



**REPORT ON THE MEETING OF THE
LIFE SCIENCES PROJECTS
TRIUMF
EVALUATION COMMITTEE MEETING
APRIL 3 & 4, 2008**

**TRIUMF
LIFE SCIENCES PROJECTS EVALUATION
COMMITTEE REPORT
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1. SUMMARY OF RATINGS

Core Services:

Excellent	LS0, LS3, LS4, LS8
Satisfactory	

Research:

5	Very High	LS56, LS60, LS66, LS69, LS78, LS89
4	High	LS72, LS73, LS76, LS83, LS85, LS86, LS87
3	Medium High	LS53, LS88
2	Medium	LS35, LS74, LS82, (LS83), LS84
1	Low	
	Completed	LS70, LS77
	Not Rated	LS39, LS80

2. OVERVIEW

At the TRIUMF Life Science Program Evaluation Committee (LSPEC) meeting held April 3-4 2008, the committee was invited to review 4 cores and 23 projects, 2 of which were completed projects and 6 were new ones. Two of the projects (LS39 and LS80) were not reviewed since there was no progress because of the problems associated with the TR13 cyclotron, which will be discussed in more details below. The committee was impressed with the value of the Life Science (LS) program to Canadian science and to Canadians in general. Several projects address critical problems in neurodegenerative diseases, metabolic diseases, cancer therapy, plant physiology and the environment, among others, some of which having potential commercial applications that should be beneficial to the BC and Canadian economy. But the strong radiochemistry program remains the most outstanding resource of the Life Science program on which all these innovative projects can be developed.

The LSPEC members were pleased to hear from Dr. Don Brooks, Associate Vice President Research of UBC, about UBC's vision and strategic plan relating to the future of the Life Science program and the TRIUMF/UBC PET program. It is the first time that TRIUMF's contribution to UBC research and visibility, most notably through the Pacific Parkinson's Research Center (PPRC) and the PET program, is formally acknowledged and that a clear vision of a common development plan is being laid out by a UBC representative. The Committee was particularly satisfied with UBC commitment to funding a joint UBC/TRIUMF position for the new Life Science director and to supporting new CFI initiatives jointly with TRIUMF.

Progress reports by two key partners of the TRIUMF Life Science program, Jon Stoessl on behalf of UBC PPRC, and Don Wilson and François Bénard on behalf of BCCA's Functional Imaging Program, were eloquent demonstrations of the essential role TRIUMF has played and will continue to play in supporting those successful programs. The LSPEC was impressed by the successful operation of the clinical PET imaging facility at BCCA. This program, presently relying on two daily FDG deliveries from TRIUMF, was able to reach its target scanning capacity of 15 diagnostic PET/CT scans per day, or 3,000 patients on a yearly basis, limited by PET/CT availability. The innovative functional imaging research program being developed at BCCA will strengthen the LS program in cancer research and will offer new grant channels to support LS research activities. The PPRC was able to secure excellent funding from CIHR (\$4.5M/5 years) and PARF (\$7M/5 years) and is pursuing an outstanding research program on the causes, treatment and basic understanding of Parkinson's disease. However, this program is now at stake due to the shortage in radiopharmaceutical supply and the complete interruption of scans for 6 months due to ^{11}C target problems.

The outstanding cyclotron physics, isotope production and radiotracer development capabilities of the TRIUMF Life Science program are therefore much more evident in the current review period, despite the problems with isotope production. These problems underscore the need for prompt resolution of what amount to easily addressable difficulties, such as installing a prophylactic cover around the TR13 to contain any radioactive leak and the necessity that became obvious over the last year to develop contingency plans to prevent interruption or shortage of radiotracer production. The committee has identified two critical actions that should be given the highest priority in order to secure radiotracer supply for LS projects:

- 1) A second ^{11}C target must be available and ready to use at all times as a backup. This target should be mounted permanently on the second port of the TR13 and be used in rotation to allow servicing and further target development without interrupting ^{11}C delivery.
- 2) A second ^{11}C radiosynthesis unit with separate hot cell must be implemented to increase ^{11}C radiotracer supply on a short turn-around basis. The committee felt that a commercial unit housed in a mini-hot cell would represent an ideal short-term solution that could be easily installed in the existing facilities.

Since UBC will be the major user and principal benefactor of these new facilities, it would make sense that UBC contributes to the implementation of these correcting measures.

Other measures that should be given high priority are:

- 3) A closed enclosure which would enable exhausts monitoring from the TR13 to prevent accidental releases of radioactivity into the Meson Hall. A simple plastic tent or temporary wall partitions would be sufficient to contain and monitor accidental release of radioactivity through a single exhaust. It surprised the committee that such a simple yet very necessary solution had not already been implemented.
- 4) A second ^{18}F target should be available as a backup to secure ^{18}F radiotracer supply.

The committee would like to re-emphasize the urgent need to invest in targetry and radiochemistry facilities in order to sustain growth and productivity of the LS program.

The LS program also needs to clearly define its service and collaborative roles. These roles are not mutually exclusive. A clear perspective of these roles will enable the program to provide appropriate input into collaborations. It will also provide definition of appropriate cost recovery for purely service functions. Finally, it will help prioritize projects. As recommended previously, a screening process for new projects should be established, ensuring that proposals submitted by BCCA, UBC or others have been peer-reviewed (and possibly prioritized) before allocating resources. Periodic meetings with BCCA and UBC would be extremely beneficial to advise on the experimental aspects of the various projects and to share information amongst LS users. Such meetings would need to include key members of the TRIUMF family, as well as biological researchers from collaborating institutions and from the scientific community at large.

The lack of optimal biologic support and expertise is becoming increasingly problematic. While the basic science with respect to radiochemistry, physics and imaging could hardly be any better, there was concern again this year among the LSPEC members that the interface with biology was often deficient and, as a consequence, the biological questions were not properly addressed. The lack of strength in the biologic sciences and deficiencies towards the biological endpoints were perceived in projects LS53, LS56, LS73, LS74, LS82 and LS88. TRIUMF needs to have better interactions with researchers versed in biologic models. There are different ways that can be implemented. A core biology facility in house could advance this program dramatically, if sufficient resources were allocated for creating new positions and supporting the core. However, a generic core biology facility at TRIUMF would hardly meet the requirements of such a diverse group of investigators and projects. Establishment of a biology facility within the LS group would likely have the result of driving the experimental program in the direction of

those who are running the core facility to the detriment of investigators proposing other projects. The general feeling was that there would be no need for LS to develop such biology expertise in house and that the biology expertise should reside with investigators who are proposing new projects. In this respect, improved and increased collaborations with the preclinical biology programs at the UBC and the BCCA need to be instituted and formalized so that isotope and radiotracer development can be optimized and development always occur with appropriate biologic goals.

With regard to science, the committee was impressed by the scope of scientific questions being addressed and by the quality of the basic science and resources provided by TRIUMF. Based on Dr. Stoessl's presentation, the neurodegenerative projects remain the strongest of the LS program, and it is crucial that issues that have hindered steady progress of this outstanding undertaking be resolved. The new clinical and basic research program being develop at BCCA will broaden the scope of TRIUMF LS into cancer related projects and strengthen the biology aspects. The environmental and industrial projects are also strong.

With regard to the imaging physics, the committee was pleased with the measures taken towards phasing out the old ECAT 953B and phasing in a used GE Advance. While not state-of-the-art, this scanner will provide the reliability and ease of use to pursue ongoing follow-up studies of Parkinson's patients without drawing excessive time and effort for maintenance, freeing staff for more creative tasks. The reported stability improvements of the microPET and HRRT scanners were also noted. The committee members were puzzled by the mixed signals received from LS scientists and from users regarding the HRRT. It may be true that the HRRT has not reached (and never will!) the reliability and ease of use of a field-tested commercial product. However after years of hard work and innovative developments, the scanner located at UBC Hospital probably is presently the best device in the world for brain imaging. It would be unacceptable and outrageous, from a scientific as well as from a taxpayer view point, that such a unique device be recycled for high throughput animal studies when it could more appropriately be used for imaging the human or primate brain with outstanding capabilities. Exquisite images were shown demonstrating that the ventral striatum and other structures of the brain can be clearly separated with the HRRT. No other scanner today and for years to come (LXe technology?), will be able to provide similar resolution and accuracy for brain imaging. Even though the GE Advance represents a substantial progress compared to the ECAT, the performance of this whole-body device is far off the HRRT. There is no justification to continue scanning patients with suboptimal performance using non-adapted scanner technology when so much more can be learned with this state-of-the-art device. The committee members respectfully request that the utilization of the HRRT be carefully reviewed and ask the LS program make sure that its operation will be fully and extensively supported for its intended use.

Having finally resolved most major issues with the HRRT, Dr. Sossi can now address other aspects of her research program that have suffered from the HRRT burden over the last several years. One concern is that she is required to carry a seemingly overwhelming research load with commitments on a large number of projects and a huge backlog of data from the HRRT to (re)analyze. Her priorities should be more carefully focused to satisfy the essential needs of the Life Science program while ensuring progress on her own projects. In spite of substantial difficulties, she was able to successfully carry on her research project in rodents (LS83) and to

secure funding for studying pathological behaviours in patients affected by Parkinson's disease (LS89).

Drs. Adam, Ruth and other collaborators have done interesting and productive chemistry over the last year and have succeeded to secure funds for some of their projects. While the chemistry proposed by Dr. Adam is outstanding, in certain cases there is no obvious overlap with the core objectives of the Life Science program. Dr. Adams' time and effort need to be evaluated and some projects should perhaps be dropped so other more relevant programs do not suffer as a consequence. He would definitely benefit from closer collaboration with a biological researcher to evaluate the products of his research and to move them forward to clinical use.

The negative ion separation methodology proposed for Re-186 has particular relevance in increasing specific activity of other radioisotopes, particularly molybdenum-99. Developing countries in particular utilize low specific activity Mo-99 for Tc-99m production and the availability of an efficient method for increasing specific activity, enabling subsequent solid phase separation of Tc-99m, would have tremendous impact on worldwide availability of Tc-99m.

The committee was pleased to see that a recruitment process for the new Life Science program director was established and a first round was completed, though unsuccessful at this stage. The committee acknowledges the UBC commitment to jointly support the position and TRIUMF commitment to select a high level scientist with high sensitivity to all aspects of the use of radiotracers for Life Science applications. It needs to be reiterated that the position of Life Science program director be filled at the earliest possible time. Dr. Ruth has done an outstanding job, and a successor is crucial: an individual with the leadership skills and vision to continue the development of this outstanding program is necessary.

To conclude, a few minor suggestions relating to the LSPEC logistics:

- The progress reports should include a specific separate section on the source of funding (currently held, applied for or expected, duration of funding, internal or external). This would help LSPEC assess the status of projects (pilot studies or funded) with respect to TRIUMF support and involvement.
- Presentations should not deviate from theme presented in the written material provided to the LSPEC committee, except for updating on recent results.
- It is proposed that LSPEC meetings should continue to be scheduled at the same time of the year (early April) in the future.

In summary, the LSPEC program continues to grow and, in spite of a serious setback in the last year and a few recurrent problems that need to be addressed, it will be in a good position to move forward during the next year, provided that the LS scientific direction and the new director issue can be resolved shortly.

