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UNDER A CONTRIBUTION FROM THE
NATIONAL RESEARCH COUNCIL OF CANADA

DECEMBER 2004

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 saw the delivery of the two new scanners which were acquired through funds from the Canada Foundation for Innovation and the BC Knowledge Development Fund. High resolution research tomography (HRRT) is the state-of-the-art tomography designed to performed neurological research at a resolution of 2.5 mm and a sensitivity of greater than 6%. These metrics are made possible by the use of the new scintillator material, LSO. The other scanner is the microPET® which uses similar technology to achieve a resolution of sub-2 mm and is designed to perform functional imaging in rodents. Both of these scanners are the subjects of a number of research proposals for 2004.

In addition to the new equipment, a number of projects formerly supported through LS8, Radiotracers, have developed programs of their own and will be the subject of separate Life Sciences projects in 2004, thus the Life Sciences Program is poised to experience growth over the next few years through these new initiatives.

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

The PET facilities comprise the TR13 13 MeV H^- cyclotron, the ECAT 953B/31 tomograph, the new high resolution research tomograph (HRRT), and the new microPET R4 small animal tomograph, and ancillary equipment such as counting and data acquisition systems.

Personnel

A research associate joined the PET program early in the year as working on camera characterization and is actively involved in the maintenance and repair of all the cameras.

TR13 cyclotron

Usage of the TR13 cyclotron decreased significantly this year in delivered beam while the number of irradiations only dropped slightly. This was due in large part to the cessation of irradiations for the production of ^{7}Be (LS8), ^{18}F to the Cross Cancer Institute in Edmonton (LS32), and in mid-year, FDG to the local hospitals (LS13 and LS24). The total number of runs decreased to 970 vs. 1038 in total last year and delivered beam has dropped to 0.43 A min from 1.26 A min.

Downtime this year was caused by relatively simple failures such as water leaks and power supplies. Spare power supplies have been purchased for the control system since these supplies are now 10 years old and failures can be expected. The cryocompressor for the vacuum system exhibited some troubles for one day but then mysteriously started functioning correctly again before a fault was detected.

No extraction foil changes were required through the year and all targets where rebuilt at least once with the exception of the ^{16}O-H_2O target for ^{13}N production while the ^{18}O-H_2O for ^{18}F production was rebuilt 3 times. Four ion source filament changes have been done along with other miscellaneous service items.

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 experimental foil target.

A number of irradiations took place this year in support of LS8 but they were typically low current runs in support of the Botany Department or graduate student projects.

ECAT tomograph

Block detector failures and programmable array logic chips continue to be the dominant modes of failure for the camera. We are routinely repairing blocks in-house and have replaced 7 blocks again this year. 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 buckets continue to fail. Chips for 8 channels have been replaced this year. In addition to this, 2 analogue boards and 3 position/energy boards, and one bucket controller were replaced in the bucket assemblies. The ECAT 953B is now no longer officially supported by CTI and parts are only available if CTI has them in stock. No new parts will be manufactured. There were only six 953B scanners made and we have not yet been successful in obtaining a decommissioned one for parts. The ECAT 951 scanner uses the same detector block and bucket electronics so we remain optimistic that used parts will be available. We are aware of at least one used part vendor with a 951 from whom we have purchased a power supply in the past.

HRRT

The HRRT scanner arrived on June 2 and was installed in a few days. The scanner is undergoing characterization and tests and has been used for some preliminary investigations with non-human primates. The patient couch has not yet been delivered. We have experienced a minimum of hardware troubles. We did some repairs when a high voltage capacitor failed and have replaced one analogue board and one phototube. The HRRT team at CTI are supplying parts and instruction as needed and team members have travelled to CTI a couple of times for service training before the machine arrived.

MicroPET

The microPET scanner was shipped with the HRRT. This scanner is shipped ready to run so it was simply a matter of plug and play to get the scanner up and running. Several members of the PET team were at Concorde MicroSystems for training on use and service of the scanner. We are a beta test site for Concorde and recently went through the installation of the latest beta software for the scanner. During that process we detected one analogue board that was faulty and it was replaced. With this exception the scanner hardware has been quite stable.

The room the microPET is housed in needs some additional modifications to accommodate the scanner and scanning procedures. The heat load of the scanner requires additional cooling to be added and oxygen and gas services still need to be plumbed into the room. We experienced delays in getting the mechanical drawings from the engineering consultant due to a change of staff there. At this time the drawings have been completed and are being reviewed by the hospital plant services. Work will proceed as promptly as possible.

Statistics

Tables XIII–XVI summarize the run and scanning statistics for the TR13, ECAT, HRRT, and microPET, respectively.

Table XIII. TR13 run statistics.

	2003	2002
Total runs conducted	970	1038
Total runs lost	18	16
Total beam delivered (μA min)	430,630	1,258,376
Delivered to – LS 3	294090	301611
– LS 4	63279	40411
– LS 8	55636	605500
– LS 13*	14066	51410
– LS 24*	3559	17246

*Please note that LS13 and LS24 refers to the FDG production for use at local hospitals; it is not apportioned to particular LS projects since a single batch is made and subsequently divided among requesters.

Table XIV. ECAT scanning statistics.

	2003	2002
Total scans conducted	388	383
Total scans lost	75	37
Lost to – patient	23	8
– cyclotron	18	16
– chemistry	3	3
– scanner	20	7
– staff sick/away	9	0
– investigator	2	3

Table XV. HRRT scanning statistics.

	2003
Total scans conducted	23
Total scans lost	2
Lost to – chemistry	2

Table XVI. MicroPET scanning statistics.

