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

The Life Sciences program is operating 3 tomographs, one cyclotron, and several chemistry systems routinely. Two periods of significant interruption marked operations this year, one involving reconstructions of ECAT data and the other operation of the gas targets on the TR13. Supply of ^{18}F for the British Columbia Cancer Agency (BCCA) continues with two deliveries per day. It is expected that this will continue for the year.

Personnel

Salma Jivan re-joined the group after one year at UC Davis. Marie-Laure Camborde left the group in the summer and Dr. Stephan Blinder has assumed her responsibilities with the HRRT camera. Maurice Dodd, formerly with the John Mallard Scottish PET Centre, has joined us part-time to assist with development and operations activities.

BCCA

TRIUMF supplies two deliveries of ^{18}F to the BCCA each operating day amounting to 431 batches this year. BCCA personnel take possession of the ^{18}F and synthesize FDG in a purpose built facility at the TR13.

TR13 cyclotron

Usage of the TR13 cyclotron was up significantly this year in both delivered beam and the number of irradiations. The total number of runs was 1099 vs. 709 last year and delivered beam is 684,901 μA min vs. 370,840 μA min for 2005.

Unscheduled downtime this year was also significant. At the end of October the windows of the F_2 production gas target failed catastrophically causing the target to decouple from the target selector and ^{18}F-F_2 escaped from the cyclotron shield enclosure. This was an unanticipated event and resulted in the head of the Science Division shutting down all operation of the TR13. After nearly two weeks and the implementation of some preventative measures, permission was granted to irradiate the ^{18}F water target which allowed BCCA to resume operations. At the beginning of December temporary permission was granted by the Division Head to resume operation of the gas targets.

Four extraction foil changes were required through the year and a total of 12 target rebuilds were conducted both as preventative maintenance and as repair. The ion source filament was changed 4 times and one of the inflector power supplies was repaired twice. The rf tuner motor was replaced in the spring which has improved the operation of the rf system. The rf tube had a small water leak that was found when the amplifier would not hold high voltage. The ion source cryopump was rebuilt as were the shaft seals on the ISIS gate valve.

Experience has shown that we need to replace the polypropylene transfer lines from the ^{18}F water target to the BCCA facility every 4 weeks due to a drop in recovered ^{18}F. We presume some surface changes with use cause water drops to be retained in the tubing.

Presently five target locations are occupied. These consist of

- one ^{18}O-O_2 gas target (aluminum body)
- one ^{18}O water target (niobium body)
- one ^{16}O water target (aluminum body)
- one N_2/H_2 gas target (niobium body)
- one location used for various solid targets.

A ^{56}Co calibration source was produced for the 8π research group at TRIUMF, as has been done in the past.

The TR13 Safety Analysis Report was updated to reflect present operating conditions and device descriptions. An amendment is being sought to remove irradiation time and isotope quantity restrictions from the licence; beam current limits would still be in place. The review of the safety report was rather slow this past year and the events with the gas target necessitate a further update to the report.

ECAT tomograph

Gantry electronics are the dominant failures for the camera. At the end of the summer we received the St. Louis ECAT 953B and we have been making use of the parts. Numerous boards have been swapped into our camera to resolve issues of errors following gantry power cycles. Computer failures in the early summer necessitated that image reconstruction code be ported to a different computing system resulting in an interruption in our ability to reconstruct 3D images from the ECAT.

The rod sources were replaced in April. Five Position/Energy boards, three analogue boards, one bucket controller, 8 entire buckets, and 10 blocks were also replaced.

HRRT

We now have a Siemens maintenance contract for the HRRT which will provide parts, with the exception of the detector head crystals. The funds for this maintenance contract were part of the original CFI funding to purchase the scanner. We continue to learn about this tomograph and to experience failures of the RAID. We have suggested to Siemens an alternate configuration for the data acquisition but it appears that we must pursue this on our own. The LTO tape drive used

for archiving failed, the acquisition RAID failed, and the file server failed this past year. Each event caused several weeks of downtime.

