Proposal for TRIUMF Commitment (5YP 2015-2020)

Date: 14 September 2012

PROJECT/COMMITMENT TITLE: Radionuclide based imaging at UBC and CCM

PROPONENT: **Vesna Sossi** **TRIUMF CONTACT:** **Paul Schaffer**

PRINCIPAL COLLABORATORS:

Institutions: Pacific Parkinson's Research Centre, UBC (PHAS, Medicine, Pharmaceutical Sciences), Triumf

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PROJECT DESCRIPTION:

Historical context. The positron emission tomography (PET) program was initiated in the early '80 as a joint UBC/TRIUMF scientific endeavour. After an initial important contribution to imaging instrumentation, TRIUMF's ongoing essential contribution and commitment to the program was through production of radioisotopes and radiotracers, while investigators from the UBC Pacific Parkinson's Research Centre (PPRC) led the Neurology related imaging research. This joint venture led to one of the best PET brain imaging centers in the world and to being the flagship of TRIUMF's Life Science-related activity, bringing TRIUMF world renown fame not only in the imaging world, but also in neurological applications. The operation of the program, including radiotracer production costs and acquisition of new PET scanners has been mainly supported through PPRC-related research grants (PPRC director Dr. AJ Stoessl, UBC Medicine), while TRIUMF has been supporting cyclotron operations, providing radiochemistry laboratory space and 2-4 scientists/technicians, until recently mainly focused on radiotracers used for brain imaging. The seamless joint nature of the program was reflected in the fact that Dr. Tom Ruth, a TRIUMF scientist, was PET Program director. Relatively recently, TRIUMF expanded its medically-related operations (now denoted as Nuclear Medicine Division, with its own head, Dr. Paul Shaffer) into non-neurology and non-UBC related activities, thus expanding its research portfolio with consequent reallocation of resources. The role of Dr. Ruth in brain imaging was taken up by Dr. Sossi (UBC Physics and Astronomy). This proposal, describing a research program, rather then a single project, thus builds on TRIUMF's commitment and interest to being a seamless part of the PET imaging program, which now also includes pre-clinical imaging instrumentation located at UBC (dedicated microPET) and at the Center for Comparative Medicine (CCM – hybrid microPET and SPECT camera).

Research related to neurodegeneration – humans. The main clinical research focus of the imaging program is Parkinson's disease (PD). Three themes are investigated: pathogenesis, treatment related complications and normal brain function. Particular emphasis is placed on imaging of asymptomatic carriers of genetic mutations that place subjects at increased risk of developing PD in order to understand the significant changes that occur in the pre-symptomatic period during which 50%-80% of the dopaminergic neurons die. These are longitudinal studies performed over at least a decade, requiring at least 8 different radiotracers examining the dopaminergic, serotonergic and cholinergic systems, as well as neuroinflammation. Subjects are recruited from all over the world and they come to UBC for PET imaging due to the local unique expertise. Outcomes of these studies will contribute to testing different hypotheses on pathogenesis while providing an ideal subject population in whom to test novel neuroprotective therapies. Other studies are examining the role of the serotonergic system in treatment related motor and psychiatric

complications such as debilitating compulsive behaviour. Outcome of these studies will contribute to the ability of designing patient-specific treatment therapies.

Dementia. Studies are being performed to understand the genetic role in the development of various dementias, including fronto-temporal dementia and Alzheimer disease. In these studies subjects are scanned with at least two different tracers over time to examine different neurochemical aspects of disease progression and relate them to clinical progression. Here also, the ultimate goal is to understand disease mechanisms, risk factors, and to identify the stage in the disease (disease often precedes clinical symptoms by decades) where novel therapeutic intervention would be most effective.

Mood Disorders. The main area of research is manic- depression and understanding effects of treatments as well as of mechanisms that explain why some subjects respond to treatment and others do not. At least 4 different tracers are required for these studies that focus on the dopaminergic and serotonergic systems.