	COMMENTS ON THE FIVE YEAR PLAN	
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The five-year program deserves the highest priority. TRIUMF is a unique institution. There is no other program, either in North America or internationally, private or public, that has the depth and breadth of the TRIUMF Life Science program. The unique availability of outstanding cyclotron physics and chemistry in addition to an excellent ligand chemistry group, as well as excellent scanner and imaging physics expertise, combined with the established collaborations with high quality programs in Neurology at UBC and Oncology at BCCA, result in a Life Science program that has few if any equals. It is particularly critical to continue to strengthen and foster the collaborative aspects of this unique resource.

The Life Sciences Program at TRIUMF has been a leader in the field of PET radiochemistry, radiotracer development, and clinical and preclinical imaging studies for the past 20 years. However, like many programs having the historical longevity of this program, there has been an inadequate reinvestment in the resources and infrastructure of the radiochemistry core of this program. Consequently, this has led to the current state where there is a significant amount of down time of outdated equipment, resulting in the cancellation of a number of funded imaging studies. This issue is exacerbated by the shortage of available hot cell space that is needed to support the increasing demands on the PET radiochemistry program. The current production capabilities of the PET radiochemistry program are only able to provide 50% of the carbon-11 labeled radiotracers needed to conduct the imaging studies currently funded. If the limitations on the PET radiochemistry program are not addressed immediately, the prospects of sustaining long term extramural funding of the imaging component of the TRIUMF Life Sciences Program will be threatened by newer PET programs having state-of-the-art facilities. Therefore, it is recommended that the following steps be taken to facilitate the expansion of the PET radiochemistry program in order to meet both the current and future demands of the PET imaging program:

1. Whenever possible, purchase of commercial radiochemistry systems. It is a waste of the talent of the staff of the radiochemistry program to build, repair, and optimize the performance of in-house built chemistry systems for conducting carbon-11 radiochemistry. The availability of commercial chemistry modules that are versatile (produce [^{11}C]methyliodide and [^{11}C]methyltriflate), reliable (low down time), and have a high throughput (faster turn-around time between syntheses) is clearly needed. Although these chemistry modules are not inexpensive, the purchase of a module represents a good investment since they will increase the capability of the carbon-11 radiochemistry program.
2. Purchase of additional hot cells. The bottleneck of the carbon-11 radiotracer production is also exacerbated by the availability of a single hot cell for conduction of ^{11}C -radiochemistry. The capabilities of this program can be further enhanced by the purchase of additional hot cells (mini cells and a full hot cell) that can house the GE FX-C module and provide multiple ^{11}C -methylation stations.

3. Additional Chemistry Systems and Hot Cells. A similar comment can be made on the production of ^{18}F -labeled radiotracers. TRIUMF should also consider the purchase of commercially available nucleophilic fluorination modules and an additional hot cell to meet the likely increased demand on ^{18}F -labeled radiotracers.
4. New cyclotron facility. The operation of the TR-13 in Meson Hall is not adequate for a variety of reasons, but another serious issue facing this program is the pending requirement to produce radiotracers used in clinical research studies under a GMP environment. No five year plan will be complete without a concrete plan that addresses this issue. The new facility must also contain a stack monitoring system so that accurate measurements of the release of radioactivity can be made. LSPEC supports the plan for major upgrades of the radiochemistry labs to meet GMP and clean room compliance.
5. New cyclotron. Although the TR13 has been a reliable cyclotron for the past 18 years, it is highly likely that it will need to be upgraded or replaced within the next five years. The feasibility of upgrading the TR13 from 13 to 19 MeV and to its full power of >100 microAmps should be investigated with respect to shielding, radiation safety and CNSC licensing. These increased capabilities would expand TRIUMF's ability to answer LS users demand and open up new possibilities for research in high yield target-chemistry systems. An even more logical plan would perhaps be to acquire a second cyclotron that would secure a much more reliable supply of radionuclides to meet future demands of the LS program.
6. Given the real potential for a shift from SPECT to PET in Canada and in the world, there is an increased need for a national strategy to supply PET radiotracers. TRIUMF LS program is in a unique position to play a leadership role in the adoption and translation of PET on a national basis, including an imperative to work on translation for both health care and commercialization.

It is part of the Life Science mission to develop and implement new instrumentation for medical imaging. Microfluidics and radiation detectors are two such technologies that should naturally be developed within the Life Science program. The existing expertise in PET scanner development and evaluation within Life Science should be leveraged to design better devices for brain and small animal imaging. The group is in an excellent position to develop new detector technologies relying on the synergy with developments for physics applications at TRIUMF. The new liquid xenon (LXe) detectors have tremendous potential for a breakthrough in PET imaging by recovering Compton interactions. There are very few places in the world where such risky venture can be undertaken and carried out with as high a probability of success as within the Life Science/TRIUMF/UBC environment. This project must be given a very high priority in the next 5 year plan.

Similar comments apply for the Mining Radionuclides project relying on the ISAC facility to produce radionuclides having therapeutic potential. Such infrastructure is unique in Canada and it has the potential, in partnership with BCCA, to develop world-unique capabilities. These ideas must be given the opportunity to be developed and investigated and thus require long-term continuous support to be brought to fruition.

The proton therapy project has been developed and operated independently of the Life Science program since its inception in 1995. It would make sense for this program to develop closer ties with the Life Science program by identifying research themes of common interest and by laying out specific research projects taking advantage of the respective expertise of the two groups. It is suggested to support the development of communication channels and explore common grounds for innovative developments in this area during the next 5 years.

3. RECOMMENDATIONS

3A. REPORTS ON PREVIOUSLY SUBMITTED PROPOSALS

LS0	PET Facilities	K.R. Buckley
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Purpose of the Core Project:

This core project supports the major equipment of the Life Science division, which includes the TR13 cyclotron and three PET scanners located at UBC Hospital (one ECAT 953B/31, one HRRT and one microPET). During the last year, a used GE Advance scanner has been purchased for cross correlation studies with the ECAT. The Advance will eventually be moved to UBC hospital once the ECAT has been decommissioned. This core also supports ^{18}F supply to BCCA with two deliveries per day, accounting for a little more than 50% of the cyclotron output in 2007. LS0 has provided 7 Life Science (LS) projects with support to do PET studies in 2007. Besides the cyclotron and PET scanners, this core provides and/or maintains some chemistry and counting equipment.

Projects Served:

The 7 LS projects listed as being served in 2007 include 3, 4, 8, 56, 72, 73 and 82, in addition to ^{18}F supply to BCCA. Note that 3, 4 and 8 are themselves core projects.

Opportunities for Students:

No students are listed as part of the core, but some are listed with the LS projects served. Equipment maintenance is not usually expected to provide opportunities for students. However there is a growing demand for cyclotron and PET scientists in Canada and worldwide, so one suggestion that was made previously was to consider training grad students (perhaps in electrical, physical or nuclear engineering?) in instrumentation related subjects. The ^{11}C target problem encountered this year would potentially offer a research subject that would provide a good challenge for an engineering student.

Strengths:

During the last year, the administration of the TR13 has been moved from the Life Science Division to the Accelerator Division. This is likely to establish a more consistent relationship between LS users and the service providers from the Accelerator and Engineering divisions, which ultimately should improve the reliability of radiotracer supply.

The committee acknowledges that a replacement path has been initiated for the old ECAT. The used GE Advance scanner will be installed at UBC for cross correlated studies with the ECAT. We urge the core to proceed as quickly as possible to commission this new scanner, which should free some staff time and effort for other projects. The ECAT downtime (lost scans due to scanner) has risen to 11% in 2007, in spite of the significantly lower demand for half of the year.

The HRRT, in spite of inherent instabilities and complicated setup procedures, appears to be manageable with a weekly calibration procedure. It seems to have reached a sufficiently stable and reliable status to be used for scans on a more regular basis. Motion information can now be routinely acquired and a faster reconstruction code is available. Unreliability of the interface between computer and gantry still persists, but it is expected that Siemens will address this problem with the allocation of two persons to support HRRT operations.

Weaknesses:

The committee would be looking forward to an increased use of the HRRT scanner for research and clinical studies, but is receiving mixed signals from LS members. It has been mentioned several times that the HRRT would never become the workhorse for brain studies that it was supposed to be. This is very unfortunate considering the unique performance of this device for brain studies and the huge amount of effort that this group has invested up to now to bring it to operation.

There have been two events that have affected LS0 operations this year: the relocation of a portion of the pneumatic pipeline along Wesbrook Mall between TRIUMF and UBC Hospital, and significant difficulties with the ^{11}C production. Nevertheless, the group led by Ken Buckley has been able to generally maintain an excellent level of availability of the major equipment, with the exception of the ^{11}C setback that will be discussed below.

The way lost runs and scans have been extrapolated in the report is quite confusing. The actual number of runs and scans performed should be reported, including those actually lost to problems with the equipment, but excluding the ^{11}C target which turned out to be a major failure.

There has been a steep drop in the number of LS projects served in 2007, from 11 in 2006 to 7 (only 4 LS research projects if we take out the 3 cores). This is likely a result of the ^{11}C target failure, which obviously had a catastrophic impact on the research program on neurodegenerative diseases. The ability to handle this problem appropriately raises several concerns. For instance, why has the ^{11}C target not been moved to the other port of the cyclotron before to resume production? How come there is no backup solution for such an important production, which is vital to so many LS projects? Is there any contingency being developed for the other radioisotope productions? These are easy questions to ask after the fact, but this catastrophic failure should be an opportunity to revise current operation, develop preventive solutions and contingency plans. As was acknowledged during the presentation, there are too many single point failures in the production process to ensure reliable supply of radiotracers and alternative solutions must now be developed urgently.

Another shortcoming of the current situation that has become evident from other LS reports is the inability to supply ^{11}C tracers on a short turnaround basis, which limits the number of scanning procedures to three per day.

Productivity:

The support staff, equivalent to 5 full-time to maintain the cyclotron and chemistry systems, and 6 for scanner and computer support, is now achieving the critical mass to provide continuous support with sufficient redundancy and overlap. With the commissioning of the GE Advance to replace the old ECAT and a partial service contract for its maintenance, some more time should be made available for direct support to research projects. It is noted that the number of scans lost to staff sick/away has decreased to none, which is a significant improvement over past years. The direct productivity corresponding to services provided to the LS projects and BCCA would have been close to 100% excellent, had the ^{11}C target problem been avoided.

Adequacy of Support:

There was no evidence that TRIUMF support was insufficient; however there are a number of issues that must be given immediate attention. Whether correcting measures should be entirely

TRIUMF's responsibility is an open question. Since UBC is the major user and principal benefactor of LS, it would make sense that UBC be part of the solution.

Recommendations:

Contingency plans must urgently be established to ensure reliable supply of all critical radiotracers to the LS projects. Specific recommendations have been summarized in the Overview.

There is still concern regarding the long term support of the ECAT. There are parts available for swapping from the old St. Louis ECAT, but for how long? It is strongly recommended to proceed as quickly as possible with the GE Advance commissioning. Finally, since the HRRT is such a unique device for brain studies, efforts should be made to ramp up scans as the staff gets more familiar with its operation.

LS3	SYNTHESIS OF RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY	M.J. Adam/ J. Green
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Purpose of the Core Project:

The function of this core is to conduct the synthesis of all PET radiotracers required by the TRIUMF Life Sciences Program. The core provides radiotracers for two human scanners (Siemens HRRT, Siemens ECAT 953B, to be replaced by a GE Advance) and one microPET (Siemens Focus 120) scanner for small animal imaging studies. The core also provides ¹⁸F-labeled radiotracers for the PET/CT operating at the BCCA.