It has been determined that the scatter parameter used in image reconstruction is set-up dependent and can even fluctuate on a daily basis. These fluctuations can lead to a 10% variation in the binding potential value. We now monitor those fluctuations, but we have to reconstruct most of the data previously scanned and reconstructed. This effort is under way.

The image data are now calibrated and motion correction is being incorporated in the list-mode image reconstruction. HRRT data can now be analyzed by the LOGAN method (ROI-based and voxel-based) and the RTM (reference tissue model/voxel-based) method.

MicroPET

The Focus 120 is used routinely for a variety of studies. A firmware upgrade and a software upgrade took place this year, and a PMT stack (voltage divider boards) was replaced, followed by the replacement of the PMT module when the stack did not solve the issue.

Statistics

Table I. TR13 run statistics.

	2006	2005
Total runs conducted	1,099	709
Total runs lost	78	3
Total integrated charge delivered (μA min)	684,901	370,840
Delivered to – LS3	277,066	310,309
– LS4	16,309	63,925
– LS8	10,331	78,518
– BCCA	365,449	–
– LS35	3,240	–
– LS56	1,594	3,757
– LS66	2,439	8,667
– LS72	5,088	–
– LS73	319	–
– LS75	2,736	–
– LS76	330	–

Table II. ECAT scanning statistics.

	2006	2005
Total scans conducted	150	174
Total scans lost	48	50
Lost to – subject	3	33
– cyclotron	31	3
– chemistry	4	5
– scanner	4	0
– staff sick/away	6	9

Table III. HRRT scanning statistics.

	2006	2005
Total scans conducted	110	27
Total scans lost	28	4
Lost to – subject	4	0
– cyclotron	15	0
– chemistry	3	1
– scanner	4	3
– staff sick/away	2	0

Table IV. MicroPET scanning statistics.

	2006	2005
Total scans conducted	173	120
Total scans lost	67	17
Lost to – subject	8	8
– cyclotron	44	1
– chemistry	3	0
– scanner	12	3
– staff sick/away	0	0
– other	0	5

Experiment LS4

Targetry

(T.J. Ruth, TRIUMF)

Previously the Life Sciences group supplied copper isotopes for the Earth and Ocean Sciences Department at UBC as part of LS60. MDS-Nordion now supplies Cu radionuclides routinely.

The principal results for this year are related to the thesis work of a Ph.D. student. This targetry work on the measurement of the (p, n) reaction on W metal foils is part of LS73. A publication on this work has appeared in the peer-reviewed journal Applied Radiation and Isotopes, on-line.

The same target holder used for the W irradiation for Re isotopes (see LS73) is also used for various radioisotopes such as ^{88}Y production for the 8π group in ISAC.

Two undergraduate students from Simon Fraser University worked on measuring methane from the ^{11}C target as a means for identifying sources of carrier that might impact the specific activity of our ^{11}C tracers. This work has helped in tracking the changes in specific activity due to target gas bottles and impurities in the methyl iodide system.

The high current target for the production of ^{18}F-fluoride from ^{18}O–O_2 has been machined. A beam line on the CP42 cyclotron has been prepared for the target. The target needs to be assembled and the services panel prepared for installation in the target cave. A safety review will need to be conducted for this tar-

get and operation above 20 μA will require a licence amendment.

Experiment LS8
Radiotracers
(T.J. Ruth, TRIUMF)

The TRIUMF accelerators continue to be exploited for the wide range of radiotracers that can be produced here. The following projects are designed to take advantage of these unique facilities.

^{13}N tracers have been used extensively at UBC to study the kinetics of nitrogen incorporation by plants for more than 15 years. The program has grown and looks forward to continued collaboration with TRIUMF in these studies.

The researchers at the University of Toronto wish to make use of ^{24}Na and ^{42}K in the future and have made a separate proposal – LS71. This project is on hold for the time being.