	2003
Total scans conducted	66
Total scans lost	10
Lost to – cyclotron	1
– subject	6
– staff sick/away	3

Experiment LS3
Synthesis of radiopharmaceuticals for positron emission tomography
(S. Jivan, TRIUMF)

The PET group at TRIUMF continues to routinely produce up to 10 radiopharmaceuticals with 3 to 4 radiopharmaceuticals synthesized on any given day. FDG shipments to local hospitals (VGH, Lions Gate and St. Paul's Hospitals) were stopped as of April 1, 2003. Of the 10 radiopharmceuticals, five (FDOPA, Raclopride, (+)DTBZ, Sch23390 and MP) are most heavily used. Two new tracers (^{11}C-Carfentanil and ^{18}F-SPA-RQ) have been successfully developed and are currently being used for non-human primate studies.

This year Health Canada requested that clinical trial applications (CTA) be submitted for all protocols using positron emitting radiopharmaceuticals for human research. We have been allowed to continue human studies with a timetable for 11 CTAs to be submitted by the end of May, 2005. Two CTAs (Raclopride and FDOPA) thus far have been submitted and approved.

Routine production

The total number of shipments to UBC Hospital for PET scanning was 400 and 74 deliveries to external users which include FDG for local hospitals and nitrogen-13 for the Botany Department at UBC. We had a total of 180 runs for research and development. These included testing new targets and checking radiochemical yields on new and existing compounds. The decrease in the number for external users is because we stopped delivering FDG to local hospitals as of April 1, 2003. There were also no shipments this year to the Cross Cancer Institute in Edmonton as they now have their cyclotron on-line and manufacture FDG on site.

We continue to use TBAF in most of the ^{11}C methyl iodide reactions to enhance and stabilize yields. Most precursors are made in-house by JML Biopharm Incorporated except Raclopride which is donated by ASTRA ZENECA AB.

New development

^{11}C-Carfentanil has been successfully synthesized and automated for routine production. The tracer is involved in looking at μ receptors in the opioid system in the brain. ^{18}Fluoromethylbromide has been successfully synthesized and is used to label SPA-RQ (substance P antagonist-receptor quantitation) which looks at neurokinin receptors.

Routine radiosyntheses for some PET radiotracers is performed *in-loop* [^{11}C]CH_3I-methylation of precursors. This year, a series of experiments was conducted to understand the mechanism of *in-loop* labelling with [^{11}C]CH_3I. These studies were applied to improve the yield and reliability of the radiosynthesis of [^{11}C]Carfentanil. This work was presented at the XVth International Symposium of Radiopharmaceutical Chemistry as well as being submitted for publication.

Experiment LS4
Targets for radioisotope production
(T.J. Ruth, TRIUMF)

The goal of this project is to develop targets for the TR13 cyclotron for production of positron emitting radionuclides. The past year has focused on the production of ^{18}F using gaseous oxygen-18 and $^{11}CH_4$ directly from the target.

Gas targets for the high yield production of ^{18}F-fluoride

With the growing pressure for increased yields for ^{18}F-fluoride around the world we designed and built a prototype target using gas target technology. This work has been published previously in the journal Applied Radiation and Isotopes **55**, 457 (2001).

The approach chosen made use of the ^{18}O-O_2 gas target concept in an analogous manner to the F_2 double shoot system. The first irradiation would generate the ^{18}F as fluoride that sticks to the walls. But instead of performing a second irradiation, the target is washed out with water in a similar fashion as used for ^{123}I production by MDS Nordion. Depending on the energy of bombardment, extremely high yields may be possible. For example the saturation yields at 13 MeV are approximately 200 mCi/μA and 250 mCi/μA at 18 MeV. At these rates one can imagine very long shipments. The advantages include straightforward recovery of the target material and efficient, higher beam currents possible than for water targets (liquids in general). Disadvantages include having to wash and dry the target between runs and finding the best material for this process. There are 2 patents pending for this system.

We have just been awarded a one year Proof-of-Principle (December 2003) grant from the Canadian Institutes of Health Research (CIHR) to build and test a working system on the CP-42 to operate at >100 μA with a design goal of producing >15 Ci in a 4-hour irradiation.

The outstanding issues to be addressed this coming year include:

1. What are the target parameters that have to be addressed in order to fabricate a fully functional target system?

2. Window strength and cooling for operating at 100 μA, or higher.

3. Target gas pressure/chamber-size ratio for cooling, density reduction, scatter and window strength.

4. ^{18}O-O_2 gas recovery to recycle enriched target material.

5. Target body material – compatible with washing to achieve high recovery factor.

6. Solution for recovering ^{18}F-fluoride to maintain chemical reactivity and target re-use compatibility.

^{11}C-CH_4 production

Our previous work on static irradiations of a H_2/N_2 target gas for the production of methane indicated that recoverable yields at 13 MeV plateaued at about 750 mCi at EOB. The relatively poor yields were attributed in part to Hot Atom interactions with the target chamber walls. In order to try and overcome this limitation, an aluminum bodied flow-through gas target was implemented and tested for the production of ^{11}C-CH_4 on the TR13 cyclotron at TRIUMF. Nitrogen gas with varying quantities of hydrogen has been used to investigate the optimum ratio for methane production. Comparison of the flow-through target with the static-target irradiations for production of methane indicates that the yields are significantly better with the flow-through system but that the specific activity is lower. The source of the carrier carbon is under investigation.

In the mean time we built a niobium bodied target for methane production and preliminary results from this target are extremely encouraging. Yields ranged from 94 mCi/μA at saturation for a 10 minute run at 20 μA to 77 mCi/μA for a 60 minute, 20 μA run. We made more than 1.3 curies of methane in the one hour irradiation. With the Al target we could never go above 750 mCi, total. Specific activities of the final product tracers, such as DTBZ and raclopride, using the Nb body target have been comparable to the aluminum cone target (several Ci/μmole). A more detailed study of this target is under way.

