Proposal for TRIUMF Commitment (5YP 2015-2020)

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PROJECT/COMMITMENT TITLE: TRIUMF Nuclear Medicine: Centre of Excellence for non-Reactor Isotope Research

PROPONENT(s): Paul Schaffer, Mike Adam **TRIUMF CONTACT: Paul Schaffer**

PRINCIPAL COLLABORATORS:

UBC PPRC: Jon Stoessl, Vesna Sossi,
BCCA: François Bénard, Kuo-Shyan Lin, Don Yapp
UBC Chemistry: David Perrin, Chris Orvig,
SFU Chemistry: Paul Li, Tim Storr
UBC (other): Anna Celler, Mark Martinez, Tony Glass, Maite Maldonado, Chris Harvey-Clark

PROJECT DESCRIPTION:

Goals for 2015-2020: TRIUMF's Nuclear Medicine Group will emerge as a national centre of excellence in all aspects of isotope research. This centre will serve as a world-class training facility performing cutting-edge basic and translational research toward new accelerator target technology, new radioisotopes and innovative radiochemistry geared toward addressing unmet clinical needs.

Accelerator science is the foundation of TRIUMF's nuclear medicine program, a program that maintains a strong isotope and radiopharmaceutical production capability enabled by four onsite cyclotrons. These cyclotrons drive the spectrum of research encompassed by the division, which starts with the physics of particle acceleration and target bombardment, followed by a deep capability in radiopharmaceutical chemistry and tracer production which is ultimately used for biological and imaging studies to gain an understanding of the physiology and disease of the human body at the molecular level. These three areas: accelerator targetry, isotope production and radiochemistry define the core capabilities of the TRIUMF Nuclear Medicine Group. These competencies define the envelope of research projects that the division itself undertakes, those that our collaborators wish to pursue as well as the future growth of the program.

TRIUMF's Nuclear Medicine division is built upon a long-standing collaboration with the **Pacific Parkinson's Research Centre**, for which we routinely provide various tracers for human and pre-clinical imaging studies. These studies aim to establish the relationship between neurochemical dysfunction and the origin and progression of Parkinson's disease, and also include studies into other neurodegenerative diseases such as Alzheimer's. The needs of this aspect of the program are the subject of a separate proposal.

This proposal describes how TRIUMF will continue to drive toward **new discoveries in all aspects of nuclear medicine** and the related fields of research. By leveraging TRIUMF's deep expertise in each of the three aforementioned core areas, the Nuclear Medicine group along with its partners have mobilized and secured over $8.5 million in grant and contribution funding since 2009. Several of these funding opportunities also provided as a means to establish or enhance existing collaborations with other radiopharmaceutical centres across the country. The focus of these funds ranged from improving TRIUMF's aging chemistry facilities for radiopharmaceutical production under GMP guidelines, to leveraging TRIUMF's expertise in accelerator-based isotope production to address the recent medical isotope crisis.

i) Research into the development of new accelerator-based isotope production technology

TRIUMF maintains a core complement of world-class individuals with deep expertise in many aspects of accelerator operations. This interdisciplinary group consists of five individuals that together focus on

advancing the field of accelerator target design – establishing new knowledge into medical isotope production. Efforts have included research into:

Solid Targets – Medical cyclotrons have long been viewed as machines for producing non-metallic positron emitting isotopes (^{18}F, ^{11}C, ^{13}N, ^{15}O) for use in PET imaging. All of these isotopes are produced from either gas or liquid target materials that are easy to manipulate via pneumatic transfer from the production space, to the chemistry space (hotcell) for radiopharmaceutical production. Positron emitting radiometals (^{44}Sc, ^{52}Mn, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{89}Zr, ^{94m}Tc, etc) have been steadily increasing in popularity due to their decay properties, facile chemistry, compatibility with aqueous media and favorable reaction kinetics; all of which enable their rapid incorporation into a growing number potential radiotracers. These vectors are used to target specific physiological structures or metabolic processes.

TRIUMF has been heavily involved with the demonstration of non-reactor production technology for Tc-99m, the world's most widely used medical isotope. The team was instrumental in the design, manufacture, testing and demonstration of new high-current target plate, housing and transfer technology for commercial-scale production of Tc-99m. It is anticipated that this effort will continue until 2016 at which point commercial-scale production for the greater Vancouver area will become a routine activity at TRIUMF's site. The technology developed by this team has caught the attention of numerous existing and private-sector partners. Demand for the expertise of this team is expected to increase over time.

