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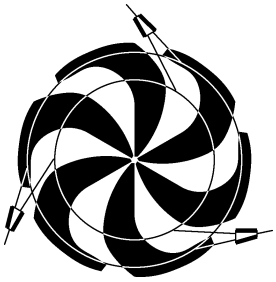

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CANADA'S NATIONAL LABORATORY
FOR PARTICLE AND NUCLEAR PHYSICS

OPERATED AS A JOINT VENTURE

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UNDER A CONTRIBUTION FROM THE
NATIONAL RESEARCH COUNCIL OF CANADA

OCTOBER 2002

The contributions on individual experiments in this report are outlines intended to demonstrate the extent of scientific activity at TRIUMF during the past year. The outlines are not publications and often contain preliminary results not intended, or not yet ready, for publication. Material from these reports should not be reproduced or quoted without permission from the authors.

LIFE SCIENCES

Introduction

This year represented the penultimate effort in establishing PET as a tool for clinical research in the local hospitals that now possess hybrid PET/SPECT cameras (Lion's Gate and St. Paul's) or have a request into government for a full body PET system (VGH) by establishing a mechanism whereby the FDG will be supplied by VGH in the coming year(s) through co-operation between the local hospitals, TRIUMF and MDS Nordion. In keeping with the TRIUMF effort to provide the resources for the affiliated universities to establish their own PET programs, we have supplied the University of Alberta with ^{18}F-fluoride with which they prepare their own FDG. This approach will continue until the installation of their cyclotron, scheduled for the summer of 2002. Thus TRIUMF has served the community well in making PET available at a relatively early stage in the Canadian context.

Strong collaborations with several departments at UBC continued to rely upon the unique radioisotope production capabilities of TRIUMF. The anticipated arrival of the new high-resolution research tomograph will herald a new era in PET imaging with resolution and sensitivity unsurpassed anywhere in the world.

Experiment LS0
PET facilities
(K.R. Buckley, TRIUMF)

The PET facilities comprise the TR13 13 MeV H^- cyclotron, the ECAT 953B/31 tomograph, and ancillary equipment such as counting and data acquisition systems.

Personnel

Dr. Dirk Becker, a postdoctoral fellow in targetry, left us in the spring to take up a position closer to home in Europe. Carolyn English returned from maternity leave at the end of the summer giving us two full time nuclear medicine technologists for scanner operations.

Dr. John Wilson of the Cross Cancer Centre came to TRIUMF in mid-November to learn cyclotron operation and carry out the irradiations for the production of ^{18}F for shipment to Edmonton. Dr. Wilson will stay until their cyclotron facility is ready in Edmonton in the spring of 2002. We are currently sending ^{18}F to the Cross Cancer Centre in Edmonton three times per week.

TR13 cyclotron

Usage of the TR13 cyclotron dropped this year in delivered beam due to a decreased demand for irradiation of lithium targets for the production of ^{7}Be (LS8). The total number of runs increased to 848 vs. 808 last year. The production of ^{18}F for shipment to Edmonton began in earnest this year with 91,240 μA min of beam being delivered to target.

Downtime this year was much less significant than last year and was caused by a variety of faults. The only repair of major significance was the need to replace the rf amplifier controller with a TRIUMF built unit. This controller looks after the startup and shutdown of the rf tube and its interlocks. The unit that came with the amplifier is obsolete and no parts are available for repairs. Other amplifiers on site and at other installations of the TR series of cyclotrons have small PLC units in place of this controller. Our controller has failed and at present the amplifier is manually started and shut down while this new controller is being assembled.

Ten extraction foil changes were required through the year and all targets where rebuilt at least once. The new niobium target for the production of ^{18}F continues to perform well. Some difficulties attributed to this target in mid-summer were eventually traced to contaminated ^{18}O-water. The target exhibited very high beam-on pressure and residual pressure in the target at beam-off. The target was disassembled and cleaned twice with no change in performance until new ^{18}O-water was tried. Fortunately only 4–5 ml of water were left in the suspect vial. Four ion source filament changes have been performed this year.

A target to allow scattered protons (from a beam of a few nanoamperes) to be extracted to atmosphere was constructed and operated in the spring and summer for a few sessions of several hours each. This target was in support of the HERMES collaboration to allow testing of a wire chamber detector. The target consisted of a carbon foil and beam stop mounted in vacuum and a thin kapton foil over a side port at 45° for the scattered protons. Interlocks of beam current and radiation fields were instituted to allow operation of the cyclotron with one shield open. The open shield space was used to install the detector to be tested. Tests were conducted in the evening to prevent disruption of the normal production runs.

Presently there are six target locations occupied of the available eight. These consist of:

- one ^{18}O-O_2 gas target;
- one ^{18}O-water target;
- one ^{16}O-water target;
- one N_2/H_2 gas target;
- one experimental gas target;
- one lithium metal target.

The lithium target (LS8) has a reserved location and is installed and removed for each production. This

target runs routinely for 15 hours at 50 μA. The target was only run once this year. At least one run of approximately 40 hours duration is needed in the near future for the production of a high activity ^{7}Be target. It is anticipated that this will be the last run required.

ECAT tomograph

Block detector failures continue to be the dominant mode of failure for the camera. We are routinely repairing blocks in-house and have replaced 7 blocks this year; all were component failures in the voltage dividers. We have still not assembled the necessary components to properly calibrate the blocks prior to returning them to the scanner. At present only a simple visual balance of PMT outputs is performed on the bench and the block set-up routine in the scanner performs the fine tuning.

Programmable logic chips in the position/energy processors continue to fail occasionally and several chips in 3 different buckets have been replaced this year. TRIUMF electronics is able to program new chips for us.

An intermittent problem with 2D reconstructions in the front end encountered late in 2000 was found to be due to the array processor, which was replaced in February.

An instability problem with the camera calibration has arisen and this is presently attributed to one high voltage power supply. A spare has been obtained to allow off-line servicing of this supply. The current required by the ECAT gantry exceeds the capability of any of the high voltage supplies available at TRIUMF.

Statistics

Table X. TR13 run data.

Total runs conducted	848	
Total runs lost	8	
Integrated charge delivered	631,357	μA-min
Delivered to – LS2	160	
– LS3	262,573	
– LS4	55,327	
– LS8	144,199	
– LS13	33,611	
– LS24	33,172	
– LS32	91,240	
– LS33	477	
– LS39	4,580	
– LS47	300	
– LS49	3,282	
– LS52	2,436	

Table XI. ECAT scan data.

