are not obvious until BCM has been reduced by more than 50–60% (Souza et al., 2006(b)). Determination of β-cell mass in T2DM patients can become relevant in the future (Rhodes et al., 2005).

4. Translation of PET imaging from animals to humans

As mentioned before, PET has been applied to determine the PK study as a brain tissue PK measurement of [^{18}F]-FK962 in the brain in monkeys and in humans. A mixture of a tracer amount of [^{18}F]-FK962 and cold FK962 was administrated orally to conscious monkeys (n=3, doses: 0.0032 mg/kg and 0.032 mg/kg) and orally to healthy subjects (n=5, doses: 0.2 mg/man and 2 mg/man). PET data showed a good linearity between the brain concentration and plasma concentration in both monkeys and humans (Fig. 8). The brain concentration in humans was found to be about 2-fold higher than that in monkeys at comparable plasma drug concentrations. In addition, the optimum dosage for oral administration was estimated at 2 mg in humans based on both human brain concentrations by PET and rat brain concentrations in a preclinical efficacy study (data not shown).

(A)



(B)

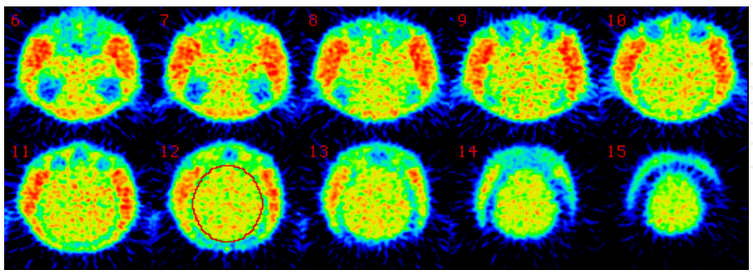


Fig. 8. (A) Correlations between FK-962 drug concentrations in plasma and the brain in monkeys and humans using PET imaging. (B) Transverse PET images showing distribution of [^{18}F]-FK9602 in the brain of conscious monkeys. PET images were taken 90-120 min after drug administration as 3.6 mm transverse slices from the lower brain (top left) to the upper brain (bottom right). The circle as presented in image 12 indicates the brain area in the skull.

Thus, non-invasive imaging techniques such as PET have become available for assessment of drug distribution *in vivo,* including determination of drug brain concentrations in

humans. Although PET enables monitoring of regional drug concentration differences with a spatial resolution of a few millimetres, discrimination between bound and unbound drug or parent compound and metabolite is difficult. Furthermore, labeling of a PET tracer is time consuming and expensive and requires special expertise on radiation exposure. PET studies in monkeys can be useful to establish the methodology for clinical PET studies. Complementary use of MB study results (see session 2.2) with PET imaging can provide more extensive drug distribution data than MB studies alone. The use of PET imaging could play an important role in future drug research and development with the potential to serve as translational tool for clinical decision making (Brunner et al., 2006).

5. Conclusions

Radiolabeled compounds are commonly used in the R&D of drugs. In ADME studies radiosotopes are relevant to a) evaluate the exposures of the parent compound and its metabolites in animals and humans for validation of toxicological species, b) identify the major metabolic pathways in humans to support drug–drug interaction studies, c) establish the rate and route of excretion of a drug candidate, and d) provide metabolism data of drugs for regulatory filing. Using radioactive materials in ADME studies in animals and humans helps to identify and quantify metabolites, and reveal the major metabolite(s) and clearance pathways.

In clinical development, radiolabeled compounds are used in MB studies to obtain information on the absorption, metabolism, and elimination of a drug. Other applications are the use in regional drug absorption studies to determine the PK of a drug in a novel modified release formulation and in microdose studies to obtain PK data after administration of a trace subpharmacologic quantity to human subjects.