Liquid Salt Targets - The widespread acceptance of new and promising radioisotopes is typically challenged by their availability and accessibility. Many radiometals have demonstrated promise in molecular imaging, however many laboratories are required to purchase an isotope generator or invest substantially in unique solid-target infrastructure for the production and isolation of radiometallic isotopes from a cyclotron - a substantial technical and financial commitment, especially if preliminary biological studies are required to warrant their purchase. These obstacles likely inhibit the development of novel tracers that may possess a better match between the physical half-life of a promising new radioisotope and the pharmacokinetic profile of the vector to which it is attached.

In order to enhance the availability of new and promising radiometallic isotopes, the TRIUMF target team has envision a modified liquid-target system to enable irradiation of select metal-salt solutions for the production of research quantities (or higher) of various radiometallic isotopes. An NSERC/CIHR-funded Collaborative Health Research Project has been funded in conjunction with the BCCA and others to develop and demonstrate this liquid/solution target approach. Recent progress has been demonstrated with Tc-94m production from solutions containing molybdenum. Future efforts are focused on ^{89}Zr, ^{44}Sc and ^{68}Ga production from isotopically-enriched salt solutions of ^{89}Y, ^{44}Ca and ^{68}Zn. In principle, solution targets are easier to handle than solid targets, and easily integrate with the existing paradigm of ^{18}F-FDG production which currently dictates the setup in modern cyclotron facilities.

By 2020, TRIUMF will be recognized as a world-class centre for target research that will train individuals, contribute to the fundamental knowledge of non-reactor isotope production and advance the field with real-world solutions, moving this technology further into the mainstream.

ii) Development of new and novel medical isotopes, production, isolation and incorporation

TRIUMF also maintains a team of individuals with expertise in isotope production, extraction and purification. In conjunction with the target work described above, efforts are underway to understand production metrics, solution dynamics, product and byproduct formation and other aspects of novel irradiation procedures and target designs. To enable these studies, a deep knowledge of isotope purification methods that involve selective recovery of trace isotope quantities from bulk target material is needed. This work is also facilitated by process automation, enabling isotope recovery quickly and safely.

Having this expertise available enables rapid mobilization to address the needs of the research program, but also provides opportunity to redefine the way isotopes are made and isolated. Examples include the adoption of Aqueous Biphasic Extraction Chromatography for the selective isolation of $^{99m}TcO_4$ from irradiated Mo-100 and the use of ion exchange resins to purify the radiometals described above.

iii) Design and synthesis of novel large molecular weight radiotracers which includes labeling peptides, proteins, oligonucleotides and peptide nucleic acids with radiometals.

Radiometals are a class of radioisotopes that exhibit a wide range of chemical behavior and radioactive emission properties that are a good match to the chemical and physiological behavior of peptides, proteins

and other large molecular weight tracers. As such, radiometals have enjoyed growing popularity as signal generators for novel PET- and SPECT-based MI probes. Despite years of use, fundamental chemical studies on radiometals remains a necessity for developing compatible radiolabeling methods. TRIUMF is uniquely positioned to capitalize on the results of the target development and production efforts described above with ready access to an array of popular and novel isotopes. Access to radiometals such as $^{94m/99m}$Tc, ^{55}Co, ^{52}Mn, $^{67/68}$Ga, ^{89}Zr have enabled several efforts into novel chelate chemistry and applications. Ongoing collaborative studies with Dr. Orvig at UBC Chemistry, funded through the NSERC CRD program, has resulted in the development of a new more powerful ligand system for the incorporation of these radiometals into large molecular weight radiotracers. Internal efforts have also seen promising results for a new class of radiometal scorpionate-based chelators for $^{67/68}$Ga, $^{94m/99m}$Tc, ^{55}Co and others. This combination of expertise will enable TRIUMF to move this area of research ahead rapidly.

The TRIUMF program will leverage its unique radiochemistry capabilities to train more students, post doctoral fellows in the art of radiopharmaceutical chemistry and to foster interactions with visiting scientists.

iii) Novel molecular imaging applications

In collaboration with PPRC, TRIUMF continues to implement brain imaging markers (for example, targeting the serotonergic and cholinergic systems) in response to an increasing recognition of the complexity of brain diseases. The ability to rapidly bring these tracers on line is essential to the PPRC collaboration and success. Novel, highly specific tracers will be produced as novel biologically relevant targets are discovered through genetic approaches. Recent efforts have seen the development of a number of novel peptide and small molecule radiotracers. Vectors have included bombesin, marimistat, folate, RGD, oligonucleotides, peptide nucleic acids, etc. The results have seen a number of tumor targets successfully imaged in collaboration with our partners.