Total scans conducted	379
Total scans lost	52
Lost to – patient	10
– scanner	13
– chemistry	6
– cyclotron	8
– staffing	15

Experiment LS2
Synthesis of radiohalogenated carbohydrates for use as imaging agents in PET and SPECT
(M.J. Adam, TRIUMF)

This project was divided into two parts. Part 1 was on the synthesis and evaluation of 2,2-dihalo-sugars for use as imaging agents. Part 2 was on the synthesis and evaluation of glycosidase inhibitors as imaging agents for lysosomal diseases.

Part 1. 2,2-dihalo-sugars

The use of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) to study glucose metabolism has seen extensive clinical applications, especially in cardiology and oncology. Because of the growing importance of FDG/PET for clinical use, we decided to study close analogues of FDG, 2,2-dihalo sugars, to see how they compared. To this end we synthesized 2-deoxy-2,2-[^{18}F]difluoro-glucose and 2-deoxy-2-[^{123}I]iodo-2-fluoro-mannose (FIM). The latter compound was synthesized as a possible SPECT version of FDG. Previous studies indicated that the fluoro substituent stabilized the iodine in position 2, as compared with 2-iodo-glucose. Unfortunately, the stability of FIM *in vitro* does not extend *in vivo*. Following injection, the product is rapidly de-iodinated. Therefore, based on this finding, we have decided to put this part of the project on hold indefinitely.

Part 2. Glycosidase inhibitors

We have previously synthesized 2-deoxy-2-[^{18}F]-fluoro-β-mannosyl [^{18}F]-fluoride and shown that it behaves as a mechanism-based inhibitor of *Agrobacterium* sp. β-glucosidase. *In vivo* experiments indicate that this compound undergoes partial hydrolysis to produce 2-deoxy-2-fluoro-mannose, which can become phosphorylated and trapped within the cell. We then turned our attention to ^{18}F-labelling at the 6 position so that the label cannot be lost during such glycoside hydrolysis, and cannot be phosphorylated. The mechanism-based glycosidase inhibitor 2,6-dideoxy-2-fluoro-6-[^{18}F]-fluoro-β-D-glucopyranosyl fluoride (2,6FGF) was synthesized in 69% overall chemical yield, and in 9% radiochemical yield (decay corrected), as a potential imaging probe for glycosidase. Unfortunately, binding studies with

glucocerebrosidase were unsuccessful after many attempts. Due to a possible fatal flaw in the experimental design, coupled with the lack of funding, we have decided to bring this project to an end. The PI will focus attention on radio-metallated carbohydrates as described in LS53.

This project has produced seven publications and two Ph.D. theses (J. McCarter and A. Wong) over its lifetime.

Experiment LS3
Synthesis of radiopharmaceuticals for positron emission tomography
(M.J. Adam, TRIUMF)

Daily routine production of up to 10 radiopharmaceuticals is currently performed with 3–4 radiophamaceuticals synthesized on any given day. FDG is sent once per week to each of Vancouver, Lions Gate and St. Paul's Hospitals for research in cardiology and oncology. Out of these 10 radiopharmaceuticals, five (FDOPA, Raclopride, TBZ-OH, SCH23390 and MP) are used most heavily. There has been a decline in the number of Raclopride preparations from last year, but Raclopride remains the most heavily used radiopharmaceutical. Most of the Raclopride preparations this year are for the "Scatchard Analysis" experiment that Doris Doudet is performing on monkeys. These experiments require 3–4 Raclopride preparations each day where one is at a high specific activity (SA) of 5–10 Ci/μmol, and the others have carrier added to give a range of SAs of 2–35 Ci/mmol at time of injection. All preparations for these experiments are assayed by HPLC prior to injection to confirm the specific activity. There was a total of 523 production runs in 2001 for CIHR/PET and external users, with 369 radiopharmaceutical syntheses carried out just for the TRIUMF/UBC PET Program.

The demand for FDG from our group remains low. However, most of our FDG production is being used by Lions Gate, St. Paul's and Vancouver Hospitals for studies in oncology and cardiology (details in LS13, 24, 40, 48 and 49 proposals). We currently send FDG to these hospitals one day per week in amounts sufficient for imaging approximately 3–4 patients. Vancouver Hospital is setting up an FDG synthesis system and the plan is to send only ^{18}F-fluoride to Vancouver Hospital in future and they will make the FDG for themselves and for all other local hospitals.

We have also started shipping ^{18}F-fluoride to Edmonton on a regular basis for clinical cancer imaging (see LS32 proposal). We began shipping approximately 1 Ci once per week and are now shipping three days per week. The Cross Cancer Centre in Edmonton has sent a chemist/trainee (Dr. John Wilson) to TRIUMF for a few months to carry out these runs and to learn cyclotron operations and PET chemistry. Nordion is handling the airline transport and Edmonton is paying all the transportation costs and the cost of the ^{18}O-water used in the target. The Cross Cancer Centre is able to carry out 5–6 patient scans with each shipment of radiofluorine from TRIUMF.

The synthesis of ^{11}C-PMP was brought into the routine category this year. PMP is an acetylcholinesterase inhibitor that will be used by Dr. Chong Lee to study dementia in Parkinson's disease (PD) and diffuse Lewy body disease. Previous studies in postmortem brains have shown that choline acetyltransferase activity, but not muscarinic cholinergic receptors, was markedly reduced in PD, diffuse Lewy body disease and Alzheimer's disease, and that neocortical cholinergic deficits correlate with severity of dementia in PD, diffuse Lewy body disease and Alzheimer's disease. As reduced cholinergic activity in the neocortex correlates with marked neuronal loss in the nucleus basalis of Meynert, these observations suggest that loss of cholinergic neurons in the basal forebrain may play a significant role in the pathogenesis of dementia in PD and diffuse Lewy body disease as well as in Alzheimer's disease.