LS8 serves as a resource for a number of LSPEC projects including:

LS76 Use of ^{13}N in plant systems – this project removed from LS8 reporting.
LS39 Positron profiling for pulp and paper fluid dynamics studies.
LS60 The physiological role of copper in marine phytoplankton.
LS71 Investigation of salt stress in rice plants.
LS80 Does cortisol regulate 5-HT$_2$ receptor binding potential in toadfish, *Opsanus beta*: a PET study.
995 An alternative approach to radioactive beam production for volatile elements.
8π Supply the group with various radioactive sources for calibration.

LS39
Positron emission profiling (PEP) for pulp and paper fluid dynamic studies
(M. Martinez, UBC)

Positron emission tomography was used to investigate the dynamics of a 0.4% (wt) fibre suspension flowing through an axisymmetric 1:5 sudden expansion (see Fig. 1). Six scans were conducted in which both the upstream velocity and the size of tracer particles labelled were varied. Images were taken upstream and downstream of the expansion plane with the upstream Reynolds number being varied from 7,000 to 14,000. The expansion plane imparts shear that disrupts the fibre network causing measurable changes in the local fibre concentration. Both an asymmetry in the flow and a water annulus surrounding the core plug are clearly visible downstream of the expansion (see Fig. 2). We consider these to be the most significant findings in this work and are currently trying to develop a mechanistic understanding of these phenomena.

Fig. 1. A schematic of the geometry considered.

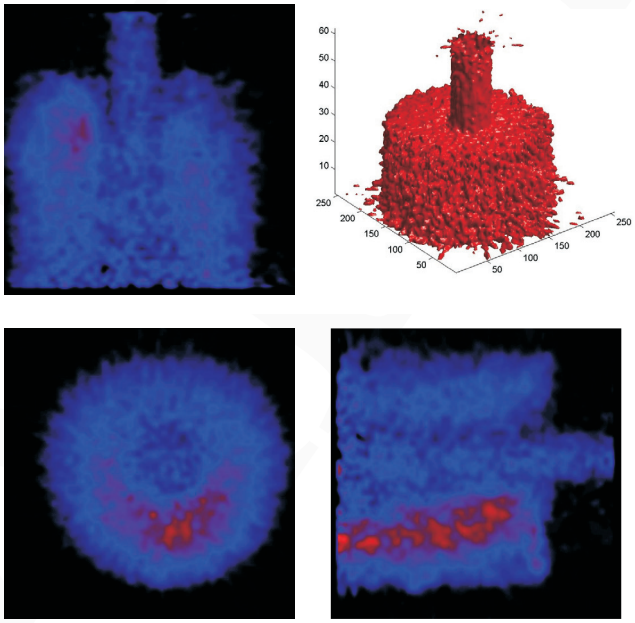

Fig. 2. Four views of the activity profile for the case in which the tracer fibres were well-mixed or fluidized after the expansion. No colour map is included in (a) through (c) but the blue represents a lower concentration than the red.

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

The major instrumentation related focus of this project is the development of the scatter correction for singles based transmission data. This development has been completed and the scatter correction has been implemented into a reconstruction algorithm. Final testing is currently under way and the application of scatter correction to post-injection transmission scanning is currently being investigated. This work resulted in two papers, which are currently in the submission process, and one conference presentation.

The biology related focus of this project consisted of establishing the mass effect for the VMAT2 marker dihydrotetrabenazine. Specific activity (SA) as low as 1100 mCi/μmole has been found to produce negligible ($\sim$1% occupancy) mass effect (Fig. 1). A Scatchard analysis to determine separately the maximum free

transmitter density B_{max} and affinity K_d was performed in a unilateral 6-hydroxydopamine rat model of Parkinon's disease (Fig. 2). The lesion was found to change B_{max} but not K_d. In pursuing these measurements, refined image analysis protocols have been developed. This work was presented at a conference and accepted for publication.