Projects Served:

This core group continues to be essential to the TRIUMF Life Sciences Program. In 2007, there were 634 production runs with 307 doses produced for the HRRT, 953B, and Focus 120 scanners. Of the 307 doses, 101 shipments were for microPET studies, 13 for primate imaging studies, and 35 doses were shared between microPET and human or nonhuman primate imaging studies. The CNS radiotracers, [¹⁸F]FDOPA, [¹¹C]raclopride, [¹¹C]methylphenidate, and [¹¹C]dihydrotetrabenazine, are produced more frequently, largely in support of the research program studying neurodegeneration. The number of production runs was lower than projected, and this was directly attributed to difficulties with the [¹¹C]target. This resulted in no new tracer development over a 6 month period. Plans this year include switching back to a [¹¹C]CO₂ target and construction of a [¹¹C]CO₂ to [¹¹C]methane conversion module needed to synthesize [¹¹C]methyl iodide. In spite of the difficulties encountered with the [¹¹C]target, this core was able to increase the number of total runs relative to the 2006 numbers. However, there was a significant reduction (-58) in the number of doses produced for imaging studies.

Opportunities for Students:

The Progress Report currently lists two Postdoctoral Fellows and only one graduate student and one undergraduate student. One graduate student (Suzy Lapi) finished their dissertation in 2007 and is currently a Postdoctoral Fellow at the University of California-San Francisco. Given the shortage of trained PET radiochemists worldwide, it is somewhat disappointing that this Core is currently not training more graduate students.

Overall Evaluation:

This core consists of a solid group of investigators that is quite capable of meeting the demands of the imaging scientists that comprise the TRIUMF Life Sciences Program. Mr. Buckley has done a commendable job in dealing with the problems associated with maintaining the performance of a cyclotron (TR13) that is ~18 years old. Dr. Adam, Ms. Greene, and the production staff are also well qualified for conducting the routine synthesis of radiotracers required for the PET imaging studies, as well as the development of new radiotracers needed to support the growth of imaging research at TRIUMF.

In spite of the positive statements above, which are a tribute to the efforts of the members of this Core, a number of concerns were raised by the review panel regarding the resources available to this core, and the ability of this core meet the demands of the investigators having funded research projects. The first and foremost concern is the low throughput of the production carbon-11 labeled radiotracers. During the presentation of the Pacific Parkinson's Disease Research

Center by Dr. Stoessl, it was stated that the existing demands for PET studies is approximately 750 – 800 scans / year. This demand is twice the current capacity of the Radiochemistry Core, and is largely caused by the dependence of the imaging program on the use of carbon-11 radiotracers. Cancellation of PET studies due to problems associated with the carbon-11-target were not helped by the fact that there is currently only one hot cell for conducting carbon-11 radiochemistry. Although plans were presented on the construction of a [^{11}C]CO₂ to [^{11}C]methane conversion module, which is necessary for the gas phase method of preparing [^{11}C]methyl iodide, it is not clear why the efforts of this talented group are focused on mundane projects such as this given the fact that there are commercially-available chemistry systems, such as the GE FX-C module, that can produce [^{11}C]methyl iodide on a routine basis. This module also has the capability to make [^{11}C]methyl triflate, a radiolabeled synthon that will be needed to produce radiotracers such as [^{11}C]PIB, whose demand will only increase in future years. These commercial modules generally have a higher reliability (i.e., less down time) and a faster radiosynthesis turn-around time than an in-house [^{11}C]methyl iodide system, which will also increase the production capabilities of the Radiochemistry Core.

Having a single hot cell for the radiosynthesis of fluorine-18 labeled radiotracers is also problematic and will not help the production capabilities of this core. Other issues, such as the monitoring of radioactivity emissions and GMP compliance, are also looming in the near future for this Core. This review panel considers the issues associated with the outdated radiochemistry facilities that this Core must contend with to be the greatest challenge currently facing the TRIUMF Life Sciences Program.

Recommendations:

It is recommended that the TRIUMF Life Sciences invest in the purchase of a commercially-available carbon-11 methyl iodide/methyl triflate module such as the GE FX-C module. Since the CNS imaging program has been affected the most by the bottleneck in the production of [^{11}C]methyl iodide, it is recommended that UBC contribute a majority of the funds needed for the purchase of this module. The purchase of this module will also enable the talents of this group to be focused on more important issues that need to be addressed by the PET community. There is currently a need for the development of a target capable of producing [^{11}C]methane in target (and not from the conversion of [^{11}C]CO₂ to [^{11}C]methane). The development of this target will lead to a dramatic improvement in the specific activity of carbon-11 radiotracers, which will be critical for imaging studies on the microPET and in human imaging studies in which there is a very low density of the target protein. It was also reported during the presentation of LS4 that they have developed a procedure for producing *electrophilic* F-18 from high specific activity *nucleophilic* [^{18}F]fluoride. If successful, this will represent an important advance in the field of fluorine-18 radiochemistry. It is projects like this that the Radiochemistry Core should focus their efforts on, not the construction and routine maintenance of an in-house built [^{11}C]methyl iodide system.

Additional recommendations include the expansion of the radiochemistry capabilities through the purchase of two additional hot cells, one for carbon-11 radiochemistry and one for fluorine-18 radiochemistry. Additional recommendations for this core are described in the Overview and the Comments on the five-year plan for the TRIUMF Life Sciences Program.

LS4	TR13 TARGET RESEARCH	T. J. Ruth
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Purpose of the Core Project:

The overall goal is to develop targets for the production of ^{18}F , ^{11}C , ^{13}N and ^{15}O on the TR13 proton only accelerator operating at 13 MeV. Note that in the PPAC draft it states that the TR13 “was designed to operate at 19 MeV with greater than 100 micro Amps of protons circulating but because of its location is restricted to 13 MeV and 25 micro Amps”. To overcome this limitation some of the development work such as the ^{18}O gas target development is being done on “CP42” being run at 24 MeV. There is important work going on to develop a CH_4 (methane target) but this has been held up by window failures.

Projects Served:

Once systems are built the positron isotopes and the radiochemicals/radiopharmaceuticals will be delivered ideally 3-4 times per week. These will primarily serve the needs of the Pacific Parkinson’s Research Community, the BC Cancer Research Centre and the BC Cancer Agency. The progress report identifies 9 C-11 and 5 F-18 radiotracers for a total of 14 projects served.

Opportunities for Students:

Two students are identified. Ms. Katie Gagnon was assisting with the set up of the CO_2 to CH_4 system and fluoride to fluorine system. It is not clear to me if she has been negatively affected by the C-11 methane target window failures. It is not clear in the report what the Ph.D. graduate student is doing. I would recommend that until the reason for the CH_4 target window failures is understood that no further undergraduate or graduate students be put on the CO_2 to CH_4 project. It may be suitable for an appropriately trained PDF. Clearly there are a lot of opportunities for PDF and graduate student projects especially if the collaborative research grant with MDS Nordion and the UBC Applied Sciences are successful.

Strengths:

The ^{18}O gas target for ^{18}F -fluoride production is well underway as well shown in Figures 1 to 11. The proposed work and milestones seem reasonable. As the work is being done at 24 MeV it is anticipated that this technology can be transferred to the typically lower energy medical cyclotrons and hence has commercial value.

Weakness:

The CO_2 to CH_4 project is still in the evaluation stage and at least three methods reported between 1997 and 2000 are being evaluated. It would have been easier to evaluate this section if a comprehensive table including all 3 methods was presented. It seems that the proposal and direction is to develop a system that exploits the best of the three methods proposed, but this is not clearly presented.

Productivity:

The project to produce $^{18}\text{F}_2$ from ^{18}F -fluoride for the FDOPA needs is not properly justified as presented. What are the benefits and needs from the Parkinson researchers which are the drivers for this project?

Recommendations:

[¹¹C]methane target: the specific activity of carbon-11 is limited by trace amounts of atmospheric carbon-12 that invades the target delivery lines and chemistry systems. Since CO₂ is present in much higher levels in the atmosphere (~300 ppm) than methane (~1.6 ppm), the specific activity of [¹¹C]methyl iodide is predicted to be much higher if [¹¹C]methane could be produced "in target" as opposed to being made from the reduction of [¹¹C]CO₂ to [¹¹C]CH₄. The problem with this approach so far is that no one has been able to make a target that can produce [¹¹C]CH₄ in the same level (Ci) as that obtained with a [¹¹C]CO₂ target. It was the impression of the committee that this is what this group was working on and it is very important for this target work to continue.

Electrophilic F₂ from [¹⁸F] fluoride: this has been the holy grail of F-18 radiochemistry. Electrophilic F₂ is much more versatile than nucleophilic fluoride with respect to radiolabeling small molecules. Unfortunately, the 2% F₂ one must add to the target, to remove the ¹⁸F from the target wall and transfer it to the chemistry module, kills the specific activity of the final product. Converting high specific activity fluoride (produced by irradiating ¹⁸O-water) to an electrophilic fluorination species will result in a dramatic improvement in the specific activity of ¹⁸F-labeled radiotracers made from electrophilic fluorination reactions. Another area this group should focus on.

There are few places in the world, besides TRIUMF, where this work can be done and the review committee considered that this work should be of the highest priority. There were basic strategic strong recommendations. One was to move the TR13 or house the TR13 so that it can be run at up to 19 MeV and at full current. It was further suggested that TRIUMF consider replacing the TR13 with a new unit if TRIUMF really wants to be a leader in the development of medical cyclotron technology. The other recommendation was to move the methane target work to the CP42 as this cyclotron is properly contained in case of target failures. Also this would avoid the problems of a shutdown in the production of ¹⁸FDG for the BCCA and of course the other projects supported by the TR13. It was pointed out that there was little down side with this second suggestion as the CP42 can be run at 20 MeV, TRIUMF owns any IP it develops on the CP42 and MDS Nordion is a natural commercial receptor.

A rating of Excellent is given to this core service.

LS8	RADIOTRACERS FOR THE PHYSICAL AND BIOLOGICAL SCIENCES	T. J. Ruth
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Purpose of the Core Project:

The purpose of this core is to provide radiotracers for the physical and biological sciences. The actual projects outlined that are or were supported in the past are: LS76 (^{13}N for plants), LS39 (^{18}F label of wood fibre), LS60 (^{64}Cu , ^{67}Cu for marine phytoplankton label), LS71 (for rice plant label), LS80 (^{11}C label of 5-HT₂ receptor agonist) and calibration sources for the 8 pi Group. This core has available to it primarily two cyclotrons: the TR13 and the CP42.

Projects Served:

LS39, LS60, LS76, LS80, 8 pi Group.

Opportunities for Students:

The two students identified are the same students that are listed in personnel for core project LS4. With the given freedom to work on cyclotron facilities, that are as good as anywhere in the world, there are excellent opportunities for PDF and graduate students in particular.

Overall Evaluation:

The group continues to provide solid support for a number of projects that are not in the “main stream” associated with the PPRC, BCCRC and BCCA. These have been, by and large, highly successful. New projects could have been started, however the decision has been to not bring on additional projects as it would compromise existing projects; at present faculty/staff are completely committed.

Recommendations:

Perhaps the projects supported, which are presented individually, should be grouped such that they receive a status similar to PPRC, BCCRC or BCCA. A comparison of the relative size of these ventures may be useful but the metrics should include non-medical translational including those related to academia and commercialization.

It is suggested that this core not further expand projects supported until the program leader is recruited and strategic planning considerations be carefully investigated.

This core service is given a rating of Excellent.