Recently, tracers for cholinergic neurons have become available for PET studies in human subjects. By using PET to explore cholinergic factors that contribute to the development of dementia in both PD and diffuse Lewy body disease, we will cultivate a better understanding of the pathogenetic mechanisms underlying dementia in PD and diffuse Lewy body disease. This should ultimately lead to better strategies for the pharmacological management of PD and diffuse Lewy body disease. This year we have carried out 18 preparations averaging over 30 mCi per run. A grant application to fund further research with this agent has been submitted by Dr. Lee and an abstract has been submitted to the American Academy of Neurology meeting.

One of the new projects started this year is the synthesis of ^{11}C-Carfentanil for Dr. de la Fuente's research on Parkinson's disease. Dr. de la Fuente demonstrated, for the first time, that there was a measurable increase in the amount of dopamine released into the synapse when a placebo was administered, thus showing a chemical basis for the placebo effect. He now wants to extend this research to look at other receptor systems that might be involved, such as the opioid system. As with most new radiopharmaceutical projects, the synthesis of the precursor is the most labour intensive part. The synthesis of the precursor will take approximately six steps starting from a commercially available intermediate. Fortunately, we have had significant help and advice from Drs. Danals (Johns Hopkins U.) and Jewett (U. Michigan) on the synthesis of the

precursor and labelled product.

The synthesis of ^{18}F-labelled oligonucleotides has also been started this year to complement the Antisense research that has been ongoing in Dr. Stoessl's lab. To start, we are repeating the procedure of the INSERM French group and are attempting to attach a fluorinated aromatic group to the phosphorothioate end of the above oligo. So far we have demonstrated that we can attach the non-radioactive label to the oligo and purify it on HPLC. Attempts to synthesize the ^{18}F-labelled version have proven to be somewhat problematic. Unfortunately, it requires a multistep synthesis where the ^{18}F is introduced in the first step, making the procedure very difficult to carry out. We are attempting to find alternative, simpler methods for the ^{18}F-labelling of these oligos.

We continue to use TBAF in most of the ^{11}C methyl iodide reactions to enhance and stabilize the yields. We are fortunate to still obtain the nitro precursor of Setoperone as a gift from Jannsen Pharmaceuticals. We are also grateful to ASTRAZENECA AB for the gift of Raclopride Tartrate, used as carrier for the Scatchard experiments, and dihydroxy-Raclopride as the precursor for labelling. This year we have implemented the "loop" method for ^{11}C-methylations. In this method the gas phase methyl iodide is passed through the HPLC loop which contains the precursor such as dihydroxy-Raclopride. However, in order to use this method, we must first convert the dihydroxy-raclopride precursor to the free base since it is originally in the HBr salt form. All other precursors are synthesized in-house, which requires a major time commitment from Dr. Lu.

The new hot cell has been installed in the PET chemistry lab and is being used for all of the ^{11}C-chemistry. All of the older FDG and FDOPA chemistry systems were installed in the old hot cell and they are now slowly being rebuilt. These systems are about 15 years old and also need to be redesigned.

Experiment LS4
TR13 targets for PET radioisotope production
(T. Ruth, TRIUMF)

The highlights for this past year were to characterize the ^{18}F-fluoride gas target and successfully operate the target at 50 μA. More recently, in collaboration with researchers from the University of Wisconsin, we have developed a flow-through target for the production of $^{11}CH_4$. This target enabled us to produce over 1.5 Ci of $^{11}CH_4$, about double our production rate using a static target. Preliminary results in measuring the specific activity (SA) indicate that there is more carrier present than in the static runs. The SA will have to be improved if this new approach is to become routine.

Experiment LS8
Radiotracers for the physical and biosciences
(T. Ruth, TRIUMF)

Researchers in the Botany Department at UBC continue to undertake a wide range of experiments, bringing together physiological and biochemical studies using ^{13}N and molecular studies at the gene level, to further our understanding of nitrogen absorption and transport within plants.

Rice research: (Australian National University, Canberra)

In continuance of our basic work on NH_4^+ absorption by rice plants, we have cloned one gene (AMT1.1) that encodes a high-affinity NH_4^+ transporter and are currently examining its expression. It appears not to respond to the N status of the plant, rather it may respond to plant carbohydrate status. The Australian National University has already developed new strains of rice over-expressing this gene and has requested our assistance to measure $^{13}NH_4^+$ uptake by these over-expressers. We have successfully demonstrated that one line of the rice variety, JARRAH (line 75-4), absorbs ~40% more $^{13}NH_4^+$ than the parental line which expresses the normal level of the gene. This 40% increase is sustained in plants grown at low N or high N, and is therefore a promising transgenic line. We will next determine patterns of $^{13}NH_4^+$ efflux in this line. Clearly, if it is effluxing $^{13}NH_4^+$ at higher levels than parental lines, we have made little progress.

Nitrogen uptake in trees: a collaboration with CELLFOR

This project is funded by NSERC and BCRI for 3 years. The goal is to over-express the high-affinity NO_3^- transporter gene, (AtNrt2.1), that we cloned from Arabidopsis thaliana [Zhuo *et al.* (1999)], in hybrid spruce and in poplar seedlings. Since spruce is notoriously inefficient at absorbing NO_3^- [Kronzucker *et al.* (1997)], our goal is to increase the seedling vigour of these plants for reforestation programs. We used tobacco as a model system to evaluate the methodology, and have successfully produced transgenic tobacco plants and obtained a limited number of lines that over-express the high-affinity transporter gene. Unfortunately, none of these shows increased $^{13}NO_3^-$ uptake. We have also generated poplar plants over-expressing this gene and will soon have results regarding rates of $^{13}NO_3^-$ uptake in these transgenic plants. Based on some work on an algal model plant conducted in Spain, it may be that two genes must be expressed in order to achieve NO_3^-uptake. Mamoru Okamoto (Ph.D. candidate) has recently cloned the second gene and we are now generating the gene constructs necessary to over-express

both genes in our tree species. Assays of NO_3^- uptake will be conducted in standard fashion using $^{13}NO_3^-$.

A preliminary report on this work was presented by Dr. Simon at Bonn, September, 2000.

$^{13}NO_3^-$ influx in the fungus Aspergillus nidulans; a structure function study of gene sequence and NO_3^- uptake: a collaboration with St. Andrews, Scotland

Together with our Scottish collaborators, we have cloned and sequenced the two NO_3^- transporters of this fungus. They have similar (but not identical) gene sequences, but have very different affinities for NO_3^- and different maximum velocities. Having the gene sequences and the physiological characterization, it will be possible to generate chimeric proteins and switch the genes' function from high to low affinity, etc. We will test the resultant strains using $^{13}NO_3^-$. This will make it possible to place NO_3^- transport kinetics on a sound structural basis and to manipulate transport within existing genes.