PET is a powerful non-invasive technique, which is used to evaluate the PK (e.g. drug exposure), PD (e.g. receptor binding) in animals and humans. For CNS targeted drugs, it is used to assess drug penetration and distribution into different areas of the brain and to determine the target (receptor/transporter) occupancy by the drug, which provides an estimation of the binding potency and durability of the drug *in vivo*. In oncology PET is used in the diagnosis of cancer, detection of metastasis, disease staging, and for the prediction of patient response to treatment. In the field of diabetes mellitus, PET imaging could be considered a relevant tool to evaluate the effects of glucose lowering drugs on preservation of pancreatic β-cells in diabetes patients.

In summary, PET imaging can be used a) to estimate the pharmacological activity of a drug, b) to select the starting dose in first-in-man studies, c) as a surrogate biomarker for efficacy, and d) to proof mechanism and/or concept of a compound. This helps to determine at an early phase of development whether or not the drug is a good candidate to take into further clinical development. Thereby, PET imaging can also help to terminate the development of unfavourable drugs at an early stage, thereby reducing unnecessary development costs.

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7. References

Kola, I. The state of innovation in drug development. Clin Pharmacol Ther 2008;83:227-30.

Penner N, Klunk L.J., Prakash C. Human Radiolabeled Mass Balance Studies: Objectives, Utilities and Limitations. Biopharm Drug Dispos 2009;30:185-203.

Marathe P.H., Shyu W.C., Humphreys W.G. The use of radiolabeled compounds of ADME studies in discovery and exploratory development. Current Pharmaceutical Design 2004;10:2991-3008.

Glaser M, Collingridge DR, Aboagye EO, Bouchier-Hayes L, Clyde Hutchinson O, Martin SJ, Price P, Brady F, Luthra SK. Iodine-124 labelled Annexin-V as a potential radiotracer to study apoptosis using positron emission tomography. Applied Radiation and Isotopes 2003;58:55-62.

Hoy CA, Lewis ED, Schimke RT. Perturbation of DNA Replication and Cell Cycle Progression by Commonly Used [^{3}H]Thymidine Labeling Protocols. Molecular and Cellular Biology 1990;10:1584-1592.

Heinemann V, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-h-D-arabinofuranosylcytosine. Cancer Res 1988;48:4024–31.

Mackey JR, Yao SY, Smith KM, et al. Gemcitabine transport in xenopus oocytes expressing recombinant plasma membrane mammalian nucleoside transporters. J Natl Cancer Inst 1999;91:1876–81.

Veltkamp SA, Pluim D, van Tellingen O, Beijnen JH, Schellens JH. Extensive metabolism and hepatic accumulation of gemcitabine after multiple oral and intravenous administration in mice. Drug Metab Dispos 2008;36:1606-15(a).

Veltkamp SA, Pluim D, van Eijndhoven MA, Bolijn MJ, Ong FH, Govindarajan R, Unadkat JD, Beijnen JH, Schellens JH. New insights into the pharmacology and cytotoxicity of gemcitabine and 2',2'-difluorodeoxyuridine. Mol Cancer Ther 2008;7:2415-25(b).

U.S. Food and Drug Administration, Department of Health and Human Services, Center for Drug Evaluation and Research: Guidance for Industry: Safety Testing of Drug metabolites, February 2008.

Combesa R.D., Berridge T., Connelly J., Eve M.D., Garner R.C., Toon S., Wilcox P. Early microdose drug studies in human volunteers can minimise animal testing: Proceedings of a workshop organised by volunteers in Research and Testing. European Journal of Pharmaceutical Sciences 2003;19:1–11.

International Conference on Harmonisation. ICH Harmonized Tripartite Guideline: Guidance on M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, June 2009.

Lappin G, Kuhnz W, Jochemsen R, Kneer J, Chaudhary A, Oosterhuis B, Drijfhout WJ, Rowland M, Garner RC. Use of microdosing to predict pharmacokinetics at the therapeutic dose: experience with 5 drugs. Clin Pharmacol Ther 2006;80:203-15.

The European Agency for the Evaluation of Medicinal Products. Evaluation of Medicines for Human Use. Position Paper on Non-Clinical Safety Studies to Support Clinical Trials With a Single Microdose. London: EMEA 2003:1-4.