LS35	DEVELOPMENT OF PET IMAGING AGENTS FOR MEASURING TISSUE HYPOXIA	D.T. Yapp/ J. Laskin
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Goals:

The goal of this study is to conduct a limited clinical trial (20 patients) assessing the changes in hypoxia and tumor vasculature in NSCLC patients upon treatment with standard chemotherapy or in combination with the antiangiogenic agent, bevacizumab. Tumor hypoxia will be measured using the nitroimidazole analog, [¹⁸F]EF5. Tumor perfusion studies will also be conducted with perfusion CT. The hypotheses are fairly clear and the expected outcomes are reasonable. The experimental design is appropriate for the stated hypotheses and expected patient outcomes. The goals have not changed from what was presented in the previous report to this Committee.

Significance:

This project has considerable significance and takes advantage of the large patient population in British Columbia diagnosed with lung cancer. This study is a good example of the application of state-of-the-art imaging techniques in measuring a positive response to chemotherapy in the field of oncology.

Relevance to TRIUMF:

This is a project that will be transitioned to the new PET facility of BC Cancer Agency once the construction of the radiochemistry lab of the BCCA Clinical PET/CT Program is completed. However, given the nature of the synthesis of [¹⁸F]EF5, which requires electrophilic [¹⁸F]F₂, there will be a need for continued technical and intellectual support from TRIUMF in order for this project to be successful. This is also a project that would benefit from the advances in the development of high specific activity electrophilic fluorination described in LS4.

Opportunities for Students:

Given that this is a clinical trial, the opportunity for students is very limited in this project.

Strengths:

The TRIUMF chemistry group is necessary for the initiation, and likely the completion of this clinical trial. The establishment of a PET/CT facility exclusively for oncological imaging studies is an important asset and should dramatically expand the capabilities of the tumor imaging program affiliated with TRIUMF. The study may provide evidence of a relationship between hypoxia and anti-angiogenic therapy, as well as additional data on the ability of *EF5 to evaluate hypoxia in non-small cell lung cancer. It may also however provide information on the relationship between hypoxia and alterations in perfusion as measured by dynamic CT. The clinical trial is industry-sponsored and will hopefully serve as a spring-board for the development of collaboration between the BCCA oncologists, functional imaging experts, and TRIUMF.

Weaknesses:

There were no perceived weaknesses in the design of the project.

Recommendations:

This request should be given Medium priority.

LS39	SYNTHESIS OF RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY PET FACILITIES	M. Martinez
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Goals:

The goal of this project is to study the mechanical engineering of papermaking using radiotracer techniques and imaging to study the dynamics of fibers. No progress has been made over the previous year because of the problems associated with the TR-13 cyclotron. Consequently, this project was not reviewed.

LS53	SYNTHESIS OF ^{99m} Tc AND ^{186,188} Re SUGAR DERIVATIVES	M.J. Adam
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Goals:

The primary goal of this project is to develop carbohydrate and lipid conjugates suitable for imaging with SPECT. Specifically, compounds that bind to hexokinase and that may provide an assessment of hexokinase activity are being sought. A second objective is to develop fatty acid-derivatized ligand systems for Ga-68/Tc-99m as novel brain and heart imaging agents.

Significance:

The project has two primary goals. One of these involves the development of a method to measure glucose metabolism using a single photon emitting isotope. Accomplishment of this goal would be a major advance for both synthetic radiochemistry and for the substantial biological applications. The second goal of developing lipid-linked Ga-68 complexes that cross the blood brain barrier has the potential for broadening the range of labelled compounds that can be used to study brain metabolism.

Relevance to TRIUMF:

This project utilizes TRIUMF chemistry development infrastructure, and is congruent with goals of development of novel chemistry. The use of TRIUMF facilities for radiochemical syntheses is very appropriate.

Opportunities for Students:

Two graduate students are currently working on the project. It is an excellent training project for both students and postdoctoral fellows.

Strengths:

The investigators have been productive, having developed several compounds which have been tested for hexokinase inhibition. The chemistry involved in the development of these compounds is innovative, and the investigators have been productive in publishing their results. The investigators have plans for seeking funding through an NSERC CRD with MDS-Nordion.

Weaknesses:

This is primarily a chemistry development program with little attention currently directed to the biological relevance of the compounds being explored. In general, although the investigators have made progress, lack of funding has slowed the pace.

Recommendations:

This is a worthwhile project from the perspective of novel radiochemistry development. Acquisition of long-term funding should continue to be pursued in order to hasten progress. As noted in previous years, the project would benefit from increased emphasis on the biological characteristics of the compounds being produced. In particular, clarification of proposed methods for evaluating uptake, biodistribution, etc. would enhance the proposal. The project is recommended with medium-high priority.

LS56	RADIOLABELLED OLIGONUCLEOTIDES FOR IMAGING	M.J. Adam/ D. Perrin
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Goals:

To develop and apply new radiochemical methods for labeling oligonucleotides and peptides using boron containing derivatives and Click chemistry.

Significance:

The development of new methods for tagging targeting vectors is an important objective because it is at the heart of creating novel molecular imaging and therapy agents. If successful, an effective general purpose labeling technology can create numerous value added research and collaboration opportunities.

Here, novel methods for labeling peptides and oligonucleotides with fluorine-18 such that the products are produced in high specific activity are investigated. This is an important objective that will, if the final objectives are met, make an important contribution to PET chemistry and should continue to attract attention from the scientific community (and likely the private sector).

Several approaches are being taken including the conversion of arylboronic esters to ^{18}F -labeled aryltrifluoroborates, the preparation of ^{18}F -fluoropyridines for labeling biomolecules, and preparation of ^{18}F -labeled alkynes for Click chemistry.

Relevance to TRIUMF:

The development of new labeling methods particularly for ^{18}F will add significant value to the TRIUMF Life Sciences program. It forms important links between the TRIUMF radiochemistry group and UBC chemistry programs which should continue to bear fruitful results for years to come. It also introduces new chemistry concepts into the radiochemistry program that are outside of the normal reactions used in PET chemistry. This type of “outside the box” thinking is important and will prevent stagnation (i.e. using the same old toolbox of reactions) while cultivating unique advances in the molecular imaging field.

Opportunities for Students:

This is an excellent training opportunity for students. Trainees will gain experience in developing new chemical and radiochemical methods. Working on platform technologies (as opposed to focusing on finding a single agent) is an effective training tool and prepares students to tackle a wide range of problems in the future.

Strengths:

The research team (Adam, Perrin, Ruth and collaborators) is a potent combination that has an excellent track record and is the core strength of this proposal. The project is making very good progress and is already funded by the CIHR which is a testament to the quality of the science. The target problems are well defined and the chemistry behind the solutions to well articulated scientific problems, is innovative.

The aryltrifluoroborates stand out as a unique component and strength of this proposal. The novelty of the chemistry and the potential value if successful distinguishes the TRIUMF program

from others. The Click chemistry will also be useful for tagging peptides and oligonucleotides and it was felt this procedure may be more useful than the proposed active ester work.

Weaknesses:

Very few. Perhaps one weakness is the number of approaches that are being investigated in parallel (click chemistry, 2-pyridyl heteroaromatics, and the trifluoroborates) which dilutes the focus somewhat. On a related point it was difficult to assess how many people are working on the various components of the proposal.

Recommendations:

This is a very strong project that has the potential for major impact. Continued support is absolutely warranted and there is a strong case here for expanding investment to accelerate progress even further. In addition to continuing the strong basic chemistry work, the investigators should consider how they plan to use these technologies to produce novel probes. Target selection and choice of targeting vector will be a key in demonstrating the value of the reported chemistry. This request is given a Very High priority.

LS60	THE PHYSIOLOGICAL ROLE OF COPPER IN MARINE PHYTOPLANKTON	M. Maldonado
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Goals:

To determine the physiological role of copper in phytoplankton growing under iron-limited conditions. The P.I. aims to determine the molecular mechanisms in which phytoplankton are capable of adapting and surviving under conditions of low iron availability. Preliminary studies indicate that phytoplankton growing in iron-deficient oceanic regions can drawdown Cu in surface waters twice as fast as those in non-Fe limited regions. These data suggest that phytoplankton growing in Fe-limited waters have a higher Cu requirement, which may be caused by an upregulation of the high affinity Fe transport system (HAFTS). A key component of the HAFTS is the multicopper containing ferroxidase, which reoxidizes Fe(II) to Fe(III) in the membrane transport step. The P.I. has also hypothesized that phytoplankton has the ability to adapt and convert from cytochrome C6, an Fe-based photosynthetic pathway, to one that utilizes plastocyanin, a Cu-based enzyme that can substitute for cytochrome C6 in photosynthesis I and II (PSI and PSII). The goal of the research proposed over the next two years is to identify the changes in gene expression and proteomics that underlie the differences in Cu utilization and kinetics of Cu uptake in phytoplankton growing under Fe-deficient oceanic waters.

Significance:

Carbon dioxide fixation by marine phytoplankton is believed to correspond to half the earth's total carbon fixation. Over the past century, industrial emissions of CO₂ have resulted in an exponential increase in CO₂ to levels not seen on earth in at least the last 400,000 years, which has resulted in a gradual warming of the earth's temperature referred to as the "Greenhouse effect". Consequently, there is an interest in devising strategies that can increase the capability of marine phytoplankton to remove atmospheric CO₂. The studies described in this research project represent one of the few examples of the application of tracer techniques in environmental research.

Relevance to TRIUMF:

This project is consistent with the scientific mission of TRIUMF. The construction of the sea-going gamma counter by Katie Gagnon of TRIUMF was essential to the study showing the differences in kinetics in the uptake of Cu between Fe-deficient and non-Fe deficient phytoplankton. However, the shift to using ⁶⁷Cu, which is provided by Nordion, has reduced the role of TRIUMF in this project.

Opportunity for Students:

Outstanding. Three graduate students (two Ph.D. and one M.S.) will be involved in this project.

Strengths:

The leadership of Dr. Maldonado and her ability to acquire important scientific data under a complex experimental design is noteworthy.

Weaknesses:

There are few weaknesses to this project. The P.I. should consider consulting the P.I. and investigators involved in LS76 (Studies in Nitrate Uptake in Plants and Fungi) for guidance in the molecular biology aspects of this project.

Recommendations:

This request should be given Very High priority.

LS66	IMAGING OF PANCREATIC ISLETS FOLLOWING TRANSPLANTATION USING POSITRON EMISSION TOMOGRAPHY	C. McIntosh
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Goals:

To establish whether dipeptidyl peptidase-4 (DPP-IV) inhibitors can be used to prolong survival of transplanted islets using animal models of type 1 and type 2 diabetes mellitus. A secondary goal is to determine if PET can be used to quantify the effect of inhibition treatment on islet mass. One concomitant goal that the investigators need to address to be able to use PET for longitudinal studies is to develop new reporter systems for tracking of islet grafts over more extended periods.

Significance:

Diabetes accounts for about 50% of all heart disease and results in significant peripheral vascular disease. Treatment with islet transplantation (e.g. Edmonton protocol) shows promise but suffers from poor islet survival with dependence on exogenous insulin returning in almost all treated humans within five years of transplantation. For diabetes, as for a number of other diseases in which cell therapy is being investigated, there is a profound need to track cells non-invasively using imaging methods. After transplantation it is essential to determine cell viability and cell function.

It is clear from the two publications in top ranked journals that the group has achieved its two goals of a) cell tracking of transplanted islets and b) the demonstration of the effectiveness of therapy using dipeptidyl peptidase-4 inhibitors. This has been done in a mouse model of type 1 diabetes mellitus.