$^{13}NH_4^+$ uptake by roots of Arabidopsis

We have isolated insertional mutants in which the gene encoding the high-affinity NH_4^+ transporter (AMT1.1) in A. thaliana is disrupted. The point of this methodology is to critically test the hypothesis that the gene in question is actually crucial for NH_4^+ transport. Since this gene was cloned in 1994, four related high-affinity genes have been identified from this species. To what extent do these other genes participate in NH_4^+ transport? By rendering the AMT1.1 inactive it is possible to evaluate the potential role of the other genes. Dr. Brent Kaiser has continued this work and has fully characterized the molecular biology aspects of this mutant. In our last report Dr. Kaiser had begun to characterize NH_4^+ transport in these mutants. He has demonstrated that despite complete disruption of this gene, the plant shows only a 30% reduction of NH_4^+ uptake. Using molecular methods, Dr. Kaiser has shown that the loss of the AMT1.1 function is compensated by over-expression of other members of this family of genes. We have isolated another gene-disrupted strain and we will soon begin to measure NH_4^+ influx in this strain using $^{13}NH_4^+$. Our ultimate goal is to be able to assign functions to all of these genes.

Nuclear orientation experiments

Researchers in the Physics Department need a long-lived isotope of silver for the nuclear orientation experiments. In April, the PET group provided a sample of ^{110m}Ag produced by proton irradiation of a Pd foil. This procedure also produces other silver isotopes, in particular ^{105}Ag. Measurements in our laboratory at UBC in May indicated that the activity of ^{110m}Ag was 280 μCi, while that of ^{105}Ag was 3.5 mCi. However, the half-lives of the two isotopes are 255 d and 40 d, respectively. Therefore, by waiting a few months, the ^{105}Ag activity would decay by an amount sufficient that a low temperature nuclear orientation (LTNO) experiment on ^{110m}Ag could be performed.

The motivation for the experiment is that there have been relatively few studies of impurities in insulating, ordered magnets, and we decided to study oriented Ag nuclei in a suitable antiferromagnet to determine the hyperfine field which reflects the atomic magnetization. A previous experiment at Louvain-la-Neuve by a UBC-Leuven collaboration had indicated a small anisotropy for γ-rays in the decay of ^{104}Ag that had been implanted into $MnCl_2.4H_2O$. However, the sample temperature in this experiment was relatively high ($\sim$90 mK) and, subsequently, thorough analysis showed that this effect could not be distinguished from zero within experimental error. Therefore, the original intent of the present experiment was to dope ^{110m}Ag into the same crystal and perform an LTNO experiment at a much lower temperature ($\sim$35 mK).

In May and June, attempts were made to grow a crystal of $MnCl_2.4H_2O$ from a saturated solution of $MnCl_2$ containing both ^{54}Mn and ^{110m}Ag (and ^{105}Ag). The former grew into the crystal as expected, but very little of the monovalent silver isotopes went in. A literature search was then made for insulating magnets with a composition that included a monovalent, metallic ion. The candidate that emerged was $Rb_2MnCl_4.2H_2O$. This is an antiferromagnet with a Néel temperature $T_N = 2.2$ K. We have grown some crystals of this salt, but we have to refine the technique to produce some plate-like samples, incorporating ^{54}Mn and ^{110m}Ag, on which to perform the LTNO measurements. This research is on-going.

In the LTNO technique, one measures the directional distribution of radiation from an oriented ensemble of nuclei. For the axially symmetric case, the normalized intensity of γ-radiation in direction θ to the orientation axis, normalized to the "warm" count at 1 K, is given by

$$W(\theta) = \sum_{k_{\rm even}} B_k A_k Q_k P_k(\cos\theta)\,.$$

Here the B_k describe the orientation of the nuclei and contain the solid state information, the A_k depend on the observed and preceding transitions in the nuclear decay, the Q_k are detector solid angle corrections, and the P_k are the ordinary Legendre polynomials. Significant values of B_k are obtained when the nuclei experience a sizeable hyperfine interaction and are cooled to millikelvin temperatures in a dilution refrigerator.

PET attenuation source

The Montreal Neurological Group, headed by Dr. Thompson, has developed a new technique for attenuation correction measurements using a positron-emitting isotope embedded in a plastic scintillator. This group wishes to explore the possibility of implanting ^{22}Na from the ISAC facility into a plastic scintillator.

Experiment LS10
Aptamer imaging agents
(H. Dougan, TRIUMF)

Work was completed and a manuscript submitted on the evaluation of DNA aptamers directed towards thrombin as potential thrombus imaging agents. The paper examines the biochemistry of aptamer binding to clot bound thrombin. Exosite 1 aptamer (directed to the fibrinogen binding site on thrombin) showed strong binding to free thrombin, and strongly inhibited coagulation, but had undetectable interaction with thrombin in clots. Exosite 2 aptamer (directed to the heparin binding site on thrombin) also binds strongly to free thrombin, but has little anticoagulant potency. However, exosite 2 aptamer readily bound to thrombin in clot models, demonstrating potential as an imaging agent. The difference between the two aptamers arises from the exosites' involvement in clot architecture, where exosite 1 on thrombin is masked by binding at specific sites on the fibrin matrix, while exosite 2 on thrombin is not masked in this way. However, in clots in living rabbits, exosite 2 aptamers did not diffuse sufficiently in the short time available to establish detectable binding compared to a non-binding control (ovalbumin). More stable nucleic acid analogues may permit imaging in the future by extending the time available for interaction between aptamer and clot. Workers in the United Kingdom have reported that the thrombin concentration is roughly 40 nM in natural human thrombi, surprisingly high for an enzyme catalyst. The central role played by thrombin in thrombosis, coupled with the reasonable thrombin concentration reported in human clots, should stimulate further efforts to master the practical problems impeding thrombin-based imaging.