U.S. Food and Drug Administration, Department of Health and Human Services, Center for Drug Evaluation and Research. Guidance for Industry, Investigators, and Reviewers. Exploratory IND Studies, 2006: 1-16.

Bergstrom M, Grahnen A, Langstrom B. Positron emission tomography microdosing: A new concept with application in tracer and early clinical drug development. Eur J Clin Pharmacol 2003;59:357–366.

Marchetti S, Schellens JH. The impact of FDA and EMEA guidelines on drug development in relation to Phase 0 trials. Br J Cancer 2007;97:577–581.

Chen K., et al. Positron Emission Tomography imaging cancer biology: Current status and future prospects. Seminars in Oncology 2011;38:70-86.

Rostomian AH, Madison C, Rabinovici GD, Jagust WJ. Early 11C-PIB frames and 18F-FDG PET measures are comparable: a study validated in a cohort of AD and FTLD patients. J Nucl Med 2011;52:173-9.

Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymont V, Ravert HT, Dannals RF, Nandi A, Brasić JR, Ye W, Hilton J, Lyketsos C, Kung HF, Joshi AD, Skovronsky DM, Pontecorvo MJ. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (Flobetapir F 18). J Nucl Med 2010;51:913-20.

Noda A, Takamatsu H, Murakami Y, Yajima K, Tatsumi M, Ichise R, Nishimura S. Measurement of brain concentration of FK960 for development of a novel antidementia drug: a PET study in conscious rhesus monkeys. J Nucl Med 2003;44:105-8(a).

Mihara T, Noda A, Arai H, Mihara K, Iwashita A, Murakami Y, Matsuya T, Miyoshi S, Nishimura S, Matsuoka N. Brain adenosine A_{2A} receptor occupancy by a novel A_1/A_{2A} receptor antagonist ASP5854 in rhesus monkey: Relationship to anti-cataleptic effect. J Nucl Med 2008;49:615-22.

Asai M, Fujikawa A, Noda A, Miyoshi S, Matsuoka N, Nishimura S. Donepezil- and scopolamine-induced rCMRglu changes assessed by PET in conscious rhesus monkeys. Ann Nucl Med 2009;23:877-82.

Mitsuoka K, Miyoshi S, Kato Y, Murakami Y, Utsumi R, Kubo Y, Noda A, Nakamura Y, Nishimura S, Tsuji A. Cancer detection using a PET tracer, ^{11}C-glycylsarcosine, targeted to H^+/peptide transporter. J Nucl Med 2008;49:615-22.

Narayanan TK, Said S, Mukherjee J, Christian B, Satter M, Dunigan K, Shi B, Jacobs M, Bernstein T, Padma M, Mantil J. A comparative study on the uptake and incorporation of radiolabeled methionine, choline and fluorodeoxyglucose in human astrocytoma. Mol Imaging Biol 2002;4:147–156.

Bruehlmeier M, Roelcke U, Schubiger PA, Ametamey SM. Assessment of hypoxia and perfusion in human brain tumors using PET with 18F-fluoromisonidazole and ^{15}O-H_2O. J Nucl Med 2004;45:1851–1859.

Piert M, Machulla HJ, Picchio M, Reischl G, Ziegler S, Kumar P, Wester HJ, Beck R, McEwan AJ, Wiebe LI, Schwaiger M. Hypoxia-specific tumor imaging with 18F-fluoroazomycin arabinoside. J Nucl Med 2005;46:106–113.

Kadir A, Nordberg A. Target-specific PET probes for neurodegenerative disorders related to dementia. J Nucl Med 2010;51:1418-30.

Noda A, Takamatsu H, Matsuoka N, Koyama S, Tsukada H, Nishimura S. Effect of N-(4-Acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate (FK960), an antidementia drug with a novel mechanism of action, on regional cerebral blood flow and glucose metabolism in aged rhesus macaques studied with positron emission tomography. J Pharmacol Exp Ther 2003;306:213-7(b).