Pre-clinical research. Studies performed on the microPET complement the human research in neurodegeneration, with a large emphasis on transgenic rodent models of PD. This is very important translational research that bridges imaging observations in humans with ex-vivo and in-vitro neurobiology research that allows the investigation of mechanisms that lead to neurodegeneration at the molecular scale. The novel hybrid microSPECT/PET (VECTor, CFI funding, P.I. V Sossi) very recently installed at the CCM (of which there are only approximately 5 available worldwide), will allow for more complex imaging protocols, where several tracers can be injected simultaneously which will allow to explore interaction between different processes. Brain and oncology related research will be performed on this scanner. Furthermore, the imaging studies enabled by this scanner will complement the research on novel tracers, which is one of the main mandates of the TRIUMF's Nuclear Medicine Division.

Imaging physics. Studies are focussed on data quantification algorithm development, kinetic modeling and novel image analysis methods. This researched enabled the PET group to obtain and optimise state of the art research scanners, such as the high resolution research tomograph (HRRT - still the highest resolution brain scanner available) and now the VECTor. Planned studies include development of multi-modality image reconstruction and analysis methods, reflecting the growing tendency of the imaging field toward multi-modality approaches to studying disease. Efforts at designing an MR compatible pre-clinical PET insert are also underway, pending successful funding (Once funding is secured, support from TRIUMF will be requested. Please see submission by F. Retiere for more detail on required support).

Radiochemistry development. A necessary prerequisite for PET images to convey the desired information about a process, is for the development of highly specific, biologically relevant PET radiotracers. **The imaging program thus requires implementation of additional radiotracers, and ideally, design of novel tracers as understanding of disease progresses**. There is an increased understanding and appreciation of genetic predisposition to various brain diseases: identification of specific biochemical mechanisms predisposing to disease is ideally suited to the development of novel radioligands for such specific biochemical targets. **This is the area where TRIUMF's personnel and intellectual resources are required (as per initial commitment of TRUMF to this program) and the area where TRIUMF could expand its core capabilities into an exciting research program** building on the unique synergy between radiotracer development and imaging, the two essentially being two sides of the same coin. In addition to being an essential component of the PET imaging program, radiotracer implementation and development fit very well in the overall TRIUMF Nuclear Medicine program.

SCIENTIFIC JUSTIFICATION:

Radionuclide based imaging provides a unique opportunity to study human function. These studies can not be performed *in any other way*. The brain diseases investigated with imaging pose a large human and economic burden especially in light of the aging population. Furthering the understanding, ultimately leading to successful treatment, is essential.

Likewise more research is required into developing better imaging probes (see above) and better and complementary imaging techniques. For example the combination of PET/CT (computerized tomography) has revolutionized management of cancer. It is expected that as soon as treatment for any of the brain diseases becomes available, development of imaging markers and imaging techniques that will allow for accurate early detection will become increasingly more important. TRIUMF is ideally suited to playing a

vital role in this evolution by (i) facilitating research in this area through radiotracer production and an ongoing symbiotic relationship with the PET program; (ii) development of novel radiotracers; (iii) development of novel imaging approaches.

RELATIONSHIP TO BROADER CANADIAN RESEARCH COMMUNITY:
Brain research and development of novel diagnostics imaging tools has been identified a top priority at UBC and by federal funding agencies (note initiatives such as Brain Canada http://www.braincanada.ca). Through its partnership with the brain –related imaging program TRIUMF is part of these initiatives and of the wider national (and international) brain research network thus maintaining and expanding (through dedicating resources to development of novel brain disease targeting radiotracers and imaging) its visibility at the Canadian and international level. It is noteworthy that in the first round of Brain Canada Multi-Investigator Research Initiative LOI competitions, an imaging application from UBC was one of only 30 applications invited to submit a full application, out of more than 160 letters submitted.