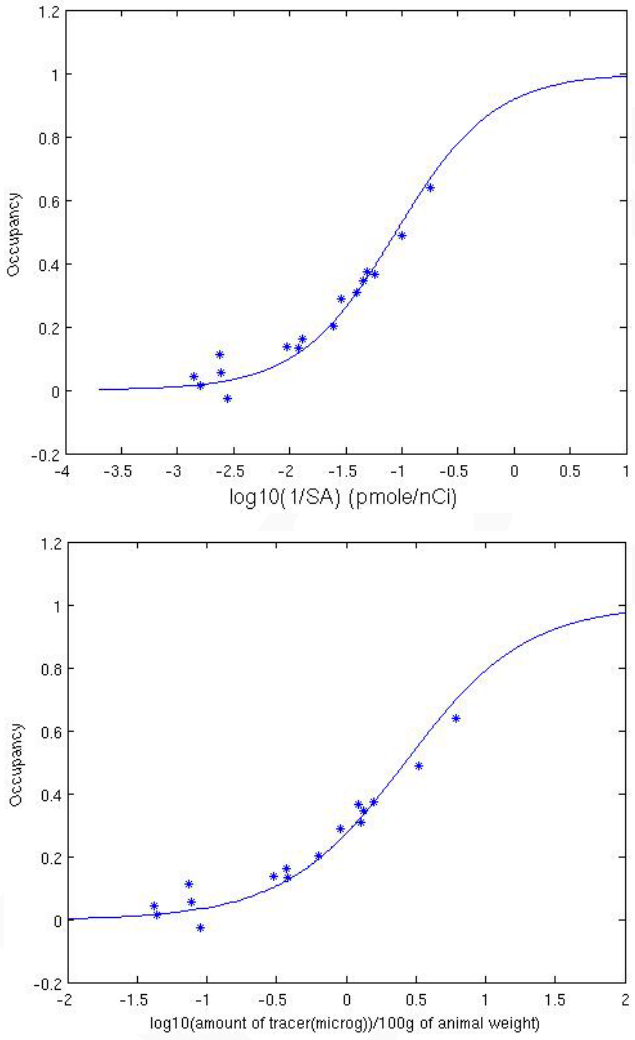

Fig. 1. Occupancy curves as a function of 1/SA (top) and amount of tracer injected (μg/100 g of animal weight) (bottom).

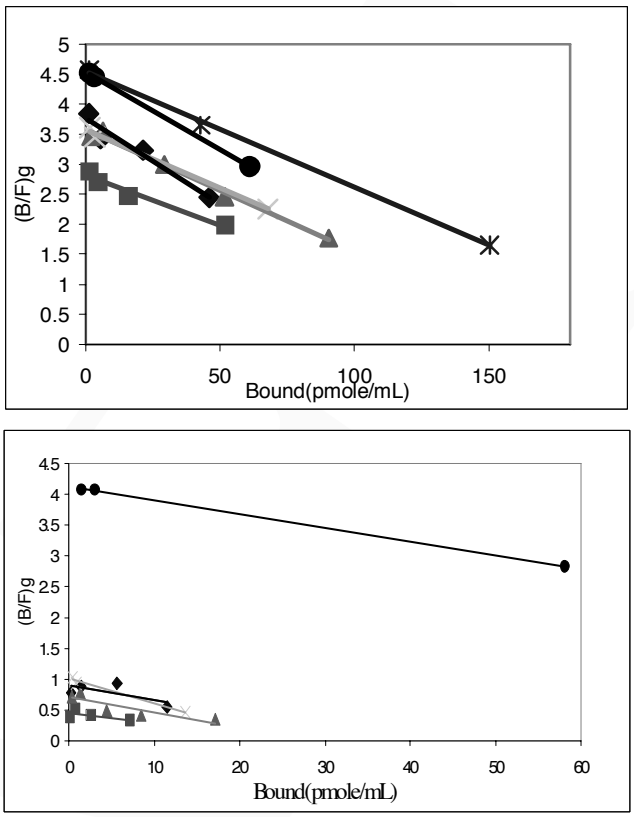

Fig. 2. Multiple ligand concentration transporter assay (MLCTA) analysis plots: ratio of bound (B) over free (F) tracer concentration as determined from the Logan graphical approach [(B/F)g] as a function of B (pmole/mL). Healthy side on the top and lesioned side on the bottom (5 out of the six rats). The same symbol corresponds to the same rat. For details refer to Sossi *et al.* [J. Cereb. Blood Flow Metab., in press].