Experiment LS29
Production and distribution of FDG (and other tracers) for clinical studies
(T. Ruth, TRIUMF)

Following the workshop on the distribution of FDG held at the LSPEC Review of 1996/1997, discussions ensued as to how best to provide FDG to the local community for clinical utility. There is no mechanism established for real-cost reimbursement. In addition, TRIUMF management does not wish to engage in a commercial venture dealing with radioactive substances. However, there continues to be interest in access to FDG and other tracers, both for research purposes and for clinical applications. While the research uses for these tracers can continue to be supplied under existing protocols, there is still a growing need for access to large quantities of either the radiopharmaceuticals such as FDG or ^{18}F-fluoride as precursor.

Since this project's first submission in 1998, a number of new and continuing developments warrant mentioning. First, a local company, IPET, has established a fee-for-service clinical PET centre at the B.C. Research facility adjacent to TRIUMF. IPET tried negotiating with MDS Nordion for the supply of FDG. As indicated above, TRIUMF has chosen not to be involved as a supplier for non-research purposes.

Over the last year, IPET has completed a Health Canada Investigative New Drug (IND) trial for the safety of ^{18}F-FDG prepared on the IPET site. That trial was to have been completed in December, 2001. Concurrently, IPET is in the process of preparing an IND application for the efficacy of FDG in monitoring metabolic status in cancer patients. In addition, MDS Nordion has expressed interest in supplying ^{18}F-fluoride once their new TR30 cyclotron has been installed and commissioned.

Results from this past year

Vancouver Hospital and Health Sciences Centre (Oak Street site): A total of 24 FDG shipments were made in 1999, a further 30 shipments in 2000 and 24 in 2001.

Lions Gate Hospital: A total of 15 FDG shipments were made in 1999, a further 27 shipments in 2000, and 35 in 2001.

St. Paul's Hospital has received 6 shipments of ^{18}F-fluoride and 5 shipments of FDG this year.

Experiment LS33
Evaluation and improvement of a dual head coincidence camera
(V. Sossi, UBC)

The ADAC molecular coincidence dual head camera was installed at Lions Gate Hospital in North Vancouver in August/September, 1997. The attenuation correction hardware and software were implemented in September, 1999.

The Siemens E.Cam Duet PET/SPECT camera was installed at St. Paul's Hospital in May, 2001.

Studies accomplished

1. Development of random event estimate from simulated single event distributions. Development of software tools for data analysis and simulations.

2. Acquisition of all the data relative to the NEMA NU-2-2001 test on the Siemens E.Cam Duet PET/SPECT camera.

Current studies

1. Implementation of a model based scatter correction method.
2. Testing of the Fourier rebinning (FORE) provided by the manufacturer.
3. Repeat of a subset of the NEMA NU-2 measurements after FORE implementation.
4. Analysis and partial analysis of the performance test done on the Siemens E.Cam Duet PET/SPECT camera.

Future studies

The software will be used to develop and implement a model based scatter correction and obtain an estimate of the random event distribution for a dual head camera. A new method to correct for random events will also be investigated.

Experiment LS35
Development of ^{18}F labelled nitroimidazole PET imaging agents for tissue hypoxia

(M.J. Adam, TRIUMF)

Hypoxia in cells and tissues is an important component of various pathological states (e.g. ischemia and stroke). Hypoxic tumour cells are extremely important within cancer treatment because they are more likely to survive radiation and chemotherapy, leading to an increase in tumour resistance to treatment. More recent evidence suggests that hypoxia is related to the aggressiveness of disease. Such studies employed a microelectrode, used in many centres, but were limited because of invasiveness and the requirement for an accessible tumour.

Derivatives of 2-nitroimidazole are used extensively as hypoxia markers. The 2-nitroimidazoles are not metabolized in oxygenated tissues, but bind to macromolecular proteins after reduction in hypoxic cells. This permits detection by a variety of techniques. For example, the products of such binding for the (pentafluoropropyl)acetamide (EF5) and (trifluoropropyl)acetamide (EF3) derivatives of 2-nitroimidazole can be detected by specific fluorescent antibodies.

The synthesis of ^{18}F-EF5 has now been developed and was achieved by preparing the allyl precursor and fluorinating it with ^{18}F elemental fluorine in trifluoroacetic acid. The radiochemical yield is 17% after HPLC purification.

Several syntheses have been performed for cell and animal studies. Initially we carried out cell studies to determine the effects of hypoxic and aerobic conditions on the uptake of EF5. This experiment indicates that about 10-fold more hot EF5 is concentrated in cells under hypoxic conditions as compared to aerobic conditions, and that the addition of cold EF5 has little effect. The gamma counting results were basically the same as those obtained by using cold EF5 and flow cytometry. These cell experiments were followed by rat experiments; rats with 9L tumours were injected with ^{18}F-EF5 and imaged on our PET tomograph, followed by dissection to determine biodistribution. An image of the brain tumour in the rat was obtained. The next stage of the research is to proceed to human studies. Two proposals have been submitted for funding. One study will focus on the use of EF5 in lung cancer, and the other on breast cancer.

Progress this year has been slow due to a lack of funds. The grant application by Stephen Chia was rejected. The budget in this application contained funds for the chemistry and automated system that is required for the routine production of EF5. A British Columbia Lung grant to Skov and Gelman will allow for an initial screening test of cold EF5 in 12 patients along with 6 hot EF5 experiments in humans. Ethics approval for these experiments is still required. During the year, Cameron Koch and Syd Evans from the University of Pennsylvania visited TRIUMF and discussed their latest research on EF5. They were very impressed with our facilities at TRIUMF and they would like to work closely with us on future collaborative experiments. At BCCA they are carrying out research on prostate cancer and its connection to hypoxia. They have determined that there are different levels of hypoxia at the 3 stages of progression of the disease. These findings suggest that PET imaging with EF5 might be useful in determining the progression of the disease.

Experiment LS38
Modelling of the ^{18}F-fluorodopa tracer

(V. Sossi, UBC)

Two areas were investigated: the role of dopamine turnover in early Parkinson's disease, and the ability of the tissue input graphical model to accurately quantify changes in dopamine synthesis and storage.

Increase in dopamine turnover occurs early in Parkinson's disease: evidence from a new modelling approach to PET ^{18}F-fluorodopa data

An increase in dopamine turnover has been hypothesized to occur early in Parkinson's disease as a compensatory mechanism for dopaminergic neuronal loss. A new approach to the determination of dopamine turnover was developed using four hour ^{18}F-fluorodopa (FD) PET data. An effective dopamine turnover, which is an estimate of dopamine turnover, has been

measured using its inverse, the effective dopamine distribution volume (EDV). This new method is based on a reversible tracer approach and determines the EDV using a graphical method.