Copper isotopes

Interest in foil irradiations has increased and we have in the past performed such irradiations using a special target jig, which uses He cooling on the foils to allow simple irradiations. For example, Pd foils for the ^{110m}Ag production for a researcher from the Physics Department at UBC have used this system.

A collaboration between the Australian Nuclear Science and Technology Organization (ANSTO) and TRIUMF has embarked on developing the use of copper isotopes for radiopharmaceutical development using Cu-61/64.

In addition, a researcher from Earth and Oceans Sciences at UBC (LS 60) has expressed an interest in using a copper isotope for her tracer studies in phytoplankton. Preliminary results indicate that we can make small amounts or relatively pure Cu-61/64, which is adequate for this program. However, we are in the process of exploring alternative means to allow for more remote handling approaches.

Experiment LS8
Radiotracers

(T.J. Ruth, TRIUMF; A.D.M. Glass, UBC)

Dr. Anthony Glass of the Botany Dept. at UBC continued to make use of tracers provided by the Life Sciences Group at TRIUMF. The Group continued to train scientists in the use of the tracer technique to address biological questions. Over the past year there was one Ph.D. student (Yu Wang), 3 PDFs (Wenbin Li, Wang Ye, Anshuman Kumar), and a visitor from Iran, Prof. Mansour Shariati.

Ongoing collaborations included researchers from the University of St. Andrews, Scotland (Profs. James Kinghorn, and Sheila Unkles), the University of San Diego (Prof. Nigel Crawford), and the University of Connecticut (Prof. Roberto Gaxiola).

Rice research

(A. Kumar)

Following his Ph.D. studies, Dr. Anshuman Kumar has been examining the manner in which cellular pools of carbohydrates and various nitrogen compounds regulate the expression of three ammonium transporter genes that he successfully cloned from roots of rice plants. This has involved measuring ammonium influx using $^{13}NH_4^+$, while measuring the cellular pools of these N and C compounds. It is evident that N and C interact at the cellular level so that the supply of N provided by the root ammonium transporters matches the availability of carbon compounds provided by leaf photosynthesis.

Nitrogen uptake in trees

(Collaboration with CELLFOR: M.Y. Siddiqi, M. Shariati, W. Li)

Our goal of increasing nitrate uptake in tobacco plants and poplar seedlings by over-expressing the high-affinity NO_3^- transporter gene (AtNrt2.1) was initially unsuccessful. We have confirmed our hypothesis that a second family of genes (the NAR2 family) must be co-expressed in order to achieve efficient NO_3^- uptake, and successfully demonstrated that mutants of Arabidopsis lacking a functional NAR2 gene fail to absorb nitrate. We have now developed strains of tobacco over-expressing both the AtNRT2.1 gene and the At-NAR 2 gene. Using $^{13}NO_3^-$ to measure nitrate uptake, we have obtained increased nitrate uptake and our preliminary growth measurements indicate increased growth in these lines. This working is actively being pursued.

$^{13}NO_3$ influx in the fungus Aspergillus nidulans

(Collaboration with S. Unkles, J. Kinghorn, St. Andrews, Scotland; A.D.M. Glass, Y. Siddiqi)

A structure function study of the NRTA gene sequence and NO_3^- uptake. With our Scottish collaborators, we have generated clones of Aspergillus modified at specific (putatively critical) arginine loci of the nitrate transporter protein. These arg sites are highly conserved in this gene family from fungi to higher plants. Replacement of arg 87 or 386 converts the protein from a high-affinity transporter with K_ms for $^{13}NO_3^-$ uptake around 10 μm to a low-affinity transporter with a K_m around 15 mM. We believe that this positively charged amino acid is critical in the transmembrane uptake of nitrate. Our data have been written up and submitted for publication.

The role of the NAR2 gene family

During his Ph.D. studies at UBC, Mamoru Okamoto isolated an Arabidopsis mutant disrupted in the NAR2 gene. We have demonstrated that mutant is unable to grow normally when nitrate is the sole source of N and that $^{13}NO_3^-$ uptake is dramatically reduced. Thus high-affinity nitrate uptake requires the participation of genes encoding both the NRT2 and the NAR2 proteins. Using molecular methods we have evidence that the two proteins are associated in the plasma membrane for normal nitrate transport function.

Studies of fluxes and compartmentation of chloride ions in barley plants
(D.T. Britto, H.J. Kronzucker, Toronto)

With the increasing use of irrigation and fertilizers throughout the world, there have been associated increases in salt accumulation in agricultural soils, affecting ∼50% of the irrigated agricultural land base globally. Soil solution concentrations of sodium, chloride, and other ions can sometimes reach excessively high levels, resulting in suppression of plant growth and, ultimately, loss of arable land. Because of the severity of this problem, much research has been focused on salt stress and its avoidance by tolerant species or cultivars. However, while the physiology of plant-sodium relations has been particularly well studied, the chloride ion, which often accompanies sodium, has been understudied in relation to salt stress in plants. The objective of our study was to establish a baseline of information regarding the transport and subcellular accumulation of chloride in barley (Hordeum vulgare) roots, particularly with regard to the influence of nitrogen strength and source.