Experiment LS66
Imaging of pancreatic islets following transplantation using positron emission tomography
(C.H.S. McIntosh, UBC)

Type 1 diabetes mellitus (T1DM) results from destruction of pancreatic β-cells. Islet transplantation is an attractive approach for treating T1DM patients but there is a massive loss of islets during and after transplantation. At present it is only possible to estimate islet mass indirectly, through measurement of circulating C-peptide and insulin levels. The present study was undertaken to establish whether PET can be utilized for determining islet graft survival. Using microPET we demonstrated that the ligand, 9-(4-[^{18}F]-fluoro-3-hydroxymethylbutyl)-guanine ([^{18}F]FHBG), was taken up and retained in mouse islets infected with recombinant adenovirus expressing a mutant herpes simplex virus 1 thymidine kinase (*HSV1-Sr39TK*) and transplanted under the kidney capsule. The microPET signal was proportional to transplanted islet number and allowed detection of small changes in mass. Expres-

sion of a therapeutic gene, viral IL-10 (*vIL-10*), was assessed in real-time and islet graft survival tracked in diabetic NOD mice, the PET signal reflecting insulin secretory capacity of transplanted islets. Additionally, we successfully imaged transplanted islets in the liver, the preferred site clinically. This study establishes the viability of quantitative *in vivo* PET imaging of islets for facilitating development of protocols for prolonging islet survival, with the potential for tracking human transplants. Future studies will focus on applying PET to facilitate the development of strategies for prolonging graft survival.

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

This study has been started and the first set of pre- and post- treatment (levodopa and pramipexole) is currently being collected and analyzed.

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

The following progress has been accomplished this year in the studies related to the high resolution research tomography (HRRT).

1. Development of a hybrid image reconstruction scheme. The necessary algorithm has been developed. We are currently comparing optimal hybrid image reconstruction schemes.
2. Full implementation of motion correction. The implementation of motion correction has been completed. We are currently testing its accuracy and impact on biological parameters.
3. Evaluation of the quantification corrections on parametric imaging on the HRRT. A preliminary study has been accomplished.

A paper has been published, one is under review and 5 HRRT related abstracts were presented at the 2006 IEEE Medical Imaging Conference.

Current and future studies

1. Finalizing image reconstruction; hybrid scheme and computation speed up.
2. Evaluation of efficient image analysis methods.
3. Final validation of motion correction.
4. Completion of the multi-centre paper.
5. Motion detection using a video camera system.

Experiment LS73
Production and evaluation of high specific activity ^{186}Re
(S. Lapi, SFU)

The goal of this project is to investigate the impact of specific activity on ^{186}Re labelled antibodies for potential cancer therapy using *in vitro* cell cultures. In addition to this we are also constructing a proof of principle ion source for the investigation of an ionization mass separation approach to producing high specific activity ^{186}Re from neutron irradiated targets.

To date we have measured the production cross sections for this isotope from proton bombardment of tungsten targets. We have utilized a dry distillation technique to extract ^{186}Re from these targets and have successfully labelled a 1H7 antibody with both in-house made high specific activity ^{186}Re and reactor produced ^{186}Re using a mercaptoacetyltriglycine chelate approach. At present we are determining binding affinity of the labelled antibody to mice embryonic fibroblasts that do and do not express receptors for this antibody. Preliminary results are given in Fig. 1.

We have constructed a cusp type ion source for the study of rhenium oxide ionization. This source and extraction assembly have been successfully commissioned with H^- ions and studies with ^{188}Re ionization are ongoing.