Six normal (N) subjects and ten very early Parkinson's disease (PD) subjects underwent a four hour FD scan. EDV and the plasma uptake rate constant K_i, a marker of dopamine synthesis and storage, were compared according to their ability to separate the PD from the N group. EDV was the better discriminator (93.8% correct classification versus 81.3% for K_i). EDV decreased by 65% in the PD relative to the N group, while the decrease in K_i was 39%.

These results show that changes in EDV are measurable with PET earlier than changes in the dopamine synthesis and storage rate, indicating that EDV is a sensitive marker for early PD and that a dopamine turnover increase likely serves as an early compensatory mechanism.

The presence of 3-O-methyl-[^{18}F]fluoro-DOPA (3OMFD) influences the evaluation of the ^{18}F-fluorodopa tissue input uptake rate constant in a disease dependent way: a study in Parkinson's disease

Introduction

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons, thus decreasing the system's ability to produce and store dopamine (DA). Such ability is often investigated using ^{18}F-fluorodopa (FD) positron emission tomography (PET) and quantified with a variety of different models. A commonly used model is the modified Patlak graphical approach [Patlak *et al.*, J. Cereb. Blood Flow Metab. **3**, 1 (1983); Patlak and Blasberg, J. Cereb. Blood Flow Metab. **5**, 584 (1985); Martin *et al.*, Ann. Neurol. **26**, 535 (1989)]. This approach allows for a plasma and a tissue input function yielding the respective uptake rate constants K_i and K_{occ}. This method requires the presence of an irreversible compartment and the absence of any non-trapped tracer metabolite. This last assumption is violated by the presence of the FD metabolite 3OMFD. For the plasma input function, this violation can be overcome [Martin *et al., op. cit.*]. The tissue input function, however, includes an indistinguishable component due to the 3OMFD, thus making the evaluation of K_{occ} susceptible to a downward bias. Nevertheless, K_{occ} has been used extensively to quantify DA synthesis and storage. The disease discriminating and quantifying ability of K_i and K_{occ} have already been widely investigated with discrepant results [Hoshi *et al.*, J. Cereb. Blood Flow Metab. **13**, 57 (1993); Takikawa *et al.*, J. Nucl. Med. **35**, 955 (1994); Dhawan *et al.*, Quantification of brain function (Academic Press, 1996) p.219]. In this study we show that contrary to the value of K_i, the value of K_{occ} depends on the time interval used for its evaluation and that the magnitude of the 3OMFD derived bias is disease dependent. Consequently, K_{occ} is likely a better disease discriminator, but less accurate in quantifying changes in DA synthesis and storage.

Methods

Six normal subjects (N) and fifteen mild PD patients (motor component of the Modified Columbia Scale score 14.3 $\pm$ 5.7) underwent a four hour FD scan (9 $\times$ 10 min, 30 min interval, 12 $\times$ 10 min). 23 blood samples were taken and selected ones analyzed for metabolites. The first 90 min of data were considered for this study. K_i and K_{occ} were evaluated from data points acquired between 20 and 70 min (K_{i70}, K_{occ70}) and 20 and 90 min (K_{i90} and K_{occ90}) for the caudate and putamen separately. The ratio K_i/K_{occ} was calculated in each case. The comparisons between K_{i70} and K_{i90} and between K_{occ70} and K_{occ90} were used to estimate the bias as a function of the time interval. The comparison of K_i/K_{occ} between the N and the PD group was used to estimate the bias disease dependence. The ratio K_i/K_{occ} is mathematically predicted to be equal to K_1/k_2 (the clearance rates from plasma into tissue and from tissue into plasma). Since K_1/k_2 would not be expected to vary appreciably between normals and PD patients [Dhawan *et al., op. cit.*], any difference in the K_i/K_{occ} ratio between the N and the PD group can be attributed to the bias introduced by the presence of the 3OMFD in the tissue input function.

Results

Results are presented in Table XII.

Observations

1. The value of K_i does not change as a function of time interval for either group. It exhibits the typical rostrocaudal gradient for the PD group. The value for K_{occ70} is larger than K_{occ90} for both groups. This is indicative of the downward bias introduced by 3OMFD. The bias is present even for the normal group even for evaluation times <90 min.
2. The K_i/K_{occ} values are appreciably higher compared to K_1/k_2 [Dhawan *et al., op. cit.*], which is indicative of the bias due to 3OMFD.
3. K_i/K_{occ} changes with time interval for both groups as expected from the K_{occ} results, but while it is the same between the two groups for the caudate (the less affected part of the striatum), it increases significantly in the PD group compared to the N group ($p < 0.05$) for the putamen, thus demonstrating a progressive underestimate of K_{occ} for increased disease severity.

Table XII. Results of plasma and tissue uptake rate constant measurements.

	Caudate	Putamen	Caudate	Putamen
	K_{i90}*		K_{i70}*	
Normal	1.89±0.26	1.81±0.19	1.89±0.24	1.81±0.17
PD	1.44±0.33	1.00±0.36	1.41±0.36	1.03±0.37
	K_{occ90}*		K_{occ70}*	
Normal	1.19±0.11	1.07±0.09	1.38±0.11	1.22±0.09
PD	0.91±0.12	0.51±0.18	1.02±0.16	0.59±0.20
	K_{i90}/K_{occ90}		K_{i70}/K_{occ70}	
Normal	1.58±0.17	1.70±0.19	1.37±0.143	1.41±0.16
PD	1.59±0.33	2.05±0.59	1.38±0.265	1.83±0.52

*values expressed in 10^{-2}

Conclusion

These results show that the presence of 3OMFD in the tissue input function causes a downward bias in the K_{occ} estimate and the magnitude of the bias is disease dependent. K_{occ} may therefore be a good disease discriminator, but may not accurately quantify changes in DA synthesis and storage capability.