This research group has now developed the tools to evaluate islet cell transplantation in animals including cell viability and function immediate and for up to 4 weeks post transplantation. This allows the evaluation of different transplant protocols and different methods of supportive therapy. The main limitation at this point is that the expression of the reporter gene system used (herpes simplex virus 1 thymidine kinase or HSV1-TK) allows only about one month follow-up of the islet graft survival in vivo due to loss of HSV1-TK gene expression. One other major limitation to translation to clinical application is that the reporter probe and gene used may not be approved for human use.

Relevance to TRIUMF:

TRIUMF's life science strategic plan is focused around neurological diseases (i.e. Parkinson's) and oncology diagnostic and therapeutic applications. However this successful metabolic disease project provides TRIUMF with an entry point into the PET reporter gene/reporter probe methodology and the major metabolic disease of our time which links strongly with the greatest medical problem of our time: heart disease.

Opportunities for Students:

There are significant opportunities for graduate students, PDFs and medical fellows in the project which demonstrates a successful application of true molecular imaging. The committee was surprised there are no students identified. Molecular imaging and cell therapy tracking is one of the fastest growing areas of medical imaging and hence training of students in this discipline would be highly beneficial to future HQP for Canada.

Strengths:

- a) A successful collaboration between the diabetes researchers, the molecular biologists (including the Stanford group), and the TRIUMF radiochemistry group.
- b) The success of the PET reporter probe/reporter gene to track transplanted islets. The demonstration in mice that a DPP-IV inhibitor can prolong transplanted islet survival.
- c) Two publications in top tier journals.

Weaknesses:

- a) Lack of students on the project.
- b) No clear path of translation of cell tracking methods to humans and/or determination of transplanted cell mass in human recipients. It was suggested by the committee that ^{11}C -DTBZ be considered to be used in the future for human studies.

Recommendations:

This is a very successful project and could be an entry point into metabolic diseases for TRIUMF. Consideration should be taken to leverage this success by incorporating metabolic diseases into the TRIUMF Life Sciences strategic plan. The request should be given Very High priority.

LS69	<i>IN VIVO</i> STUDIES OF DOPAMINE TURNOVER USING A PARKINSON'S DISEASE RAT MODEL AND A MICROPET	V. Sossi
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Goals:

The overall goal of this project is to investigate the role of disease- and treatment- induced changes in the central kinetics of levodopa-derived dopamine (DA) in the occurrence of motor complications in PD. The major hypotheses are that dyskinesias are related to changes in the dynamics of levodopa induced dopamine release, that these changes are related to changes in the expression of the dopamine transporter (DAT) over time, and that levodopa-derived DA and DAT expression are differentially affected by treatment. The investigators will use a rat model of PD with microPET studies of dopamine release and DAT before and after treatment with levodopa and dopamine agonists.

Significance:

This study will investigate the mechanisms underlying a very important and disabling clinical phenomenon. By comparing the results of this study to currently ongoing human studies, these data will also provide further validation of the rat model of dyskinesia. The use of in-vivo imaging with microPET will allow longitudinal tracer studies to be performed on the same animals, thus eliminating a large source of biological variability and reducing the number of animals required for this study. The project could have long term implications for treatment of PD. Evaluating the changes associated with levodopa vs dopamine agonist treatment will have implications on other imaging studies in PD.

Relevance to TRIUMF:

This project makes use of many features available at TRIUMF including the microPET system, radiotracer production and the expertise in modeling and data analysis.

Opportunities for Students:

One graduate student is presently involved in this project, which is a very good training project for students in biology and physics/engineering.

Strengths:

Previous concerns were expressed regarding the number of scans proposed in this project. The investigator has established, however, that the scope of the project does fall within the capabilities of the group and significant progress has been demonstrated in spite of problems related to C-11 tracer production and the microPET upgrade. The proposal benefits from the substantial expertise of the principal investigator and the strong research team with excellent productivity in the relevant areas. The ideas are novel, and the hypotheses testable. The receipt of a CIHR grant is excellent evidence of the strength of the ideas.

Weaknesses:

This is an extremely ambitious project in terms of the number of studies being contemplated. The major problems relate to the number of microPET studies required. Although microPET access is not likely to be an issue, there will be competition for radiochemical syntheses between this project and other related neurological projects using C-11 compounds.

Recommendations:

This is an elegant study with interesting and potentially clinically important goals. Setbacks have been related to microPET and cyclotron issues, but hopefully these problems have been solved. It is important that the program as a whole provide the infrastructure support required to ensure continuing access to the required tracer compounds and imaging facilities. The project is recommended with Very High priority.

LS70	QUANTIFICATION OF HIGH RESOLUTION BRAIN IMAGING	V. Sossi
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Goals:

The goal of this project was to implement quantitative methods for parametric brain imaging with the HRRT scanner. Achieving this goal involved several challenges with respect to image reconstruction and correction, dynamic imaging and patient motion, analysis of the huge data set generated by the HRRT, not to mention data archiving, among others. This is the final report for this project with a summary of the progress accomplished during the last year dealing with:

1. Development and implementation of an accurate scatter correction method.
2. Implementation of faster image reconstruction.
3. Evaluation of the impact of statistical uncertainty on BP accuracy.
4. Development of an image analysis protocol leading to biologically meaningful results.
5. Implementation of data archival.

Significance and Relevance to TRIUMF:

All human and primate brain imaging projects carried out within the framework of the Life Science program should logically migrate to the HRRT scanner. Therefore, the work performed under LS70 to bring this scanner to full speed was essential and critically important for the entire Brain Neurodegenerative Disease Research of the Life Science program and the Pacific Parkinson's Research Center.

Opportunities for Students:

The HRRT is the most advanced and most complex existing PET scanner, designed purposely for brain imaging. The commissioning and use of this device have offered several excellent opportunities for training students. Several graduates who were trained under this LS project now hold research positions in other universities. It is unfortunate that the list of trainees was not included in this final report.

Strengths:

The group has succeeded to bring the HRRT to a fully operational status, which is in itself a major achievement. The committee members acknowledge that some planned developments were abandoned to concentrate on the more pressing issues raised by the exploitation of the HRRT for human studies. The project has built on the previous experience of the investigators in the evaluation of PET scanners and on their extensive expertise in quantitative PET data processing. Most developments around the HRRT lead to original work that provided exceptional visibility to the TRIUMF/UBC group, as demonstrated by the impressive list of refereed papers and conference proceedings that evolved from this work. Several collaborations all across the world have been established as a result of the multi-center investigation that was led by the principal investigator.

Weaknesses:

After years of frustration, the group's heroic efforts to fix the instability problems with the HRRT scanner appear to have come to fruition. The importance of proper data correction and

analysis methods to lead to biologically meaningful results clearly was demonstrated. Nevertheless, it is quite concerning to see the dramatic changes in measured parameters as a result of those corrections. One is left with some doubts about the accuracy and precision of the extracted biological parameters after such extensive data processing.

One issue that was not addressed in this report relates to the implementation and validation of tools to compare data obtained on the HRRT and ECAT. This would be a necessary step to transfer ongoing projects to the HRRT and initiate the phasing out of the ECAT. It was felt from this report and from other presentations at the LSPEC that the group has given up on the objective to make the HRRT the basic imaging device for LS brain studies.

Recommendations:

Since most brain research projects carried out by the Group on Neurodegenerative Disease and the PPRC critically depend on the access to imaging with the HRRT, outstanding issues with respect to the scanner will be addressed as part of the new LS88 proposal to improve the resolution and quantitative accuracy of the HRRT.

Methods to enable the migration of all brain scans from the ECAT (and eventually GE Advance) to the HRRT still need to be developed and validated. Even more important would be a clear indication and a plan to make such a unique imaging device as the HRRT the basic resource for all human and primate brain studies. Additional recommendations on this matter can be found in the General Comments.

Nevertheless, congratulations for having taken up the challenge to bring a prototype scanner to a fully operational device for brain research!

LS72	IMAGING AND THERAPY OF LYSOSOMAL STORAGE DISEASES	M.J. Adam
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Goals:

This is a continuing study of glucose cerebrosidase in lysosomal storage disorders.

Significance:

While these diseases are present in a very small proportion of humans, study of mechanisms underlying lysosomal storage disorders is indeed laudable; the investigators have concentrated on an enzyme of probable relevance.

Relevance to TRIUMF:

Has potential: the development of such radiotracers and particularly their use in other diseases e.g. cancer make this an interesting project.

Opportunity for Students:

Considerable. Understanding enzymatic processes has considerable research opportunities that may lead to Masters' or doctoral theses. There appears to be considerable opportunity for students to carry out cell biology experiments.

Strengths:

Progress has been made as detailed in the proposal a year ago. Possibility of using the methodology in the assessment of other diseases including cancer makes this a project worthy of pursuit.

Weaknesses:

The broad application of this methodology is unlikely, given esoteric nature and rarity of lysosomal storage disorders.

Recommendations:

Study other systems, including lysosomal disorders in more common disorders including cancer. This request should be given High priority.

LS73	PRODUCTION AND EVALUATION OF HIGH SPECIFIC ACTIVITY ¹⁸⁶ RE	D.W. Becker
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Goals:

To produce ¹⁸⁶Re, which is a radioisotope of rhenium with a half life of 90 hours, with a high specific activity. (Note that MDS Nordion is providing ¹⁸⁶Re commercially so a private sector receptor has already been identified).

Significance:

Rhenium has a number of attractive properties that may make it successful for open source therapy: a) chemistry that is similar to technetium-99m, b) a half life of 3.8 days which matches the half-life of many larger targeting vectors such as antibodies and c) a radio decay scheme with most of the decay energy being directed in the form of kinetic energy of electrons.

The negative ion separation methodology proposed for Re-186 has particular relevance in increasing specific activity of other radioisotopes, particularly molybdenum-99. Developing countries in particular utilize low specific activity Mo-99 for Tc-99m production and the availability of an efficient method for increasing specific activity, enabling subsequent solid phase separation of Tc-99m, would have tremendous impact on worldwide availability of Tc-99m.

Relevance to TRIUMF:

TRIUMF scientists have the expertise to develop a method to produce high specific activity ¹⁸⁶Re. It is clear from the literature that there is no competing nuclear reaction that could be used to produce ¹⁸⁶Re that would not be diluted by stable Rhenium isotopes. Hence mass spectrometry separation is the method that must be used and this requires placing an electrical charge on ¹⁸⁶Re and the stable isotopes (¹⁸⁵Re and ¹⁸⁷Re) so that the charge/mass ratio differences can be used as the basis for separation.

Hence this project fits well into the oncology strategic direction for TRIUMF and potential for translation to patient care and commercial applications are high.

Opportunity for Students:

There is a good opportunity for one PhD and one graduate student to work on this project. There is considerably more opportunity in the downstream use of ¹⁸⁶Re as its incorporation into therapy agents is developed.

Strengths:

Strengths include a) past experience in producing ¹⁸⁶Re, b) preliminary results using the “Negative Surface Ionization Process” and c) a proven private sector partner. Also it was pointed out by the review team that this method of separation may be important for other applications.

Weaknesses:

The weaknesses are a) the dependency on mass spectrometry separation and possibly the amount of material that can be separated (i.e. production rate) b) the uncertainty in the eventual effectiveness of ¹⁸⁶Re as a radiotherapy open source radioisotope.

Recommendations:

Determine the production rate and evaluate the technology at higher levels of activity. Once high specific ^{186}Re is available aggressively pursue a) incorporation into oncology targeted molecular probes and b) test efficacy of therapy in animal models. This proposal should be given High priority.