Nakahara T, Kita A, Yamanaka K, Mori M, Amino N, Takeuchi M, Tominaga F, Kinoyama I, Matsuhisa A, Kudou M, Sasamata M. Broad spectrum and potent antitumor activities of YM155, a novel small-molecule survivin suppressant, in a wide variety of human cancer cell lines and xenograft models. Cancer Science 2011;102:614-621(a).

Iwasa T, Okamoto I, Suzuki M, Nakahara T, Yamanaka K, Hatashita E, Yamada Y, Fukuoka M, Ono K, Nakagawa K. Radiosensitizing effect of YM155, a novel small-molecule survivin suppressant, in non-small cell lung cancer cell lines. Clin Cancer Res 2008;14:6496-504.

Iwasa T, Okamoto I, Takezawa K Yamanaka K, Nakahara T, Kita A, Koutoku H, Sasamata M, Hatashita E, Yamada Y, Kuwata K, Fukuoka M and Nakagawa K. Marked anti-tumour activity of the combination of YM155, a novel survivin suppressant, and platinum-based drugs. British Journal of Cancer 2010;103:36-42.

Iwai M, Minematsu T, Narikawa S, Usui T, Kamimura H. Involvement of Human Organic Cation Transporter 1 in the Hepatic Uptake of 1-(2-Methoxyethyl)-2-methyl-4,9-dioxo-3-(pyrazin-2-ylmethyl)-4,9-dihydro-1*H*-naphtho[2,3-*d*]imidazolium Bromide (YM155 Monobromide), a Novel, Small Molecule Survivin Suppressant. Drug Metabolism & Disposition 2009;37:1856-1863.

Satoh T, Okamoto I, Miyazaki M, Morinaga R, Tsuya A, Hasegawa Y, Terashima M, Ueda S, Fukuoka M, Ariyoshi Y, Saito T, Masuda N, Watanabe H, Taguchi T, Kakihara T, Aoyama Y, Hashimoto Y, Nakagawa K. Phase I study of YM155, a novel survivin suppressant, in patients with advanced solid tumors. Clinical Cancer Research 2009;15:3872-3880.

Tolcher AW, Mita A, Lewis LD, Garrett CR, Till E, Daud AI, Patnaik A, Papadopoulos K, Takimoto C, Bartels P, Keating A, and Antonia S. Phase I and Pharmacokinetic Study of YM155, a Small-Molecule Inhibitor of Survivin. Journal of Clinical Oncology 2008;26:5198-5203.

Lewis KD, Samlowski W, Ward J, Catlett J, Cranmer L, Kirkwood J, Lawson D, Whitman E, Gonzalez R. A multi-center phase II evaluation of the small molecule surviving suppressor YM155 in patients with unresectable stage III or IV melanoma. Invest New Drugs 2011; 29:161–166.

Giaccone G, Zatloukal P, Roubec J, Floor K, Musil J, Kuta M, van Klaveren R.J., Chaudhary S, Gunther A, and Shamsili S. Multicenter Phase II Trial of YM155, a Small-Molecule Suppressor of Survivin, in Patients With advanced, Refractory, Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 2009;27:4481-4486.

Nakahara T, Yamanaka K, Hatakeyama S, Kita A, Takeuchi M, Kinoyama I, Matsuhisa A, Nakano K, Shishido T, Koutoku H, Sasamata M. YM155, a novel survivin suppressant, enhances taxane-induced apoptosis and tumor regression in a human Calu 6 lung cancer xenograft model. Anticancer Drugs 2011;22:454-462 (b).

Souza F, Simpson N, Raffo A, Saxena C, Maffei A, Hardy M, Kilbourn M, Goland R, Leibel R, Mann JJ, Van Heertum R, Harris PE. Longitudinal noninvasive PET-based beta cell mass estimates in a spontaneous diabetes rat model. J Clin Invest 2006;116:1506-13(a).

Simpson NR, Souza F, Witkowski P, Maffei A, Raffo A, Herron A, Kilbourn M, Jurewicz A, Herold K, Liu E, Hardy MA, Van Heertum R, Harris PE. Visualizing pancreatic beta-cell mass with [^{11}C]DTBZ. Nucl Med Biol 2006;33:855-64.