The first analysis of chloride fluxes and compartmentation in a non-excised plant system is presented, examining ten ecologically pertinent conditions. The short-lived radiotracer couple $^{38}Cl/^{39}Cl$ was used as a Cl^- tracer in intact barley (Hordeum vulgare L. cv. Klondike) seedlings, which were cultured and investigated under four external $[Cl^-]$, from abundant (0.1 mM) to potentially toxic (100 mM). Chloride-nitrogen interactions were investigated by varying N source (NO_3^- or NH_4^+) and strength (0.1 or 10 mM), in order to examine, at the subcellular compartmentation level, the antagonism, previously documented at the influx level, between Cl(-) and NO(3)(-), and the potential role of Cl^- as a counterion for NH_4^+ under conditions in which cytosolic $[NH_4^+]$ is excessive. Cytosolic $[Cl^-]$ increased with external $[Cl^-]$ from 6 mM to 360 mM. Cl^- influx, fluxes to vacuole and shoot, and, in particular, efflux to the external medium, also increased along this gradient. Efflux reached 90% of influx at the highest external $[Cl^-]$. Half-times of cytosolic Cl^- exchange decreased between high-affinity and low-affinity influx conditions. The relationship between cytosolic $[Cl^-]$ and shoot flux indicated the presence of a saturable low-affinity transport system (SLATS) responsible for xylem loading of Cl^-. N source strongly influenced Cl^- flux to the vacuole, and moderately influenced Cl^- influx and shoot flux, whereas efflux and half-time were insensitive to N source. Cytosolic pool sizes were not strongly or consistently influenced by N source, indicating the low potential for Cl^- to act as a counterion to hyperaccumulating NH_4^+.

Isotope preparation The chlorine isotopes ^{38}Cl ($t_{1/2}$ = 37.2 min) and ^{39}Cl ($t_{1/2}$ = 55.6 min) were produced by irradiation of natural argon gas with 41 MeV protons accelerated by the CP42 cyclotron located at TRIUMF. A water-cooled aluminum target body of 75 cm^3 volume was filled with approximately 250 psi (1.7 MPa) of Ar gas and irradiated with protons at currents between 5 and 7 μA. A typical run at a current of 5 μA for 30 min yielded approximately 555 MBq of Cl radioactivity, as measured 15 min following irradiation. The Cl isotopes adhered to the walls of the target and were rinsed off with a slightly alkaline aqueous solution after the target gas was released, then caught on a Sepak strong anion-exchange column. The only other radioisotope produced in appreciable quantities was ^{38}K ($t_{1/2}$ = 7.6 min), which was removed by passage through the exchange column. The Cl isotopes were eluted from the Sepak with 20 ml of 10 mM $CaSO_4$, and then used immediately for labelling experiments.

Results were published in Planta, an international journal of plant biology (available on line, December, 2003).

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

This study is now continuing exclusively as Barry Pointon's Ph.D. project. He is developing a model based random correction method in parallel to the scatter correction method. His methods will be tested on the ECAT 953B scanner located on the UBC campus. Results from this work have been presented at the 2003 SNM and the IEEE/MIC meeting.

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 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 percursor and fluorinating it with ^{18}F elemental fluorine in trifluoroacetic acid. The radiochemical yield is 17% after HPLC purification.

Progress this year was stimulated by the arrival of Dr. Donald Yapp at the BC Cancer Research Centre and the installation of the MicroPET tomograph at the UBC Hospital. His main research interest is in the use of EF5 as a PET marker for hypoxic tissue. Since his arrival we have reactivated this project, improved the synthesis of hot EF5 at TRIUMF, and carried out our first MicroPET imaging in a mouse tumour model. This experiment took a significant amount of planning and coordination and established a strong link between the Cancer Agency and the TRIUMF/UBC PET program. From a chemistry perspective, the progress this year was to establish a QC HPLC system for the EF5 product and to reactivate the manual production system for the radiolabelling. If this project is to continue past the pilot study stage we will need to invest some resources into refining and automating the chemistry system.

The other significant development this year that had an effect on this project was the Health Canada regulations on the human use of positron emitting radiopharmaceuticals (PERs). Our original plan was to carry out human PET imaging first, however, that was not deemed feasible this year given the requirements of the regulations. We are planning to develop a Clinical Trial Application and submit it for Health Canada approval sometime in 2004. Upon approval we intend to bring back the human lung cancer and other studies that we planned to carry out this year. Due to the availability of Cu PET isotopes at TRIUMF we are also proposing to synthesize Cu-ATSM, developed by another group, as a hypoxia marker, and compare this agent to EF5 in animals.

Experiment LS39/LS44
Positron emission profiling (PEP) for pulp and paper fluid dynamic studies/ Development of a high-speed formation (areal density) measurement system for paper

(M. Martinez, UBC)

Recently positron emission profiling has been shown to have utility in following certain physicochemical processes that have aided in the understanding of the mechanisms of these processes. The models used to describe the motion of fibres in the manufacturing of paper are limited by a lack of understanding about the micro-dynamics of the interaction of the various fibre sizes during motion. By labelling the fibres with a positron-emitting isotope it may be possible to monitor the sedimentation process to provide better parameters for the models.

Previously we have visualized the motion of different fibres sizes during sedimentation and we are in the midst of developing this method to visualize fibre motion in a new geometry, namely a hydrocyclone. A hydrocyclone is an industrial apparatus used to separate fibres into different length or weight fractions.

Flow visualization of a hydrocylcone using PET with applications for the pulp and paper industry

Papermaking fibres are hollow, flexible rod-like particles that have a wide distribution in both length and diameter depending upon species and growing conditions; when liberated from the tree they can curl or kink. North American fibres are typically 40–50% cellulose, 20–35% hemicellulose, 15–35% lignin, with the remaining fraction containing resins, tannins, ash and miscellaneous compounds. Solid-solid separation of papermaking fibre suspensions is of importance to the pulp and paper industry. Traditional unit operations such as screening, cleaning, and fractionation are traditionally described as solid-solid separation processes. For example, during fractionation, a dilute fibre suspension is separated into a number of different length-fractions. Despite the longstanding use of these unit operations, little is known about the mobility of the various fibre fractions that make up the suspension. One of the essential difficulties lies in the incomplete understanding of the long-range multi-body hydrodynamic interactions. Another difficulty is that these properties are strongly dependent upon the microstructure of the suspension which itself changes as these fibres tend to mechanically entangle or flocculate. Ascertaining these effects is not easy as these suspensions are opaque and difficult to visualize at reasonable penetration depths. These issues make the understanding of the behaviour of these suspensions particularly difficult. Clearly, there is a need to visualize the motion of the individual classes of components in a fibre suspension in order to better control the physical properties of paper.