BROADER IMPACTS:
Impact occurs at all three levels indicated.
People. The program is attracting high calibre Faculty as visitors and permanent Faculty members. Examples include Dr. M Farrer who recently obtained the UBC CERC in Molecular Genetics; an important factor in his recruitment was the existence of the PET imaging program. Dr. Yu-Shin Ding (one of the top radiochemists in the world) recently spent a sabbatical stay at TRIUMF, which resulted in the implementation of two additional brain tracers. There is a growing interest in PET imaging amongst UBC researchers, for example Dr A Diamond (one of the founders of the field of Developmental Cognitive Neuroscience, UBC CRC Tier 1), is interested in using PET to explore cognition. Many international collaborations (clinical, radiochemistry and physics) are being formed as a consequence of this program. In addition the interdisciplinary nature of this program is attracting a large number of HQPs at the student, postdoctoral and medical fellow level.
Knowledge. The program has impacted at the world level (i) understanding of Parkinson's disease (examples include, first demonstration of toxin-induced Parkinson's disease, first demonstration of the neurochemical effects of placebo; first quantitative demonstration of dopaminergic deficit in genetically-related PD; highly cited insights into compensatory mechanisms and mechanisms underlying complications of therapy); (ii) production of radiotracers (novel synthesis methods for brain imaging tracers); (iii) imaging physics (development of data quantification and novel data analysis methods). Hundreds of publications support these claims. Outcomes of the proposed studies will continue generating novel knowledge in all three areas.
Entrepreneurial. We are in the process of establishing collaborations with industrial partners for (i) testing new therapeutic approaches for neurodegenerative diseases, which continues and strengthens our activities in this area; (ii) testing of new radiolabels (especially on the VECTor scanner). We are planning to expand this area through an increasing number of industrial collaborations. TRIUMF will directly benefit form this expansion. The program is also receiving funds from private donations and various foundations.

MAJOR MILESTONES:

Description	Date
This is an ongoing program requiring resources on an ongoing basis: cyclotron operation, routine tracer production and development of novel tracers.	

RESOURCE REQUIRMENTS:

CASH FLOW REQUIREMENTS						
\YEAR SOURCE \	ONE	TWO	THREE	FOUR	FIVE	TOTAL
TRIUMF*	435,000	443,700	453,000	462,000	471,000	2,264,000
EXTERNAL	2,000,000	2,000,000	2,000,000	2,000,000	2,000,000	10,000,000
TOTAL	2,228,000	2,228,000	2,228,000	2,228,000	2,228,000	12,264,000
TRIUMF NON-CASH RESOURCES						
\YEAR RESOURCE\	ONE	TWO	THREE	FOUR	FIVE	TOTAL
TR13 Cyclotron operation	20 hours/week	20 hours/week	20 hours/week	20 hours/week	20 hours/week	20 hours/week
Radiochemistry laboratory space	35 hours/week	35 hours/week	35 hours/week	35 hours/week	35 hours/week	35 hours/week

EXTERNAL FUNDING INFORMATION:

Funds are obtained from a variety of funding agencies (CIHR, MJFF, Parkinson's Society of Canada, NSERC, CFI) and private donations. The current level of funding is ~ 2M/year. Several grant applications are currently being submitted to CIHR, Brain Canada, CHRP and MJFF to ensure continued funding at the same or higher level.

ONGOING OPERATIONAL REQUIREMENTS:

Funds are required for 1 production chemist (~ $65,000 including benefits), 1 development chemist (~ $90,000 including benefits), 2.5 FTE of technical support (~ $90,000 including benefits), 0.5 FTE of a newly hired chemist (as replacement for M. Adam upon his retirement, $100,000 including benefits) and cyclotron operation.Cyclotron operation has been estimated to represent an approximately $312,000 yearly cost. Continued space allocation for radiotracer production is also required.

DECOMMISSIONING REQUIREMENT:

None.