LS74	ASSESSMENT OF TUMOUR MICROENVIRONMENT WITH MICROPET AND MRI	D.T. Yapp
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Goals:

The objective stated in the written proposal is to use a variety of imaging (MRI and PET) tools and in vitro assays/screens to characterize a tumour model of colorectal cancer and to then investigate the impact of a pharmaceutical treatment on the tumour model. It should be noted that the presentation covered projects that appeared to be outside of the core research proposal/summary. To be consistent, the comments provided here focus mainly on the written summary.

Significance:

Given the morbidity and mortality associated with colorectal cancer, the proposed research is in an area of critical importance. Its long term significance lies in how the resulting data can be used to improve the clinical management of colorectal cancer. The proposed research will also nicely demonstrate how in vivo imaging can complement ex vivo characterization of tissue samples to better understand the molecular basis of disease and pharmaceutical efficacy.

Relevance to TRIUMF:

This project is an important component of the Life Sciences program and forms a strong link between the tools and expertise available at TRIUMF with the Cancer research community in BC. These are the types of projects that should increase in number and will help drive the expansion of the Life Sciences program and warrant acquisition of new equipment.

Opportunity for Students:

This program will attract researchers from both the life/health sciences and physical sciences. It will require contributions from cancer biologists, animal specialists, chemists, clinicians and imaging physicists. The latter role is particularly important to extract the relevant information from the images.

Strengths:

The target cancer of interest in this proposal is a real strength as are the combination of expertise of the investigators. The hypothesis is sound and is based on solid evidence. If proven true, the outcomes of the work will have significant impact and garner external attention and international recognition.

Weaknesses:

One of the challenges with this project is that its scope is rather large which means that interpretation of all the data in a meaningful way could become an issue. It was not clear if all the image reconstruction expertise is available to ensure that all the data is appropriately and effectively extracted from the various components of the study.

A second concern is the translatability of the results from an immune compromised animal model to humans. As a number of the imaging protocols are suitable for human use, why not focus efforts on a small scale human trial?

The number of publications that relate to this project is relatively low but that is likely the result of the outbreak of pinworm which hindered working with the animal models. One additional weakness is that the material presented only very loosely related to the work described in the written summary. It was difficult to get a sense of the overall hypothesis and the extent of progress towards specific objectives.

Recommendations:

Assuming the animal issues are resolved shortly, this project should make significant progress over the next year. The LSPEC asks that for next year the written report and the presentation focus on the same work and the achievements around a set of specific objectives that relate to the material summarized in 2008. This request should be given Medium priority.

LS76	STUDIES OF NITRATE UPTAKE IN PLANTS AND FUNGI	T. Glass
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Goals:

To understand nitrogen metabolism using N-13 nitrous oxide.

Significance:

Very high. The understanding of basic nitrogen metabolism in plants and fungi is of critical importance in plant biology.

Relevance to TRIUMF:

Very high. This is an area where the unique strengths of TRIUMF are being optimally utilized.

Opportunities for Students:

Dr. Glass has nurtured many students, and the educational aspects of the research remain considerable.

Strengths:

An ongoing effort that has already yielded a lot of information on nitrogen turnover in plants, and utilizes the radioisotope production from TRIUMF in a unique manner, this exemplifies the sort of research that must be done, and can be done uniquely with TRIUMF.

Weaknesses:

Dr. Glass does not appear to have a clearly defined succession plan, nor the will to extend the interpretation of his results to investigate fundamental issues with respect to crop growing, such as the use of fertilizers in agriculture.

Recommendations:

Support project strongly, and determine who will carry on this work, and how. This request should be given High priority.

LS77	IMAGING TUMOUR VASCULATURE NON-INVASIVELY WITH POSITRON EMISSION TOMOGRAPHY AND CATIONIC LIPOSOMES	D.T. Yapp
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Completed.

LS78	DEVELOPMENT OF LIQUID XENON DETECTORS FOR PET	L.Kurchaninov
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Goals:

The goal of this ambitious project is to develop liquid Xenon (LXe) detectors that can be used as coincidence Compton cameras for PET imaging with unequaled resolution and sensitivity. The program involves extensive simulations of the proposed LXe PET system focusing on Compton scattering reconstruction studies, measurements of LXe charge diffusion and light output on a prototype to confirm important aspects of the LXe detector performance, and assembly of one complete prototype PET ring sector.

Significance:

The successful development of a working LXe detector could lead to a major breakthrough in PET imaging technology, featuring sub-mm resolution in all three dimensions, faster time response reducing random coincidences, superior energy resolution for reduced scatter fraction, and improved sensitivity through coincidence Compton detection. This is a truly exciting project that may redefine the performance standard of PET imaging. However, the challenges are huge and several previous attempts during the last 30 years at implementing this technology have failed badly. The suggestion was also made that LXe detectors could potentially be used for Compton imaging with conventional nuclear medicine radiotracers, but the currently achieved energy resolution would be a significant limitation.

Relevance to TRIUMF:

The development of LXe detectors for PET imaging is a major challenge that could never be undertaken without the broad scope of technological expertise and laboratory facilities available at TRIUMF. These include cryogenic, detector and electronic engineering, as well as real-time data processing and computing. TRIUMF is one of very few places in the world and the only one in Canada having the required human and material resources to carry out such developments. Integration of this project as part of the LS program is a logical move to provide the necessary input and realism to adequately satisfy the requirements of imaging applications. Developing and eventually utilizing such technology to address biomedical problems is consistent with the mission of TRIUMF and of the LS program.

Opportunities for Students:

Exceptional opportunities exist for training students and PDFs in the physics and engineering components of this project at the present time, and in imaging physics at the next stage of evaluation of the technology. Three students have already been involved in the project.

Strengths:

There has been significant progress since this project was first proposed two years ago. Most of the deficiencies that have affected and have eventually lead to failure of previous attempts at using LXe detectors for imaging appear to have been identified. The proposal makes an extensive review of the technological aspects of the project, pointing out critical steps and proposing solutions to expected shortcomings. The team led by Dr. Bryman obviously brings together the body of expertise required to address the multiple technological facets of this huge project. The test results with the prototype PET ring sector will enable further optimization of

the technology and provide the necessary “proof-of-principle” to go ahead (or not) with a full PET system.

Weaknesses:

There is a tendency to underevaluate the characteristics of current PET technology, as well as to overestimate the expected performance of the new detector for PET imaging. This was particularly obvious from the simulated image of a resolution phantom for the microPET Focus scanner, which by no means is as bad in the real world as what was shown during the presentation. The statement that resolution phantoms are normally scanned without being immersed in water is incorrect. Such resolution phantoms are made of water-equivalent materials (e.g. Lucite), which is equivalent to immersion in water. The effect of annihilation non-collinearity is being underestimated in the comparison with the Focus, because the effective interaction diameter is significantly larger than the internal ring diameter with LXe detectors. The count rate limitations resulting from pileup of the slow drifting electrons needs to be reconsidered in the context of PET imaging. That kind of misinterpretation could be avoided by a closer interaction with members of the PET imaging group who could provide the missing experience with respect to imaging issues. The actual cost of a complete scanner, including DAQ electronics, ancillary systems and computer hardware for data storage and off-line processing must also be reassessed more rigorously. LXe may be quite inexpensive, but the scintillator materials being used in small animal scanners is not the major cost of these devices either.

Adequacy of Support:

The project was initially funded by the Laboratory for Advanced Detector Development (LADD), a CFI-supported project of UBC, Montreal and TRIUMF. The current work, including the construction of the prototype PET ring sector, is supported in part by this grant. Additional funding from CECR, CFI and NRC for maintenance will be sought for the construction of a complete scanner.

Recommendations:

The project is recommended with Very High priority. Completing and experimenting with the prototype is essential to confirm the potential of this new detector technology for PET imaging. It will be important to involve investigators with imaging experience during this phase of the project. A complete reassessment of the pros and cons in the light of these results will be necessary before going ahead with a full system.

LS80	DOES CORTISOL REGULATE 5-HT₂ RECEPTOR BINDING POTENTIAL IN TOADFISH, A PET STUDY	D. McDonald
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Goals:

To determine the effects of stress on neurotransmitter function in a fish model. No progress has been made over the previous year because of the problems associated with the TR-13 cyclotron. Consequently, this project was not reviewed.

LS82	METHIONINE-PET FOR THE PREDICTION OF TREATMENT OUTCOMES IN RADIATION TREATED ACOUSTIC NEUROMAS	S.A. Reinberg
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Goals:

This is a proposal to study the utility of C-11 labeled methionine to evaluate acoustic neuromas, and to assess response to therapy in this disease.

Significance:

Since the initial proposal, the field of amino-acid imaging has developed considerably. While still of relevance to imaging of intracranial neuromas, the choice of radiotracer has become more questionable.

Relevance to TRIUMF:

The relevance would be far greater if TRIUMF was actively involved in the choice of a radiotracer. C-11 methionine is not a novel agent, and its application has been replaced in most cases by F-18 labeled tracers, particularly tyrosine.

Opportunities for Students:

Also unclear. There will be opportunities for students to study methodology for C-11 labeling, which is critical to an understanding of radiochemical synthesis using short-lived radiotracers, but otherwise relevance is unclear. Perhaps students could be involved in the evaluation of amino-acid kinetics in neuromas, but this is not specified.

Strengths:

Methionine is an ideal agent in many ways for the study of intra-cranial neoplasms since there is little normal tissue uptake of methionine in the head and neck. Utilization of the unique features of TRIUMF, including Dr. Ruth's expertise as well as instrumentation (both PET and cyclotron) will be optimal. Most importantly, the project underscores a developing collaboration between UBC and the cyclotron/radiochemistry facility.

Weaknesses:

(From the prior review: As stated above, C-11 labeled amino-acids have decreasing relevance in the study of neoplasms. Moreover, the agent is being studied in a disease with relatively low prevalence. If cure is around 95%, why do more outcome studies in neuromas? Further, how will a sample size of 5 patients (with 95% cure) provide any meaningful data other than that in the literature? There is unfortunately no coordination with radiation therapy – a collaborative study would be far more useful.) In addition, only one patient has been studied since the proposal was approved a year ago. This underscores the tenuous nature of the project, and the lack of enthusiasm for a successful outcome.

Recommendations:

It is unclear why C-11 methionine should be pursued, and the group is encouraged to consider tracers such as F-18 ethyl tyrosine (the use of an amino-acid is most appropriate). A follow up scan at 6 months after stereotactic radio-surgery is also unclear – evidence of unsuccessful therapy is necessary as soon as possible after the therapy has been completed e.g., one week. (At 6 months after radiosurgery, the incremental utility of PET over MRI may be difficult to establish.) Hypotheses for parameters of C-11 methionine uptake that would predict for response are needed to better design further studies. This request should be given Medium priority.

LS83	ANALYSIS AND INTERPRETATION OF DOPAMINERGIC TRACER PET IMAGING IN RODENTS	V. Sossi
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Goals:

The primary goal of this project is to establish the tracer mass effect as a function of tracer specific activity for two radiotracers used in the study of the CNS: the presynaptic dopamine transporter (DAT) marker ^{11}C -methylphenidate (MP) and the D2 receptor marker ^{11}C -raclopride (RAC). Studies are performed using PET imaging in a 6-hydroxydopamine rat model of Parkinson's disease. The investigation involves the correlation of autoradiography (AR) and PET results using MP and ^{11}C -dihydrotetrabenazine (DTBZ+), and the investigation of optimal analysis methods. Another ancillary goal of the project is to investigate the feasibility of imaging the brain dopaminergic system in a mouse model.