Since 1999, the motion of ^{18}F radioactively-labelled papermaking fibres moving in the midst of a suspension of non-radioactive fibres has been studied using PET. These unique data were then used in conjunction with the equations of motion to characterize the rheological behaviour of these suspensions. This work has quickly been adopted by industry, namely Canfor (Prince George, BC), the Pulp and Paper Research Institute of Canada, and Cascade (Kingsey Falls, QC).

From these studies it is clear that this visualization technique has the potential to help clarify the behaviour of mixtures of fibres. We would like to extend this technique to measure the motion of fibres in a flowing device, in general, and to a hydrocyclone, in particular. We propose a hydrocyclone as this device (i) has relevance to industry; (ii) has a size and is operated in a manner which allows for PET profiling; (iii) has a geometry that is amiable to numerical analysis; and (iv) is supported by local experts in Vancouver who would help develop an industrially-relevant experimental protocol.

Recently, we have tested the feasibility of this idea by building a transportable hydrocyclone which we could profile using PET.

Experiment LS42
Configuration modelling and image reconstruction studies on a depth encoding research tomograph
(V. Sossi, UBC)

The HRRT tomograph was delivered in May. Hardware performance testing has been completed. The focus of the research on this tomograph will now be data quantification with more studies on reconstruction methods. However, since a large component of the present proposal was crystal simulation, we consider this proposal completed and we submitted a new proposal entitled "Quantification of high resolution brain imaging" which is intended to be a logical continuation of this proposal. The detector modelling part of this study was published [Astakhov *et al.*, IEEE Trans. Nucl. Sci. **50(5)**, 1373 (2003)].

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

In recent years the UBC/PET neurologists have published *in vivo* antisense experiments focused on Parkinson's sisease. Antisense DNA directed to the D1 receptor mRNA and to dopamine transporter mRNA was infused into rat brains. The rats developed behavioural disorders and biochemical changes consistent with depletion of the "sense" mRNA by the "antisense" DNA probe. The LS50 report for 2002 related how the UBC investigators wished to extend their observations with unlabelled DNA to make new imaging agents based on DNA radiotracers. During 2002, ^{125}I labelled antisense DNA was developed at TRIUMF for pilot *in vivo* trials. The labelling process involved incorporating a labelled radiochemical – (4-halogen-benzyl)-2-bromoacetamide (BBA) – into the DNA molecule. A separate project (LS56) was initiated to develop innovative new concepts for ^{18}F DNA. During 2003, extensive biological studies were carried out with antisense DNA labelled with ^{127}I BBA and preliminary imaging trials were carried out with ^{125}I BBA. The basic methodology is under investigation. A new DNA analogue – locked nucleic acid (LNA) – was labelled with ^{125}I BBA. LNA is quite stable *in vivo* and is significantly less toxic to brain tissue than phosphorothioate DNA, the original analogue used in this study.

A successful proposal (T. Ruth, PI) was submitted to CIHR, leading to funding related to LS50, LS56, and LS64.

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

Project LS51 examines the potential for treatment of prostate cancer through DNA damage and cell killing induced by the Auger electrons released following the decay of ^{123}I and ^{125}I. Radioiodine incorporated into an iodoandrogen steroid EMIVNT is brought into proximity of DNA by the androgen receptor protein (AR); the cancer cell DNA is consequently targeted by the Auger electrons of the radioiodine decay, followed by death of the cancer cell, in this proposed scheme for treatment. The basic idea is described in more detail in the 2002 TRIUMF Annual Report. TRIUMF is collaborating with The Prostate Centre. In previous years at TRIUMF we prepared a stannylated precursor for EMIVNT and developed radioiodination giving [^{125}I]EMIVNT at nearly 2,200 Ci/mmole and [^{123}I]EMIVNT at much higher specific activity. At The Prostate Centre, the graduate student has found that EMIVNT binds the rat androgen receptor with an affinity similar to testosterone. TRIUMF's contribution to this project is complete, except to prepare EMIVNT as needed for The Prostate Centre. Now it is The Prostate Centre's turn to perform the biological investigation for Auger killing.

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

An NSERC strategic grant was awarded (October, 2001, 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 is collaborating with Dr. Orvig in the UBC Chemistry Dept. and AnorMED (M. Abrams, CEO). A post doctoral fellow (Dr. Simon Bayly) and two graduate students (Cara Fisher and Charles Ewart) have also been working on this project for approximately two years.

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 12h 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 100–300 keV gamma photons, 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.

Progress this year centres around the synthesis of a number of bi- and tri-dentate sugar ligands. Several of these sugar derivatives have now been successfully labelled with ^{99m}Tc. HPLC conditions for the analysis of the products and the intermediate "Alberto" reagent have been worked out. Labelling kits (Isolink) have been obtained from Mallinckrodt free of charge to prepare the Alberto reagent more consistently. A collaboration has been established with MDS Nordion to provide us with ^{186}Re in order to carry out test labelling. Several sugar complexes have been labelled with ^{186}Re but using different labelling conditions to that of the kit method used in Tc labelling. This year other radiometals are also being tested. For the PET imaging program we have an interest in Cu isotopes and other radiometals, such as ^{68}Ga. We have recently produced ^{61}Cu and ^{55}Co and both of these have been successfully incorporated into some of our sugar chelates. With regard to publications we have recently submitted a paper to Bioconjugate Chemistry and have presented this work at the International Radiopharmaceutical Chemistry Symposium held in Sydney, Australia (Fisher). This year (year two of the project), NSERC reviewed our progress report and deemed progress to be satisfactory and have released the funding for year 3.