Experiment LS39
Positron emission profiling (PEP) for pulp and paper fluid dynamic studies

(T. Ruth, TRIUMF)

Multiphase flows are very common in industrial applications. One such example is in the pulp and paper industry where a suspension of wood pulp fibres is filtered and consolidated, at very high speeds, to form a sheet of paper. Papermaking suspensions are composed typically of a mixture of fibres with a wide distribution in both length and diameter. Each class of fibre behaves differently during the filtration process depending upon the hydrodynamic force applied and its degree of mobility in the formed network. Ascertaining these effects is difficult as these suspensions are opaque and difficult to visualize at reasonable penetration depths. Clearly, there is a need to visualize the motion of the individual classes of components in a fibre suspension in order to better understand the development of the physical properties of paper.

Recently, we have conducted a gravity-settling experiment at TRIUMF to test the feasibility of using PET as a novel visualization method. In this work, a selected class of "long-fibres" was radioactively labelled and allowed to settle in an untreated fibre suspension (with a distribution of fibre lengths). The suspension was agitated and allowed to settle under the action of gravity in a cylindrical jar. A similar study was conducted in March, and the data are now being used to develop a mathematical description of the motion of fibres in a network.

From these studies it is clear that this visualization technique has potential to help clarify the behaviour of mixtures of fibres with differing lengths. We propose that this technique be used to visualize the motion of fibres in a swirling flow; this is relevant to an apparatus called a hydrocyclone. A hydrocyclone employs centrifugal forces to separate solid particles from the suspending fluid. Hydrocyclones are used primarily to remove dirt particles, but have recently been used to separate the fibre suspension into different length classes.

During this past year, we explored the transient settling process of papermaking fibres with positron emission tomography (PET). Approximately 4 days of camera time were used for this. Here, the motion of fluorine-18 labelled papermaking fibres were visualized settling in the midst of a suspension of non-radioactive fibres. The experimental conditions were such that the particle Reynolds number was always low and the consistency of the suspension was set at the levels found industrially. From this we identified two distinct regimes of settling depending upon the initial consistency of the suspension. At low consistency, the sedimentation rates of the individual fibre fractions within the suspension were found to be somewhat similar. At higher consistencies, fibres began to flocculate and differences in mobility between the individual fractions that make up the suspension were observed. In a separate study, these differences in mobility could be linked to the final paper properties.

Experiment LS42
Configuration modelling and image reconstruction studies on a depth encoding research tomograph

(V. Sossi, UBC)

Summary

The high resolution research tomograph (HRRT) has been purchased and is expected to be delivered by CTI in April/May, 2002. The final detector design

consists of two 10 mm deep layers of LSO and LYSO (LSO doped with yttrium) respectively. Novel reconstruction methods and quantification algorithms will be explored for this tomograph.

Accomplished

Crystal position decoding algorithms were investigated. Spatial resolution estimates as a function of γ incidence angle were obtained by simulating two detectors placed opposite to each other at varying angles.

Current work

Spatial resolution estimates for a specific source location in the tomograph are under way. Data sets from the HRRT located in Cologne have been obtained and existing reconstruction and normalization source code was obtained from CTI. Patient motion correction issues are being investigated.

Future plans

The following issues are going to be addressed:

1. Data reconstruction techniques.
2. Design of a point source to map the tomograph point spread function.
3. Detector normalization algorithms.
4. Data transfer and storage schemes.
5. Patient motion correction.

Experiment LS44
Development of a "formation" (areal density) measurement device for pulp and paper studies

(T. Ruth, TRIUMF)

This research aims at developing an experimental device to measure areal density (areal density has units of mass/surface area and is traditionally called basis weight in the pulp and paper industry) or "formation" of paper directly using a linear β-radiation source. In this work we propose to measure formation by pulling a paper sample through a collimated beam of electrons from a source embedded in a long linear rod. The source will be perpendicular to the motion of the paper. The emergent radiation intensity will be sampled by a linear detector and used to analyze mass-density variation. The key advantage of the proposed apparatus is that areal density variations can be measured over large areas continuously. This will aid in understanding the development of paper properties and enable optimization of the forming section of paper machines.

Background

The term "formation" is traditionally used by papermakers to describe the uniformity or cloudiness of the paper sheet. For about two thousand years, formation has been traditionally evaluated by a "look through" in which the paper sheet is held in front of a bright light. As light transmission is affected by many factors, such as surface roughness and the degree of bonding, true measurements of formation are currently conducted by the attenuation of γ-radiation.

The simplest method to characterize formation is to define its contrast, that is the standard deviation of the areal density distribution. The most commonly employed laboratory instrument is a point-to-point measuring device using a ^{147}Pr point source having a circular inspection zone of 1 mm in diameter. The measuring head traverses the paper sample and records a large number of local basis weights. From this the standard deviation is calculated. In another method, the paper is sandwiched between a ^{14}C sheet and an X-ray film. The paper is exposed for a period of time and the film is developed. The intensity of the image on the film is proportional to the areal density of the paper. This image is then digitized and the formation analyzed in the same fashion as the optical formation analyzer. Both of these techniques are inherently slow. A fast, automated, 2-dimensional method of measuring the areal density variation over a piece of paper is required before formation is accepted as a quality control parameter.

Project description

The proposed instrument would resemble a desktop scanner that uses a β-radiation source and detector instead of a visible light source and detector. The instrument consists of several sub-systems that need to be developed and integrated. These systems include (1) a uniform linear radiation source, (2) linear β-ray detector, (3) mechanical scanning system, and (4) image construction and analysis software.

Work accomplished this year

- Sub-systems (1) and (2) have been purchased and have been delivered.
- The mechanical scanning system has been designed and is currently being fabricated.
- Image construction and analysis software has been designed and programmed.

Experiment LS46
Modelling of the dopaminergic system in more severely affected PD patients

(V. Sossi, UBC)

Parkinson's disease is characterized by a progressive loss of dopaminergic terminals and by a reduced neurotransmitter dopamine level in the striatum. The radiotracer ^{18}F-fluorodopa (FD) is often used to quantify the uptake rate constant of the neurotransmitter dopamine (DA) into the pre-synaptic vesicles. Traditionally the FD kinetics are described by an irre-

versible model approach reflecting the DA trapping in the vesicles. The plasma input or the tissue input Patlak graphical approach is applied to the tracer time activity distribution to obtain the uptake rate constant K_i or K_{occ}, respectively. In patients with advanced PD the ability to retain dopamine can be so decreased that the irreversibility assumption is no longer valid, leading to a model dependent bias in the parameter estimate.