Significance:

The mass effect is one of the major limitations for imaging the brain receptor/transporter system. Establishing the range of useful specific activity of two important tracers for investigating the CNS will help tune the tracer synthesis and PET imaging protocols in the rat brain for optimum results. So far, an atlas-based ROI analysis was shown to significantly improve reproducibility and reliability of DA receptor/transporter binding potential estimates in the rat brain. This was performed by correlating PET data with autoradiography measurements over a wide range of lesion severity (LS). These results were reported at the 2007 IEEE Medical Imaging Conference. In addition, the negligible effect of anesthesia in the lesioned as compared to the unlesioned hemisphere was confirmed. Finally, the comparison of four modeling approaches pointed towards a modified simplified reference tissue model (SRTM) as the method of choice for the analysis of binding potential (BP).

Due to the increasing availability of transgenic mouse models of CNS diseases, there is a high interest in PET imaging of the mouse brain. Collaboration has been established with molecular geneticists from the Mayo Clinic in Jacksonville, Florida, and the feasibility of raclopride scan of a mouse brain was demonstrated.

Relevance to TRIUMF:

The project requires the facilities and expertise present at TRIUMF for synthesis of the radiotracers, and will benefit from the service support from the LS0 core for maintenance of the microPET scanner.

Opportunities for Students:

Most of the proposed work is being carried out by one graduate student, Geoff Topping as part of his MSc project. There would be plenty of topics around this theme for other student projects. One or two more students or trainees should be enrolled into this project in order to expand the scope of the research and streamline transmission of expertise within the Life Science program.

Strengths:

The project builds on the strong expertise that was developed in this field within the Life Science program and will benefit from the experience gained in carrying out a similar project using

another tracer. The validation of PET data by correlation with autoradiography is important for the correct interpretation of the PET images.

Weaknesses:

No significant weakness on the scientific level but some methodological issues should be revisited.

PET imaging of the mouse brain is a difficult undertaking, considering the small size of cerebral structures and the limited resolution of microPET scanners. Even though the feasibility of mouse brain imaging with raclopride was demonstrated, poor accuracy is expected for the estimation of binding parameters due to the difficulty to reliably place ROIs without additional guidance and due to important partial volume effects. It will be very difficult to accurately compensate for these affects without coregistration with a suitable anatomical image of the concomitant structures. Why have the MRI measurements been dropped from the project? It was also suggested last year that TRIUMF should consider adding a CT imager to the PET scanner. This would allow the CT (and consequently the already registered PET image) to be coregistered accurately to MRI. The attempt to exploit PET/CT/MRI coregistration could be more successful if it were first investigated and validated for imaging the rat brain.

Adequacy of Support:

Apparently, external funding has not yet been secured for this project. TRIUMF support for radiopharmaceuticals supply (RAC, MP and DTBZ+) and maintenance of the microPET scanner is essential to the continuation of this project.

Recommendations:

This is an important study to increase confidence in the PET measurements of the CNS in the 6-hydroxydopamine rat model of Parkinsons's disease. A High priority is recommended for the mass effect studies and model validation. A Medium priority is suggested for the mouse brain imaging part of the project, under the assumption that it should first be applied to the rat brain and combination with an anatomical imaging modality for image coregistration will be required to warrant a successful outcome.

3B. REPORTS ON NEW PROPOSALS

LS84	FERROCENE CONJUGATES AS POTENTIAL ANTIMALARIAL AGENTS	M. Adam
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Goals:

To prepare and screen a series of organometallic derivatives of chloroquine to identify new malarial treatments. An emphasis will be placed on strains that are resistant to treatment with existing agents.

Significance:

Malaria remains a major health concern and with resistance to existing anti-malarial compounds increasing the development of new agents must be a priority.

Relevance to TRIUMF:

This project has a sound rationale and is of high quality in terms of the chemistry. It does not however seem to mesh with the stated mandates and priorities of the Life Sciences program at TRIUMF.

It should be pointed out that the TRIUMF Life Sciences program has a good track record of successful collaborations in the bioinorganic chemistry field. This area of chemistry, which is at the heart of the current proposal, is increasing in importance because of the growing use of radiometals for molecular imaging and therapy applications. Unfortunately the proposal does not tie the two areas together.

Opportunities for Students:

This is an excellent training opportunity for students. Students will benefit from working with internationally recognized radiochemistry and bioinorganic chemistry groups. This project will likely attract top tier students.

Strengths:

The strength of this project is that it focuses on an important problem and there is sound evidence that the identified class of compounds should be active (to what extent can only be determined after the experiments are completed). The people running the project are also well qualified to do so and have already published in the area. Their track record of success nearly ensures that the objectives will be met.

The proposed chemistry is also sound. Although synthetic details were not available, the methods needed to prepare the derivatives should be straightforward given the extensive work that has been done on synthesizing ferrocene derivatives for biological applications (redox probes).

Weaknesses:

Perhaps the greatest weakness is that the project does not match with the stated goals of the Life Sciences program and it does not take advantage of the infrastructure around radionuclides and imaging. The other issue is that the project at its core is a drug discovery effort. It focuses on compound development and screening where success will depend upon finding a lead compound

(very high risk). Perhaps a link with the recent CECR award at UBC on pharmaceutical research could be made (this project would certainly add a unique component to that program).

In the context of finding leads, preclinical imaging is being used earlier and earlier in drug development to the point where it is being incorporated into the early compound discovery phase. Is there an opportunity here to merge the proposed chemistry with the preclinical imaging infrastructure and expertise at TRIUMF? That would be a potent combination. This missing link to imaging and the resulting lack of relevance to TRIUMF underscores once again a recurrent weakness in the biological component of the chemistry based projects of the Life Science program.

Recommendations:

The committee acknowledges the quality of the chemistry and the importance of the stated objectives but does not see the relevance to TRIUMF. If external funding for the proposed research can be raised and a stronger link to the Life Science program develops, then the requested support (time from M. Adam) should be given. As a consequence of the above, this project is given Medium priority.

LS85	EVALUATION OF NOVEL BIFUNCTIONAL CHELATES FOR ANTIBODY IMAGING WITH CU-64	C. Ferreira
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Goals:

- 1) To evaluate novel bifunctional chelates for Cu-64 radiolabelling of antibodies
- 2) Increase knowledge of radiochemistry and conjugation chemistry
- 3) Foster future collaborative efforts between MDS Nordion, TRIUMF, and the BC Cancer Agency
- 4) Publish results in peer-reviewed journals

Significance:

There is a real need to develop better methods to form covalent linkages between radioisotopes of Cu and emerging targeting vectors including new biologics. This project if successful will develop new chelates and bioconjugation strategies to address this need.

Relevance to TRIUMF:

This project clearly links to the core strengths of the Life Sciences group at TRIUMF, however all aspects of the project (isotope supply, radiochemistry, bioconjugation chemistry) is being performed solely by the industrial partner (MDS Nordion).

Opportunities for Students:

The nature of the study would offer excellent training opportunities in radiochemistry and bioconjugation chemistry. It was not clear to what extent the project would involve graduate student training although there is the involvement of an undergraduate student listed on the proposal.

Strengths:

The objectives of the study are sound and laudable. The fact that the ligands exist will save a great deal of time in the project (no synthesis required) and there is very good preliminary data. The structures of the ligands and the physical properties of the Cu complexes (log P, solubility, charge, etc.) were not provided in the original report but were presented at the meeting. All data suggest that the project is on track to reach its objectives.

The expertise of the team is the strength of the proposal as is the fact that the project is an industry-TRIUMF partnership which so long as the mutual benefits are defined should be of value to the Life Sciences program in terms of scientific achievements and exploitation of the resulting intellectual property. Furthermore, successful labeling and bioconjugation technologies will create additional justification for the allocation of more resources to the isotope production/radiochemistry programs.

Weaknesses:

Very few. The choice of the targeting vector was initially a concern but Dr. Ferreira explained that Herceptin is being used only as a model system as part of demonstrating the value of the chelate. Perhaps the only other issue is the amount of work proposed and the timeline may not be congruent particularly given that 40% of the time of the PI is to be spent on the project along with 100% of an undergraduate student's time.

Recommendations:

This project should be supported and TRIUMF should look to find ways to get more involved as opposed to simply providing space. At the moment the project is run solely by the industry partner and focuses on problems they are interested in. TRIUMF should work to see if there are problems of mutual interest to gain added benefit from the high quality of the proposed work. This request is assigned High priority.

LS86	FRONTOTEMPORAL DEMENTIA WITH UBIQUITINATED INCLUSIONS: CLINICAL, GENETIC AND PATHOLOGICAL CHARACTERIZATION	N. Kandiah
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Goals:

The goal of this project is to develop an imaging biomarker for the ubiquitinated subtype of frontotemporal lobar degeneration (FTLD-U). The proposed research utilizes FDG and PIB PET scans in asymptomatic individuals who are at risk for the development of symptomatic dementia by virtue of carrying the progranulin mutation that underlies this condition in some families. The use of FDDNP as a marker for tau-related pathology will also be considered.

Significance:

In Canada, FTLD accounts for 12% of referrals to dementia clinics in individuals <70 years old, many of whom have a familial form of the disorder. The discovery of the associated mutation in the progranulin gene has spurred the development of methods to detect presymptomatic forms of the disease. Identifying presymptomatic changes will help clarify the natural disease course, and assist in early diagnosis and management. Ultimately, early diagnosis will become very important if specific treatments are developed for this progressive condition.

Relevance to TRIUMF:

This project makes use of the established PET instrumentation and radiochemistry capabilities of TRIUMF.

Opportunities for Students:

A clinical fellow is currently involved in the project. There is the potential for a fellow or graduate student to be involved in the imaging data analysis.

Strengths:

The proposal benefits from the expertise of the principal investigator and the breadth of his experience in dementia research, and from the strength of the PET team. The award of a CIHR operating grant provides further evidence of the strength of the ideas. The project has made some progress, with PET studies done in 13 patients. No problems are anticipated in recruiting appropriate subjects, or in meeting the scanning access or radiochemistry requirements of the program.

Weaknesses:

While the investigators suggest that FDDNP binds to tau rather than amyloid (in contrast to PIB, which is thought to bind to β -amyloid but not tau), and that this imaging agent may therefore be worth exploring in FTLD-tau, this aspect of the proposal is not well developed. It is unclear how FTLD-tau patients will be identified. It is mentioned that tissue staining in pathological specimens will be performed to assess the specificity of FDDNP for tau, but details regarding these experiments were not provided. There is concern regarding the overall coordination of the project, given the observation that the spokesperson was unable to discuss other aspects of the study related to magnetic resonance imaging of this patient group.

Recommendation:

This is a worthwhile project that addresses a significant clinical problem, utilizing PET imaging tools that are well established at TRIUMF/UBC. In order to learn more about the binding properties of PIB vs FDDNP, the investigators should consider using both of these agents in their patient studies. Before embarking on PET image analysis, the investigators would benefit from the establishment of a standardized, blinded approach to region of interest placement, in order to minimize this potential source of significant experimental error. The project is recommended with High priority.

LS87	ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)	N. Kandiah
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Goals:

The goal of this project is to follow longitudinal changes in PET and MR imaging associated with progression of Alzheimer's disease (AD), minimal cognitive impairment (MCI), and age-matched controls. This is part of a large multi-centre trial involving about 60 sites in Canada and the U.S. At this site, 8 MCI patients, 4 AD patients, and 4 controls will undergo 1.5 T MRI at 6-12 month intervals, over a total of 2 years for AD patients, 3 years for MCI patients and controls. Subsets of patients will be randomized to receive 3 T MRI, FDG/PET, and PIB/PET studies.