Experiment LS56
Synthesis of radiolabelled nucleotides and oligonucleotides
(M.J. Adam, TRIUMF)

This is a progress report on the development of chemistry for the F-18 labelling of oligonucleotides. One of the strategies that we are pursuing is to develop a general method to label the phosphorous atom directly with nca F-18 fluoride so that there is little structural change to the molecule. Thus, the biological activity of the oligo will be preserved. Model compound systems were developed this year to determine if P(III) and P(V) containing derivatives could be labelled with nca fluoride. We were able to successfully incorporate F-18 into both P(III) and P(V) model compounds. Another approach makes use of the fact that fluoride anion reacts readily and quantitatively with ethers of silicon to give a very stable silicon fluoride bond. Grant applications to both NSERC and CIHR have been submitted to continue this work. An abstract to the 2004 Society of Nuclear Medicine meeting has been submitted and a manuscript is in preparation on the P-F work.

Experiment LS57
Quantitative imaging with the Concorde microPET
(V. Sossi, UBC)

The microPET R4 scanner was delivered in May. Preliminary camera evaluation studies have been performed and two areas that need further improvement have been identified: normalization and attenuation correction. Figures 177 and 178 show transaxial profiles of a cylinder uniformly filled with radioactivity for several scanning conditions (see legend). It is apparent that both the absolute values and the shape of the profiles depend on the correction methods applied and none provides sufficient image uniformity. The optimum method thus needs to be developed and implemented to achieve proper quantification. Preliminary results of these studies have been submitted to the Society of Nuclear Medicine meeting [Camborde *et al.* (in press)].

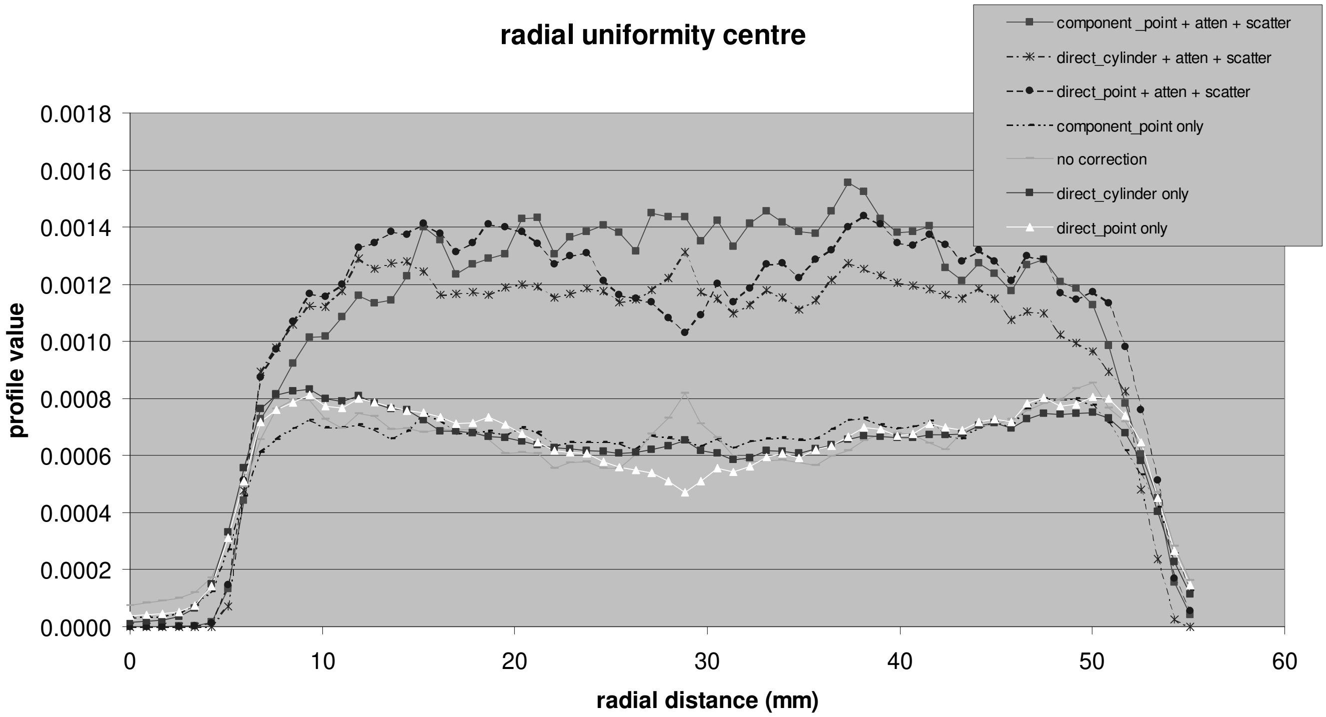

Fig. 177. Profiles obtained with and without attenuation correction using either a cylinder or a point source as normalization source and a direct or component based normalization procedure.