Moving forward, TRIUMF-based efforts in the labeling and use of substrates and/or inhibitors of the cystine transporter are planned, with the focus on elucidating the *in vivo* behaviour of this amino acid transporter during cellular oxidative stress – and its role in the initiation, onset and progression of a host of conditions. Preliminary studies will likely focus on those conditions that do not image well with ^{18}F-FDG, such as prostate and pancreatic cancers. By 2020, novel applications, such as oxidative stress imaging will be enabled by all facets of the Nuclear Medicine program – from identification of a clinical unmet need to implementing a solution by developing an appropriate technology. Additional applications are expected to emerge as the program grows.

iv) Facilities

For more than 20 years, the TR13 has been the heart of the TRIUMF Nuclear Medicine Program. This machine is ageing and given the growing demands for isotope production, replacement will be required in the near future. In addition, the maximum allowed energy (13 MeV) of the proton beam has long been dictated by the location of the cyclotron being in an open area of the proton hall, severely constraining the options available for isotope production. In order to continue delivering on our existing commitments and also grow the program, a replacement cyclotron is needed. This machine will need to be housed in a new vault with close proximity to the radiochemistry facilities.

A new opportunity is now available with the relocation of the UBC centre for comparative medicine across the street from TRIUMF. An imaging centre is being developed there which will be coupled to the TRIUMF isotope production facilities by a short delivery pipeline enabling unique research on animal models with short-lived radiotracers. This is anticipated to be fully operational in the current five year plan. Support for research personnel associated with these unique facilities will be needed.

The newly built MHESA basement laboratory is the first step in upgrading the Nuclear Medicine Research capabilities to support the expansion of the program as envisaged above, Part of this upgrading program was financed by Nordion, Inc. and it is anticipated that private sector collaborations of that type will grow. The refurbishing of the whole basement of the MHESA will be required and is assumed to have been completed by the end of the current five year plan.

v) New Personnel

With the anticipated hire of new research scientists, the portfolio of the TRIUMF Nuc. Med. research program is expected to grow substantially in scientific breadth, while remaining focused on our core competencies. By 2020, the division will function to enable research for a team of scientists that are

supported by the individuals requested in this proposal while the research itself will be performed by securing additional, peer-reviewed external funds. Two additional scientists will be needed, first to address imminent retirements followed by a need to expand the Nuclear Medicine Program. New hires will be sought to drive the core competencies of the division: Physics/Target Research, Nuclear Chemistry/Isotope Production and Radiochemistry/Novel Applications.

SCIENTIFIC JUSTIFICATION:

Molecular imaging (MI) has enabled health professionals and basic researchers to probe the function of living systems at the molecular level, enabling non-invasive studies into the changes that take place during the onset and progression of disease, well before anatomical changes occur. This understanding will dramatically change the way disease is diagnosed, staged and treated and will ultimately enable a personalized treatment regiment for affected patients.

MI is heavily reliant on fundamental physical and chemical research for the development of contrast-enhancing biological probes that emit an appropriate signal for detection using imaging scanners, such as MRI, CT, ultrasound and nuclear. MI using radioactive probes (also known as radiopharmaceuticals), exhibit the highest degree of sensitivity amongst the imaging methods used in modern medicine. These probes are used in nearly 40 million single photon- and positron emission tomography (SPECT and PET) scans per year around the globe in patients suffering from heart ailments, cancer and neurological diseases like Parkinson's and Alzheimer's. As new biological questions about these diseases emerge, novel ways to produce medical isotopes and chemically modify them into pharmaceuticals for delivery to the tissue of interest are of paramount importance.

RELATIONSHIP TO BROADER CANADIAN RESEARCH COMMUNITY:

TRIUMF’s multi-decade relationship with the UBC PPRC has long defined success for molecular imaging programs both domestic and international. This success continues with TRIUMF’s target and production expertise having led the NRCan-funded, multi-institutional proof of feasibility and proof of concept Tc-99m production effort on Canada’s existing cyclotron infrastructure. These translational efforts have seen new technology developed and delivered, concomitantly strengthening collaborative ties to centres in several Canadian provinces. Couple this with the historical program focus on the delivery of radiopharmaceuticals for human neurological studies and the more recent efforts to enable oncology imaging studies in conjunction with the BC Cancer Agency, and the relationship to the molecular imaging community becomes evident.