We have found that in this situation a quantitative assessment of disease progression becomes analysis model dependent. Care therefore needs to be taken when assessing effects of therapy or when investigating compensatory mechanisms that compare changes in different dopaminergic sub-processes involved in Parkinson's disease.

Experiment LS50
Antisense imaging nucleic acids for Parkinson's disease
(H. Dougan, TRIUMF)

Parkinson's disease is a debilitating movement disorder which afflicts nearly 100,000 Canadians. It arises from progressive loss of dopamine-producing cells in the midbrain. Parkinson's disease is a principal research interest for the TRIUMF PET group and the Neurodegenerative Disorders Centre at UBC. The current imaging technology is based on labelled neurotransmitter and receptor antagonists. Important aspects of the loss of dopamine-producing cells are thought to depend on processes downstream from the receptors. There is an interest in measuring expression of the relevant genes through imaging of the mRNA of known genes of interest. In their past work, the UBC collaborators introduced antisense DNA directed to the D2 receptor mRNA and to dopamine transporter mRNA into rat brains. Delivery by capillary tubes assisted crossing the blood-brain-barrier and targeting the midbrain. The rats developed behavioural disorders and biochemical changes consistent with depletion of the "sense" mRNA by the "antisense" DNA probe. Ideally one could image and quantify such mRNA using radiolabelled DNA probes, as suggested by the experiments with rats. Working towards this goal, we have been successful in the radioiodination of the specialized sulfurized DNA used in the experiments with rats. The intention is to detect the mRNA by autoradiography based on ^{125}I, and then go on to imaging the mRNA using positron emitters.

Experiment LS51
Auger therapy for prostate cancer
(H. Dougan, TRIUMF)

Prostate cancer is the most prevalent cancer in men and the second leading cause of cancer death in Canada. Prostate cancer is the principal research interest of the Prostate Centre in Vancouver. Early treatment is effective when the tumour is confined to the gland. When the cancer has spread outside the gland, androgen ablation therapy leads to the death of 99% of the malignant cells by an apoptosis-dependent mechanism. Normal prostate cells are also lost. The surviving 1% of tumour cells have altered phenotype, namely androgen independence (AI). Ideally, the killing of the small AI tumour cells could be improved, leading to improved therapy. The present proposal exploits the Auger electrons released following the decay of ^{123}I and ^{125}I. The aim is to test the hypothesis that the interaction of an iodoandrogen steroid (EMIVNT) with the androgen receptor will deliver the iodoandrogen in close enough proximity to the DNA that the ensuing DNA damage will cause cell death. To date we have been successful in preparing two suitable steroids (EMIVNT and ZMIVNT) with potential for Auger therapy. Both have been labelled to high specific activity using ^{125}I. Biochemical assay of receptor binding has begun and is encouraging. The intention is to complete the biochemical characterization. Then the ^{123}I compound will be prepared and assayed with cancer cells to determine whether killing due to Auger electrons is observed.

Experiment LS52
Comparison of commercial FDG synthesis systems
(T. Ruth, TRIUMF)

A comparison will be made between two commercial FDG synthesis units to ascertain their reliability and the purity of the FDG product and the efficiency of production. These results will enable the local community to choose the most appropriate route for preparing FDG for the Lower Mainland. The studies will involve 10–20 syntheses using each unit, and monitoring yields and purity of FDG.

The results for the case where the synthesis box at the IPET scan centre was used involved two sources of ^{18}F-fluoride, the TRIUMF niobium water target and the silver target from PETNet in Seattle. For the ^{18}F-fluoride produced from the Nb target the decay corrected FDG yield was 61% ($n = 16$) and for the Ag-target the yield was 51% ($n = 15$).

In a separate study, we sent ^{18}F-fluoride to the University of Alberta PET Centre, located at the Cross Cancer Centre, where they produced FDG using a different synthesis unit and slightly different chemical process. The decay corrected yield for this unit was 64% ($n = 34$).

From these results it appears that the two synthesis units are comparable with respect to decay corrected

yields and that the niobium target provides higher radiochemical yields.

Future experiments will make use of a third synthesis unit located at Vancouver General Hospital.

Experiment LS53
Synthesis of ^{99m}Tc and ^{186,188}Re sugar derivatives
(M.J. Adam, TRIUMF)

An NSERC strategic grant has recently (October, 2001) been awarded (M.J. Adam, PI, $78,200/year for 3 years) to carry out research on the synthesis of technetium and rhenium labelled carbohydrates for use in nuclear medicine imaging and therapy. Dr. Adam will be collaborating with Dr. Orvig in the UBC Chemistry Dept. and AnorMED (M. Abrams, CEO). A post doctoral fellow (Dr. Simon Bayly) and a graduate student (Cara Fisher) have been hired to complete the group.

Radiolabelled carbohydrates have been of significant interest to nuclear medicine due to the success of 2-^{18}F-fluoro-2-deoxy-glucose (FDG) as an imaging agent in positron emission tomography (PET). This success has naturally raised the question of whether a single-photon emitting glucose analogue with similar properties to FDG can be developed for use with single-photon emission computed tomography (SPECT). Because of the relatively short half-life of ^{18}F (110 min) its use is limited to facilities that have an accelerator in close proximity to chemistry laboratories and medical facilities. This fact makes it impractical for the FDG method to be widely used in medicine. ^{99m}Tc is the most widely used isotope in SPECT due to the fact that it is a generator produced, commercial isotope which makes it convenient to use and relatively inexpensive. It also has ideal physical properties for imaging. The drawback to this isotope is that it must be attached to the molecule via a chelate or organometal conjugate, which may perturb the system being studied. A SPECT analogue based on a widely available isotope such as ^{99m}Tc would make these agents available to the broader medical community. Among elements of the same series as Tc, the isotopes ^{186}Re and ^{188}Re show promise in the development of therapeutic strategies. For a β^- emitting radioelement to be therapeutically useful, a half-life of between 12 h and 5 days is preferred; moreover, for a 1 MeV β^- particle, the depth of penetration into tissue is approximately 5 mm. Furthermore, if some of the disintegrations are accompanied by a 100–300 keV photon, the behaviour of the radioelement can be conveniently followed by using a gamma camera. The nuclear properties of ^{186}Re and ^{188}Re are optimal for these purposes.