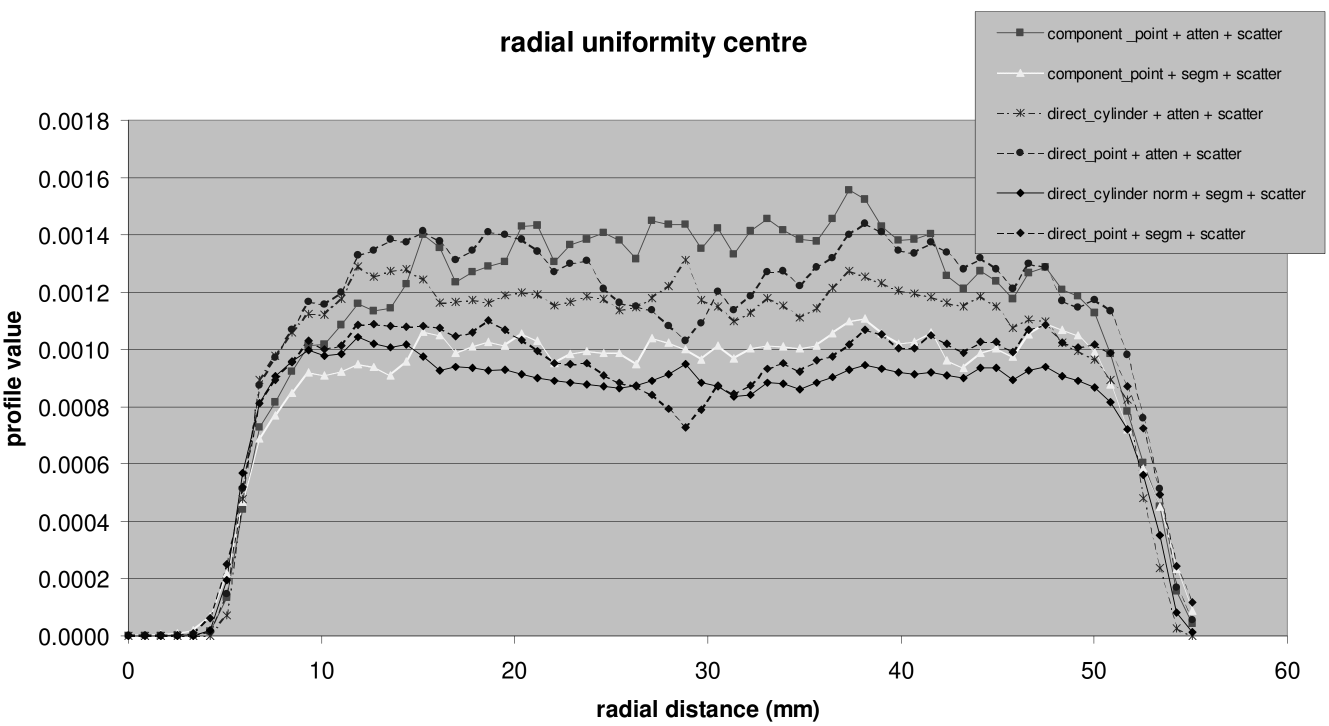

Fig. 178. Similar to Fig. 177, but now a measured (atten) and segmented attenuation correction methods are also compared.

Some preliminary animal measurements have also been performed: (+)^{11}C-dyhidrotetrabenazine (DTBZ) and ^{11}C-methylphenidate (MP) scans on healthy, unilaterally mildly and more severely 6-hydroxydopamine (6-OHDA) lesioned rats, a triple RAC study with a 50 mg/kg IP of administration of levodopa (+ 10 mg/kg benserazide) approximately 45 min before the second RAC injection to investigate the feasibility of measuring levodopa induced raclopride displacement (an indirect measurement of DA turnover, see research proposal). This last study was also performed on a unilaterally lesioned rat. Two objectives were pursued with these studies: a) feasibility of the studies themselves, especially for the indirect measure of DA turnover and b) ability to measure differences between healthy state and lesions of different severity. In each study the binding potential was estimated using the tissue input Logan graphical approach. Results are presented in Tables XVII–XIX and Fig. 179.

These results clearly show the feasibility of measuring levodopa induced RAC displacement and to quantify pre-synaptic differences between healthy and lesioned striata. We have also tried imaging using the pre-synaptic tracer FD to investigate the possibility of a direct estimate of DA turnover. In agreement with verbal reports from other PET centres, not enough specific uptake was observed in the striata to allow the use of this tracer.

The next steps of this research will include the development of a correct attenuation and normalization method for this scanner to obtain quantitative images, further investigation of image reconstruction methods with particular emphasis on the development of methods that take into account the spatially variant nature of the point spread function, and development and validation of bloodless scanning procedures. In parallel we will also be evaluating the mass effect for several pre- and post-synaptic tracers.

Table XVII. Binding potential values obtained for DTBZ for 2 rats with unilateral severe and moderate 6-OHDA lesion.

	Un-lesioned	Mild lesion	Severe lesion
DTBZ	3.6	1.6	1.3

Table XVIII. Binding potential values obtained for MP in a rat with a severe unilateral 6-OHDA lesion.

	Un-lesioned	Moderate lesion
MP	1.05	0.43

Table XIX. Binding potential values obtained for the triple RAC scan in a rat with a moderate unilateral 6-OHDA lesion. 50 mg/kg IP of levodopa (+ 10 mg/kg benserazide) was administered approximately 45 min before the second RAC injections. The three injections were separated by 2 h.

	Lesioned side	Control side
RAC 1	2.31	2.72
RAC 2	1.67	2.56
RAC 3	2.56	2.22

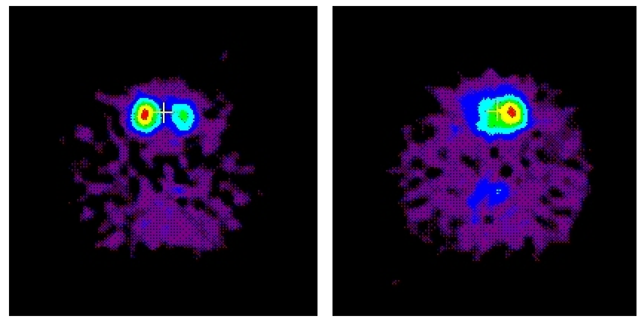

Fig. 179. RAC (left) and DTBZ (right) image of a severely unilaterally 6-OHDA lesioned rat. There is a lower DTBZ and a higher RAC uptake in the lesioned side as expected.