Murthy R, Harris P, Simpson N, Van Heertum R, Leibel R, Mann JJ, Parsey R. Whole body [^{11}C]-dihydrotetrabenazine imaging of baboons: biodistribution and human radiation dosimetry estimates. Eur J Nucl Med Mol Imaging 2008;35:790-7.

Goland R, Freeby M, Parsey R, Saisho Y, Kumar D, Simpson N, Hirsch J, Prince M, Maffei A, Mann JJ, Butler PC, Van Heertum R, Leibel RL, Ichise M, Harris PE. ^{11}C-dihydrotetrabenazine PET of the pancreas in subjects with long-standing type 1 diabetes and in healthy controls. J Nucl Med, 2009;50:382-9.

Kung MP, Hou C, Goswami R, Ponde DE, Kilbourn MR, Kung HF. Characterization of optically resolved 9-fluoropropyl-dihydrotetrabenazine as a potential PET imaging agent targeting vesicular monoamine transporters. Nucl Med Biol 2007;34:239-46.

Kung MP, Hou C, Lieberman BP, Oya S, Ponde DE, Blankemeyer E, Skovronsky D, Kilbourn MR, Kung HF. In vivo imaging of beta-cell mass in rats using ^{18}F-FP-(+)-DTBZ: a potential PET ligand for studying diabetes mellitus. J Nucl Med 2008;49:1171-6(a).

Tsao HH, Lin KJ, Juang JH, Skovronsky DM, Yen TC, Wey SP, Kung MP. Binding characteristics of 9-fluoropropyl-(+)-dihydrotetrabenzazine (AV-133) to the vesicular monoamine transporter type 2 in rats. Nucl Med Biol. 2010;37:413-9.

Kung HF, Lieberman BP, Zhuang Z-P, Oya S, Kung M-P, Choi SR, Poessl K, Blankemeyer E, Hou C, Skovronsky D, and Kilbourn M. In vivo imaging of VMAT2 in pancreas using a ^{18}F epoxide derivative of tetrabenazine. Nucl Med Biol 2008;35:825-837(b).

Freeby M, Goland R, Ichise M, Maffei A, Leibe R and Harris P. VMAT2 quantitation by PET as a biomarker for β-cell mass in health and disease. Diabetes, Obesity and Metabolism 2008;10 (Suppl. 4):98–108.

West CML, Jones T, Price P. The potential of positron-emission tomography to study anticancer-drug resistance. Nature Reviews 2004;457-469.

U.S. Food and Drug Administration, Department of Health and Human Services; Center for Drug Evaluation and Research: Guidance PET Drug Applications - Content and Format for NDAs and ANDAs, February 2011.

Aukema TS, Vogel WV, Hoefnagel CA, and Vald´es Olmos RA. Prevention of Brown Adipose Tissue Activation in ^{18}F-FDG PET/CT of Breast Cancer Patients Receiving Neoadjuvant Systemic Therapy. J Nucl Med Technol 2010; 38:12–15.

Zander T, Scheffler M, Nogova L, Kobe C, Engel-Riedel W, Hellmich M, Papachristou I, Toepelt K, Draube A, Heukamp L, Buettner R, Ko YD, Ullrich RT, Smit E, Boellaard R, Lammertsma AA, Hallek M, Jacobs AH, Schlesinger A, Schulte K, Querings S, Stoelben E, Neumaier B, Thomas RK, Dietlein M, and Wolf J. Early Prediction of Nonprogression in Advanced Non–Small-Cell Lung Cancer Treated With Erlotinib By Using [^{18}F]-Fluorodeoxyglucose and [^{18}F]-Fluorothymidine Positron Emission Tomography 2011;29:1701-1708.