Significance:

Dementia is a significant clinical problem in Canada, with a prevalence that is expected to increase with an aging population. AD is the most common cause of dementia. It is uncertain how to predict which patients with MCI will progress to frank dementia. This ambitious project will provide substantial information relating to progression of both AD and MCI, with the potential of establishing a biomarker that may be useful in early diagnosis and management. This will become particularly important if treatments are developed that may alter the natural history of these conditions.

Relevance to TRIUMF:

This project makes use of the established PET instrumentation and radiochemistry capabilities of TRIUMF.

Opportunities for Students:

Two clinical fellows are currently involved in the project. Image analysis will be done centrally, limiting opportunities for further student involvement in this aspect of the research.

Strengths:

Participation in this type of multi-centre study is important in establishing the group's reputation as a major clinical research centre involved in imaging studies of dementia. Funding through this large NIH operating grant attests to the strength of the overall proposal. The proposal benefits from the expertise of the principal investigator and the breadth of his experience in dementia research, and from the strength of the PET team. The project has made some progress, with 5 patients recruited. No problems are anticipated in recruiting appropriate subjects, or in meeting the scanning access or radiochemistry requirements of the program.

Weaknesses:

As with LS 86, there is concern regarding the overall coordination of the project, given the observation that the spokesperson was unable to discuss other aspects of the study related to magnetic resonance imaging of this patient group.

Recommendations:

This is a worthwhile project that addresses a significant clinical problem, utilizing PET imaging tools that are well established at TRIUMF/UBC. Consideration should be given to whether TRIUMF is receiving financial support for its component of the required infrastructure (radiochemistry) through this NIH-supported program. The project is recommended with High priority.

LS88	IMPROVEMENT OF THE RESOLUTION AND QUANTITATIVE ACCURACY OF THE HRRT	V. Sossi
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Goals:

The goal of this project is to address outstanding issues regarding quantification accuracy with the HRRT, first to improve the accuracy of attenuation correction, and second to explore the feasibility of increasing spatial resolution by applying oversampling motion. This project is in fact the continuation of LS70 (Quantification of High Resolution Brain Imaging) which was just completed this year.

Significance:

Inaccurate corrections for physical factors such as attenuation and scatter have a direct impact on the accuracy of biologically relevant parameters obtained from PET data. This is particularly relevant to the calculation of binding potential with a reference tissue method, for instance when the cerebellar time activity is used as the input function, since radioactivity concentration estimates in different structures can be often affected by inaccurate attenuation correction. The large fraction of scatters in transmission scans measured in singles mode is known to affect the accuracy of the measured linear attenuation coefficients. Until now, only approximate compensation techniques applied by manually segmenting the transmission images have been used to minimize these effects on the HRRT. This effort can be subjective and quite time consuming, and it was shown that the attenuation coefficient maps often contain artifacts after applying such segmentation. The proposed method, based on an analytical calculation of single-scattered photons in projections, has already been implemented and validated for singles transmission measurements on microPET scanners (paper to be published in IEEE Transactions on Medical Imaging). It is expected that the segmentation process will be rendered more accurate by first correcting the transmission data for scatter.

Oversampling motion can improve the resolution of scanners by compensating for missing data due to gaps between detectors or when the sampling frequency on the projection is smaller than the Nyquist frequency corresponding to the maximum reconstructed resolution of the scanner. With a resolution of 2.5 mm (max frequency of $\sim 0.8 \text{ mm}^{-1}$) and a sampling distance of 2.1 mm/2 = 1.05 mm (sampling frequency of 0.95 mm^{-1}) on the HRRT, the Nyquist criteria is satisfied. Therefore, the maximum gain to be expected by wobbling the bed is from filling missing data due to the ~ 17 mm gaps between the 8 detector panels forming the HRRT. The gain of oversampling will also decrease as moving outward from the center of FOV due to parallax degradation of the resolution. Finally, as pointed out in the report, increased noise in wobbled acquisitions might well overshadow the gain in resolution, especially for count-limited images, as is the case in many receptor-based studies. Overall, there appears to be relatively little to be gained from bed wobble. However, data reported during the presentation showed that there is some improvement in resolution to be gained from oversampling bed motion.

Relevance to TRIUMF:

The methodological developments proposed to improve image quality and quantification accuracy are consistent with the mission of TRIUMF.

Opportunities for Students:

Both projects represent nice training opportunities, though not overly original, for graduate students. One PhD student has already undertaken to carry out both projects.

Strengths:

The project builds on the strong expertise that was developed in this field within the Life Science program and the experience of the PhD student who has already implemented the wobbling protocol on a microPET scanner. Both methods should improve the quantification accuracy of the HRRT. The proposed research plan is sound and appropriate to reach the stated goals. The scatter correction for singles transmission on the HRRT will be the first implementation of this method on a human scanner.

Weaknesses:

Although implementing both of these improvements on the HRRT is not an easy task, there is some lack of originality and innovation in the proposed approaches. The objectives being pursued by implementing the bed wobble motion should be clarified and better justified. Even though there is lots of free time on the HRRT that could potentially be used to decrease the cost associated with animal research, this would be achieved by trading off image quality and quantification accuracy as compared with a microPET. The HRRT scanner should be reserved primarily for human and large animal applications; therefore efforts should be directed towards increasing the pace of clinical studies rather than recycling the HRRT for small animal scans.

Adequacy of Support:

The project requires only very minor contributions from TRIUMF in the form of 11C and 18F activity for phantom experiments, which may likely be obtained from excess production for other applications. Some hardware and electronics development will be required to implement the wobble mechanism on the HRRT.

Recommendations:

A high priority is recommended for the attenuation correction work on the HRRT since this is an important enhancement to improve the quantification accuracy of human studies. A medium priority should be given to the second part of this project because the expected gain in resolution would be marginal and the positive impact for small animal research is not entirely warranted. Overall, the project is recommended with Medium High priority.

LS89	INVESTIGATION OF TREATMENT RELATED COMPULSIVE BEHAVIOURS AND IMPULSE CONTROL DISORDERS IN PARKINSON'S DISEASE	V. Sossi
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Goals:

This is a new proposal to study imaging correlates of behavioral dysfunction in Parkinson's Disease. The proposal builds upon a considerable body of imaging carried out by this group in this disease.

Significance:

Very high. The proposed studies build upon the considerable progress in imaging Parkinson's Disease developed at UBC and TRIUMF. Elucidation of biochemical changes in this disease has implications for appropriate therapeutic management. The lack of future availability of the PET device proposed to be used limits enthusiasm.

Relevance to TRIUMF:

This is a new project that is part of a significant development effort in imaging Parkinson's Disease at TRIUMF and represents one element of a very productive partnership between TRIUMF and UBC. If adequate support (financial and time and effort) is procured, it will provide impetus to the development of more standardized methods for production of DTBZ, DOPA and raclopride.

Opportunities for Students:

Considerable. Not only will chemistry students be able to study methods for optimization of radiotracer production for clinical use, biology and clinical trainees will benefit from the molecular imaging.

Strengths:

The group is outstanding and has not only contributed to the understanding of biochemical abnormalities in PD using imaging, but also delivered on goals and timelines set.

Weaknesses:

The feasibility of carrying out 375 scans in the specified time is doubtful, especially given the uncertain provenance of the HRRT, though the investigator has established that she can deliver in other proposals.

Recommendations:

Support for this project is important; it should however be used as a platform to establish a "fair trade" relationship with collaborators, to ensure that TRIUMF obtains adequate recompense (in terms of supported personnel as well as for equipment related costs) and that radiotracers are transferred for biology. This may also be a good platform for establishing the continuation of Dr. Sossi's outstanding work at TRIUMF. This request should be given Very High priority.



**TRIUMF
LIFE SCIENCES PROJECTS
EVALUATION COMMITTEE MEETING
APRIL 3 & 4, 2008
TRIUMF AUDITORIUM
AGENDA**

THURSDAY, APRIL 3, 2008

(New proposals are identified by the asterisk.)

time			Spokesperson
	07:30	In camera meeting with breakfast in the Board Room Auditorium	
30min	08:30	TR13 Report	K.R. Buckley
20	09:00	LS 8 Radiotracers for the Physical and Biological sciences	T.J. Ruth
		LS 4 TR13 targets for PET Radioisotope Production	T.J. Ruth
15	09:20	LS 0 PET Facilities	K.R. Buckley
15	09:35	LS 3 Synthesis of Radiopharmaceuticals for Positron Emission Tomography	J. Greene
15	09:50	LS 73 Production and Evaluation of High Specific Activity ¹⁸⁶ Re	D. Becker
15	10:05	Coffee	
45	10:20	LS 53 Synthesis of ^{99m} Tc and ^{186,188} Re Sugar Derivatives	M.J. Adam
		LS 56 Synthesis of Radiolabelled Nucleotides and Oligonucleotides	M.J. Adam/D. Perrin
		LS 72 Imaging and Therapy of Lysosomal Storage Diseases	S. Withers/M.J. Adam
		LS 84* Ferrocene Conjugates as Potential Antimalarial Agents	M.J. Adam
15	11:05	LS 60 Physiological Role of Copper in Marine Phytoplankton	M.T. Maldonado
20	11:20	LS 85* Evaluation of Novel Bifunctional Chelates for Antibody Imaging with Cu-64	C. Ferreira
30	11:40	Report on Pacific Parkinson's Research Centre	J. Stoessl
15	12:10	UBC plans in the Life Sciences	D. Brooks
50 min	12:25	Lunch in the Board Room	
15	13:15	LS 66 Imaging of Pancreatic Islets Following Transplantation Using PET	S-J. Kim
60	13:30	LS 88* Improvement of the Resolution and Quantitative Accuracy of the HRRT	V. Sossi
		LS 69 In Vivo Studies...Dopamine Turnover..Rat Model	V. Sossi
		LS 83 Analysis and Interpretation of Dopaminergic Tracer PET Imaging in Rodents	V. Sossi
		LS 89* Investigation of Treatment Related Compulsive Behaviours and Impulse Control Disorders in Parkinson's Disease	V. Sossi
25	14:30	LS86* Frontotemporal Dementia with Ubiquitinated Inclusions: Clinical, Genetic and Pathological Characterization	N. Kandiah
		LS87* Alzheimer's Disease Neuroimaging Initiative (ADNI)	N. Kandiah
20	14:55	Coffee	
15	15:15	LS 82 Methionine-PET for the Prediction of Treatment Outcome in Radiation Treated Acoustic Neuromas	S.A. Reinsberg
20	15:30	LS 35 Development of PET Imaging Agents for Measuring Tissue Hypoxia	J. Laskin
		LS 74 Assessment of Tumour Microenvironment with MicroPET and MRI	D. Yapp
15	15:50	LS 76 Studies of Nitrate Uptake in Plants and Fungi	T. Glass
15	16:05	LS 78 Development of Liquid Xenon Detectors for PET	L. Kurchaninov

16:20 In camera meeting Board room
19:00 Committee Dinner: Trafalger's 2603 West 16th

FRIDAY, APRIL 4, 2008

	07:30	In camera meeting with breakfast in the Board Room Presentations on the future plans for the Life Sciences	
30min	10:15	Report on the BC Cancer Agency Functional Imaging, Clinical and Research Programs	F. Benard D. Wilson
30	10:45	Life Sciences in the TRIUMF 5 Year Plan and CFI Proposal	T. Ruth
	11:15	In camera meeting with lunch in the Board Room	