Experiment LS69
***In-vivo* studies on regulation of dopamine turnover using a Parkinson's disease rat model and a microPET**
(V. Sossi, UBC)

In this study we are planning to investigate disease and treatment induced regulatory changes of the dopamine transporter, their relation to dopamine turnover and to the onset of motor complications using a rat model of Parkinson's disease and a microPET. Preliminary data for this proposal can be found under LS57.

Experiment LS70
Quantification of high resolution brain imaging
(V. Sossi, UBC)

This proposal is a continuation of LS42. The proposal focuses on the implementation of the quantitative aspect and further development of reconstruction algorithms for the high resolution research scanner (HRRT) with the ultimate goal of assessing the HRRT ability to produce robust parametric images. Preliminary resolution measurements on this scanner show a reconstructed resolution better than 3 mm in each direction and a sensitivity of approximately 6%. This is the best performance to date for a human brain scanner and is expected to allow the investigation of new brain areas and the detection of more subtle and/or widespread disease induced changes of the neurotransmitter systems. In order to achieve this we are planning to develop accurate data quantification with fast image reconstruction and image analysis methods that will allow for the investigation of the entire image volume.

This planned study builds on significant progress that we already made in the area of algorithm development – development of a list mode based reconstruction algorithm and development of a method that, given information on patient motion, incorporates such information into the reconstruction procedure. Figure 180 shows the effect of motion correction on the data on a simple phantom study. A radioactive line source placed into a cylinder was scanned in three separate scans: between each scan the cylinder with the source was rotated by a known amount. Data from the three scans were then summed into a single data file and reconstructed without and with motion correction. It can be easily seen that the motion correction algorithm correctly reconstructs the data as if the line source had not been moved. This correction is particularly important for the HRRT, since patient motion will not be negligible compared to the scanner resolution.

We also developed a new method to perform random subtraction in the iterative reconstruction algorithms. This new method substantially reduces the non-negativity constraint induced bias that is generally present in the high count rate – low number of acquired events data sets, thus improving quantification accuracy over a wide range of scanning conditions. Two papers related to this research are under revision [Rahmim *et al.* (submitted to IEEE Trans. Nucl. Sci.); Rahmim *et al.* (submitted to Phys. in Med. and Biology)].

Significant progress has also been made in the development of printed point sources. A successful technique has been designed that now allows us to obtain 0.5 mCi of activity in 9 point sources. An example of an image of such point sources is shown in Fig. 181. This method is now routinely used whenever we need to image very small point sources. This work has been submitted for publication [Sossi *et al.* (submitted to IEEE Trans. Nucl. Sci.)].

We are now planning to extend these techniques to the printing of extended sources. Detailed studies will be done to examine the feasibility of obtaining sources of sufficient uniformity to be used as scatterless normalization sources.

The results of the studies planned in this proposal will impact all the studies performed in our centre. They will determine the optimum utilization of this brain scanner and will provide essential guidance in the estimate of the feasibility of new clinical studies. Their impact, however, will not be limited to our centre: they will directly benefit all the HRRT users and the PET imaging community. From a medical research point of view they will be instrumental in providing new tools to provide insights into presently unanswered questions.

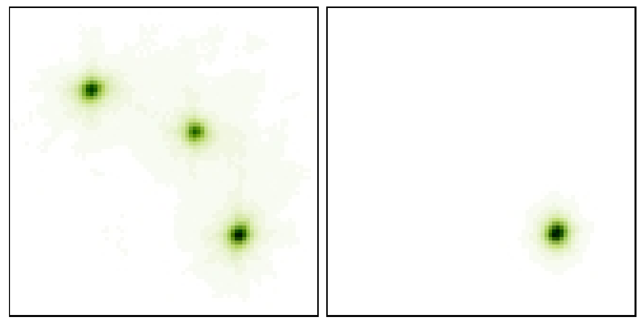

Fig. 180. Image reconstructed with (right) and without (left) correction for motion. A radioactive line source placed into a cylinder was scanned in three separate scans: between each scan the cylinder with the source was rotated by 45°.

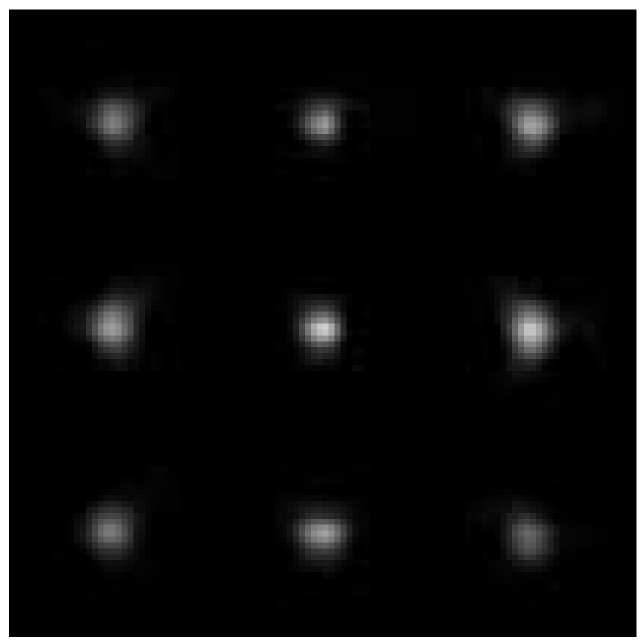

Fig. 181. Example of an image of 9 printed point sources obtained with the microPET. The sources are 0.5 mm in diameter and are separated by 1.5 cm.