Mileshkin L, Hicks RJ, Hughes BGM, Mitchell P, Charu V, Gitlitz BJ, Macfarlane D, Solomon B, Amler L, Yu W, Pirzkall A, and Fine BM. Changes in ^{18}F-Fluorodeoxyglucose and ^{18}F-Fluorodeoxythymidine Imaging in Patients with Non-Small Cell Lung Cancer Treated with Erlotinib. Clin Cancer Res 2011;17:3304-3315.

Talbot D, Ranson M, Davies J, Lahn MM, Callies S, Andre VAM, Kadam S, Burgess M, Slapak CA, Olsen AL, McHugh P, de Bono JS, Matthews J, Saleem A, and Price PM. Tumor Survivin is Downregulated by the Antisense Oligonucleotide

LY2181308: A Proof of Concept, First-in-Human Dose Study. Clinical Cancer Resrearch 2010;16:6150.

Kawasaki F, Matsuda M, Kanda Y, Inoue H, Kaku K. Structural and functional analysis of pancreatic islets preserved by pioglitazone in db/db mice. Am J Physiol Endocrinol Metab 2005;288:E510-8.

Zeender E, Maedler K, Bosco D, Berney T, Donath MY, Halban PA. Pioglitazone and sodium salicylate protect human beta-cells against apoptosis and impaired function induced by glucose and interleukin-1beta. J Clin Endocrinol Metab 2004;89:5059-66.

Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, Leonard T, Buckingham RE. Beta-cell mass dynamics in Zucker diabetic fatty rats. Rosiglitazone prevents the rise in net cell death. Diabetes 2001;50:1021-9.

Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. Am J Physiol Endocrinol Metab 2007;292:E871-83.

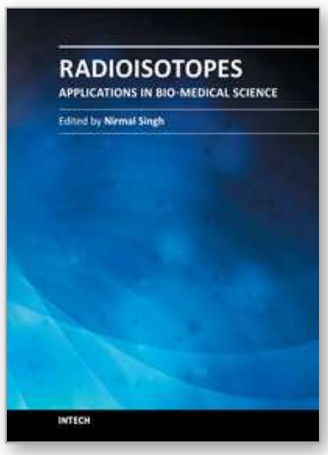
Lin KJ, Weng YH, Wey SP, Hsiao IT, Lu CS, Skovronsky D, Chang HP, Kung MP, Yen TC. Whole-body biodistribution and radiation dosimetry of ^{18}F-FP-(+)-DTBZ (18F-AV-133): a novel vesicular monoamine transporter 2 imaging agent. J Nucl Med, 2010;51:1480-5.

Souza F, Freeby M, Hultman K, Simpson N, Herron A, Witkowsky P, Liu E, Maffei A, Harris PE. Current progress in non-invasive imaging of beta cell mass of the endocrine pancreas. Curr Med Chem. 2006;13:2761-73(b).

Rhodes CJ. Type 2 Diabetes-a Matter of β-Cell Life and Death? Science 2005;307:380-384.

Normandin M, Skaddan M, Petersen K, Calle R, Weinzimmer D, Skovronsky D, Treadway J, Carson R, Ding Y-S, and Cline G. PET imaging of pancreatic beta cell mass with [^{18}F]FP-DTBZ. J Nucl Med 2010;51(Suppl. 2):130.

Brunner M, Langer O. Microdialysis versus other techniques for the clinical assessment of in vivo tissue drug distribution. AAPS J 2006;14;8:E263-71.



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The book Radioisotopes - Applications in Bio-Medical Science contains two sections: Radioisotopes and Radiations in Bioscience and Radioisotopes and Radiology in Medical Science. Section I includes chapters on medical radioisotope production, radio-labeled nano-particles, radioisotopes and nano-medicine, use of radiations in insects, drug research, medical radioisotopes and use of radioisotopes in interdisciplinary fields etc. In Section II, chapters related to production of metal PET (positron emission tomography) radioisotopes, 3-dimensional and CT (computed tomography) scan, SS nuclear medicine in imaging, cancer diagnose and treatments have been included. The subject matter will by highly useful to the medical and paramedical staff in hospitals, as well as researchers and scholars in the field of nuclear medicine medical physics and nuclear bio-chemistry etc.

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