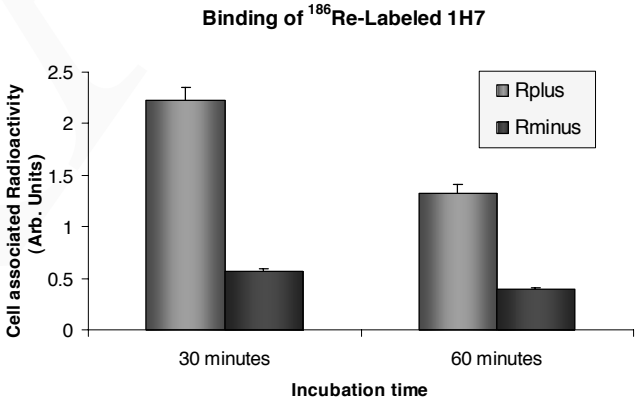

Fig. 1. Preliminary results.

Experiment LS76
Studies of nitrate uptake in plants and fungi
(A.D.M. Glass, UBC)

Increased nitrogen uptake in tobacco

This is a former collaboration with CellFor (Drs. M.Y. Siddiqi, emeritus, Mansour Shariati, visiting scientist from Iran, Wenbin Li Post-Doctoral Fellow, and John Vidmar, Alberta Agriculture Council). This work has demonstrated encouraging results in full greenhouse trials. The tobacco lines overexpressing *NRT2.1*

and *NRT3.1* generated >20% yield increase. A second trial has given even more promising results with a 40% dry matter increase. We have overexpressed *AtNRT2.1* and *AtNRT3.1* in the host plant *Arabidopsis thaliana* and these transgenic plants will be evaluated by graduate student Zorica Kotur, using $^{13}NO_3^-$. The collaborating group at Alberta has selected lines of canola genetically modified to overexpress *NRT2.1* and *NRT3.1*. These lines will also be tested for $^{13}NO_3^-$ influx during 2007.

Nitrogen uptake in the fungal model system *Aspergillus nidulans*

We have continued in our collaboration with our Scottish colleagues and have been pursuing the transport systems involved in nitrite transport. Two nitrate transporters (encoded by genes *NRTA* and *NRTB*) are present but when these are inactive in double mutants, the latter are able to grow on nitrite but not nitrate. Using ^{13}N we have been able to demonstrate that nrtA and nrtB are nitrate/nitrite transporters. However, growth on nitrite in the double mutants is due to a separate nitrite transporter which transports nitrite exclusively. Our Scottish collaborators have successfully cloned the gene encoding this transport system and will be visiting Vancouver in February and March, 2007 to undertake structure function studies of the gene/protein by use of site-specific mutations to this gene, using $^{13}NO_2^-$.

Nitrate reductase (NR)

This enzyme appears to be necessary for the normal functioning of the nitrate transporters. Using $^{13}NO_3^-$ we have been able to show that NR mutants have only ~5% of normal $^{13}NO_3^-$ influx, yet mRNA encoding the high-affinity nitrate transporter nrtA is expressed at higher abundance in the mutant than in the wild type. Likewise, Western blots show that nrtA protein is at higher abundance in the NR mutants. This points to regulation at the protein level, perhaps through protein modification e.g. by phosphorylation. We are presently undertaking site specific modification of serine residues and will test the recombinants for $^{13}NO_3^-$ influx.

The role of the *NRT3* genes in nitrate transport in *Arabidopsis thaliana*

We have been investigating the role of a third family of genes involved in nitrate transport in roots of higher plants. We refer to this family as the NRT3 group. The gene encodes a small membrane protein (~25kD). By using ^{13}N to measure nitrate uptake in mutants disrupted in this gene we have shown that high-affinity nitrate uptake is reduced by >96%. This work has been accepted for publication. Using molecular/biochemical methods it appears that the NRT3 proteins interact within the membrane with the NRT2 proteins (responsible for high-affinity transport).

The role of *NRT2.1* and *NRT2.2* in nitrate transport in *Arabidopsis thaliana*

Using recently obtained mutants disrupted in *NRT2.1* and *NRT2.2* we have been able to establish that *NRT2.1* is the principal nitrate transporter in *A.thaliana*. When *NRT2.1* is disrupted by mutation, NRT2.2 partially compensates for this mutation by overexpression.

Experiment LS80
Does cortisol regulate 5-HT$_2$ receptor binding potential in toadfish, *Opsanus beta*: a PET study
(D.M. McDonald, Miami)

The neurochemical serotonin (5-HT; 5-hydroxytryptamine) is a key regulatory component in many physiological and behavioural processes. For this reason, the dynamics of 5-HT have been the focus of mammalian research for some time. Research on serotonergic processes in lower vertebrates is not as advanced, but enough progress has been made to indicate that 5-HT is a critical regulatory element in them as well. That there is an interaction between 5-HT and the endocrine system has been well documented but is not clearly understood; grasping the intricacies of this interaction is critical for our comprehension of the vertebrate stress response in general, and understanding this interaction in lower vertebrates will give us an indication of what is common throughout the animal kingdom.

The gulf toadfish, *Opsanus beta*, provides an excellent model for studying the relationship between serotonergic and endocrine systems. When stressed, the toadfish excretes urea across the gill in distinct pulses, an event that is regulated by the coordination of a urea transporter and the serotonergic and endocrine systems. Thus, the pulsatile excretion of urea, a process that is a hallmark of the toadfish, marks a consistent and measurable, daily interaction between 5-HT and the stress hormone, cortisol. By exploiting the pharmacology of the different 5-HT receptors, the 5-HT$_2$ family of receptors has been identified as the target for 5-HT-induced urea excretion in toadfish, specifically the 5-HT$_{2A}$ receptor.

We hypothesize that circulating cortisol is interfering with urea transport indirectly, by potentially impeding 5-HT$_{2A}$ receptor function, since only when cortisol levels are at their minimum will a urea pulse occur. The objective of the present study is to determine the effect of cortisol on the 5-HT$_{2A}$ receptor binding potential in toadfish using positron emission tomography (PET).

Preliminary experiments indicate that it is feasible to obtain binding values for serotonin receptor in the toadfish using F-18 setoperone, a selective 5-HT_{2A} receptor antagonist as shown in Fig. 1.

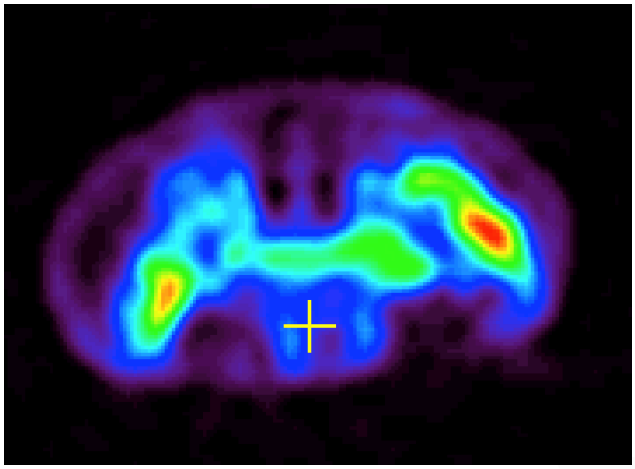

Fig. 1. Coronal section through a toadfish following injection of F-18 setoperone. The rainbow colour scale shows high uptake in reds to low uptake in blue and purple. The gills of the fish show relative high uptake.

Experiment LS83
Analysis and interpretation of dopaminergic tracer PET imaging in rodents
(V. Sossi, UBC)

This study pursues the following goals:

1. Establishment the tracer mass effect for the presynaptic dopamine transporter (DAT) marker ^{11}C-methylphenidate (MP) and D2 receptor marker ^{11}C-raclopride (RAC) as a function of tracer specific activity in a 6-hydroxydopamine rat model of Parkinson's disease. This work will follow the methodology established as part of LS57.
2. Establishment of *in-vivo* to *in-vitro* correlates using PET measures and autoradiography as a function of different PET analysis methods for MP, RAC and (+)^{11}C-dihydrotetrabenazine (DTBZ+).
3. PET/MRI coregistration methods for mice imaging.

Preliminary data to address these questions have been obtained as part of other studies. Here we are planning to take a systematic approach to define optimal methodological aspects and interpretation of the PET data.