Our team of interdisciplinary experts, in conjunction with our collaborators and industrial partners are a unique entity in Canada – one that other centres look to for technical and administrative leadership. In turn, TRIUMF continues to look to its collaborators for guidance, leadership and collaboration in various applications. The relationships are potent and symbiotic and epitomize a Centre of Excellence in Accelerator-Based Isotope Research.

BROADER IMPACTS:

People. The program is attracting high calibre faculty as visitors and applicants. Examples include Dr. Yu-Shin Ding (one of the top radiochemists in the world) recently completed her sabbatical at TRIUMF, which resulted in the implementation of two additional neurological tracers. In addition, a number of prominent scientists have actively participated in TRIUMF’s Life Sciences Peer Evaluation Committee (LSPEC) with several others inquiring about involvement. A number of institutions have looked at TRIUMF’s governance model in an effort to identify effective management and review systems for their own programs. In addition, the interdisciplinary nature of this program is attracting a large number of HQPs at the student, doctoral and postdoctoral level.

Knowledge. The program has impacted at the world level (i) understanding of Parkinson’s disease (ii) production of radiotracers (novel synthesis for small and large molecule tracers); (iii) novel, state-of-the-art isotope production methods and (iv) novel applications for new tracers. Hundreds of publications support these claims. Outcomes of the proposed studies will continue generating novel knowledge in all areas.

Private Sector. We are in the process of maintaining collaborations and establishing new relationships with industrial partners from around the world for (i) testing new isotope production technology; (ii) testing of new chemistry to better radiopharmaceutical processes and (iii) developing new imaging applications.

MAJOR MILESTONES:

Description	Date

RESOURCE REQUIRMENTS:

CASH FLOW REQUIREMENTS						
\YEAR SOURCE \	ONE	TWO	THREE	FOUR	FIVE	TOTAL
TRIUMF	Division Ops ($20K), Core FTEs (11ppl @ $100K ea), Facilities ($65K+) Total~$1.26 million	~$1.28 million	~$1.31 million	~$1.33 million	~$1.36 million	$6.54 million
TRIUMF (new cyclotron)	$6.0 million (facility)	$4.0 million (machine)				$10.0 million
EXTERNAL	TBD	TBD	TBD	TBD	TBD	TBD
TOTAL	$1.26m+	$1.28m+	$1.31m+	$1.33m+	$1.36m+	$16.54m+
TRIUMF NON-CASH RESOURCES						
\YEAR RESOURCE\	ONE	TWO	THREE	FOUR	FIVE	TOTAL
TR13 cyclotron operations	20 hours/wk	22 hours/wk	25 hours/wk	30 hours/wk	30 hours/wk	
Radiochemistry facilities (RCA1-007)	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	
Radiochemistry facilities (MHESA – 6 rooms)	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	
Chemistry facilities (RCA1 – 103, 110)	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	
New cyclotron ops	0 hours/wk	15 hours/wk	30 hours/wk	30 hours/wk	30 hours/wk	

EXTERNAL FUNDING INFORMATION:

The funds requested here are for core operations of the TRIUMF Nuc. Med. effort, in order to have available a core complement of individuals and state-of-the-art facilities that are poised to capitalize on additional external funding opportunities. This model has worked effectively historically, with an external to internal funding ratio of greater than 8:1 during the 2010-2015 period.

ONGOING OPERATIONAL REQUIREMENTS:
Funds are required for:
Scientists: 4 FTEs (~$120,000 each including benefits)
Accelerator Target Team: 4.5 FTEs (~ $100,000 each including benefits),
Cyclotron Ops: 1.5 FTEs (~$100,000 each including benefits)
Facility Manager (chemist): (~ $90,000 including benefits)
Cyclotron operation has been estimated to represent an approximately $312,000 yearly cost.
Continued space allocation for isotope and radiotracer research is also required.

- RCA1-005,007,103 and 110
- MHESA basement area (7 rooms: Nordion joint research, wet chem., biology, radiochem, target shop)
- TR13 area
- New cyclotron – location to be determined

DECOMMISSIONING REQUIREMENT:
Decommissioning of TR13 will be required at end of use. Various components will be active and addressed according to TRIUMF's master decommissioning plan. Other aspects of the Nuc. Med. facilities will require physical dismantling with no anticipated long-term radiological hazards.

Accepted:	Date: