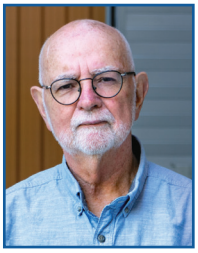
A Brief History of the Life Science Program at TRIUMF

by Tom Ruth



The story of the Life Science program at TRIUMF starts in the mid 1970s, when the first real images related to glucose function in the living human brain were taken with the positron emission tomography (PET) technique, and the (then) TRIUMF Director, Jack Sample, asked Associate Director Brian Pate to develop a program to make use of the nuclear chemistry capabilities at TRIUMF for the production of radiotracers for medicine. While the use of positron decay to create images of in-vivo biological function had been discussed for decades, in 1976 a collaboration involving Brookhaven National Lab in NY, where the radioactive tracer (^{18}F-fluoro-deoxyglucose, FDG) was developed, the University of Pennsylvania, where the detector was installed**,** along with the medical and technical staff and the National Institutes of Health, where the basic concept of using autoradiography using ^{14}C-deoxyglucose, was developed to study glucose function in rodent brains. Around the same time, a collaboration was negotiated between TRIUMF and Atomic Energy of Canada, Limited (AECL) to establish laboratories for accelerator-based radioisotope production. Initially the program made use of the main 500 MeV cyclotron, where the main interest for AECL was the 500 MeV beam dump where a target system was developed to produce radioisotopes from the spallation of various targets. In parallel, John Vincent was developing a target system to produce I-123 and have it shipped to different hospitals for testing. I-123 was seen as a potential safer radioisotope than I-131 for imaging.

With the success in the US of using the glucose analog, ^{18}F-fluoro-deoxyglucose, for imaging brain function, scientists at TRIUMF and UBC pursued a PET program in Vancouver. Pate along with Pat McGeer, a neuroscientist, William Webber, Dean of Medicine, and Bernard Riedel, Dean of Pharmaceutical Sciences, sought $675,000 (the sum quoted by AECL) in funding from the Medical Research Council to construct a PET camera, using a design already in operation by Lucas Yamamoto at McGill University. At that time commercial scanners were not widely available.

Almost simultaneously, AECL decided to purchase a cyclotron for the production of medical radioisotopes at lower proton energies (30 MeV) to provide isotopically purer commercial products such as Tl-201, Ga-67, In-111 and I-123. It was to be installed at TRIUMF to take advantage of existing accelerator expertise and infrastructure.

The next phase in the PET program development was to hire experts in radiochemistry and radionuclide production. To this end a collaboration was established with Professor Laurie Hall, a (sugar) chemist at UBC, who enlisted his most recent PhD graduate, Mike Adam. The other position was filled by the recruitment of Tom Ruth from Brookhaven National Lab where FDG had been developed. It was felt this tandem could tackle the issues in producing FDG — while Mike had no radiochemistry experience, Tom brought expertise in radiochemistry and radionuclide production. The Chemistry team was completed with the hiring of Salma Jivan, who worked closely with Mike and Tom for more than 20 years, helping with the development of all the tracers (^{18}F-fluorodopa, ^{11}C-raclopride, etc.) used in the program over that period.

Initially the only source of F-18 for labeling research was from a gas target (loaded with a mixture of 0.1% F_2 and Ne) inserted at the beam dump of the 500 MeV beam, just ahead of the AECL spallation targets. While the yields were not very high, it allowed the development of a number of labeling techniques and production of FDG labeled with F-18. It was not until the AECL cyclotron, the CP-42, was purchased (1982) from the Cyclotron Corporation in Berkeley that the PET program could begin producing FDG in sufficient quantities to be used in the scanning of subjects. The TRIUMF PET users had 10 hours of beam available per week for their development and production for scanning. The beam quality only allowed for the production of ^{18}F as F_2.

Meanwhile, in mid-1980, AECL in Chalk River informed Brian that the scanner that they had contracted to build could not meet the specifications outlined in the purchase agreement. The principal problem was the fraction of the events measured in an image that resulted from scattered radiation. AECL informed the TRIUMF team that they

Summary

A short history of nuclear medicine (now life sciences) at TRIUMF, through the eyes of one of the founding fathers and driving forces behind the program.

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would need at least 6 months and an additional $250,000 funding. TRIUMF did not have the extra funds and needed urgently to fulfill the terms of the MRC grant. So, the contract was broken and TRIUMF recovered its deposit, but was left without a scanner.

Brian then went to the new Director of TRIUMF, Erich Vogt, and recommended that TRIUMF build its own scanner. Brian had previously been a faculty member at Washington University in St. Louis, MO which had successfully built several PET scanners. The most recent version at that time was called the PETT VI and had been installed in several US locations. Brian's contacts at Washington University were John Hood, a Mechanical Engineer with the cyclotron group and a Physicist, Michel Ter Pogossian, who had been instrumental in designing and building all of the PETT scanner versions. The Washington U group willingly allowed TRIUMF scientists and engineers to visit and bring back mechanical drawings, as well as suggested improvements for the scanner. The team that went to St. Louis included Don Haywood, an electronic expert, and Joop Burgerjon, an engineer.

Upon their return, a team of about a dozen scientists, engineers and electronic and mechanical technicians was assembled to build the TRIUMF version of the PETT VI (see Fig. 1). As part of the agreement with TRIUMF Management, the funds from the MRC grant would be spent on the material costs and TRIUMF would supply the personnel, similar to other TRIUMF experiments. This was late 1981. The mechanical aspects of the Wash U. scanner were basically kept but the electronics from the detectors downstream were totally modified to improve the timing and coincidence characteristics.

Over the next 18 months, the scanner was put together, commercially available components were ordered, and the physical gantry was constructed in the TRIUMF machine shop. The new electronics design led to the assembly and disassembly of the detectors and electronic components a number of times to deal with the various complications associated with a near prototype machine. By late 1982, the scanner was assembled and basic tests were performed. After this success, the scanner was disassembled and shipped to the UBC hospital where the PET program had offices and labs for the research activities.

During this time, a 2.7 km pneumatic pipeline, consisting of a bundle of 4 polyethylene tubes encased in concrete about one meter below grade, was installed to transport the scanning agents from the TRIUMF chemistry labs to the UBC hospital PET scanning laboratory (see Fig. 2). The route went from the PET chemistry lab in the AECL building, through the TRIUMF property, and then north parallel to Wesbrook Mall. The pipeline was installed in sections with access holes at approximately 300-meter intervals. To transport the radioisotopes, plastic bullets were designed with a plug at the rear end sealed with an "o"-ring. Into this bullet, a multi-injection vial with the desired radioactivity would be placed for shipment. The pipeline was connected to a large ballast tank held at 90 psi, so that the bullet was transported to the hospital by air pressure in less than 2 minutes. This pipeline delivery system is still in operation after more than 35 years, although modifications of all aspects of the system have been made over the years.

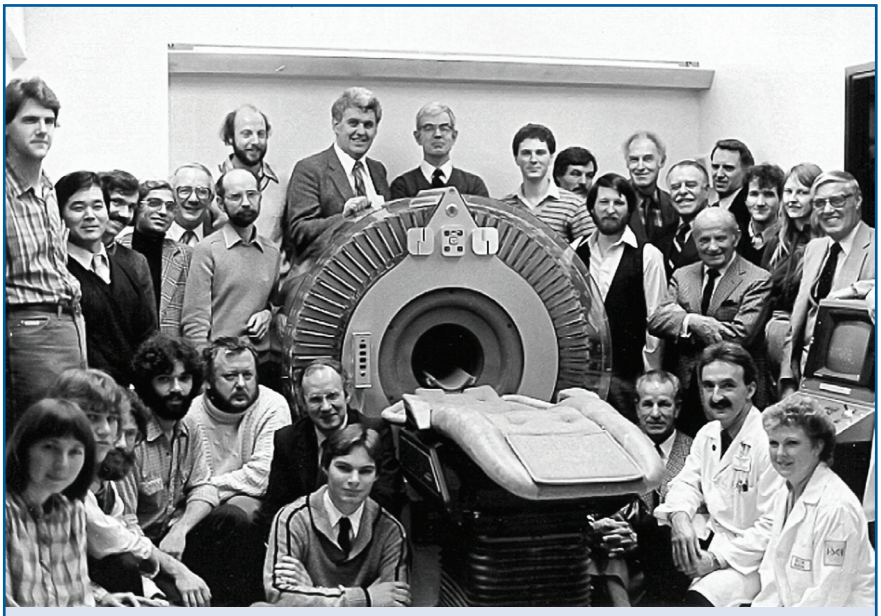

Fig. 1 Development group posing in 1982 with the newly TRIUMF-built positron emission tomograph (PETT VI). Standing behind the centre of the PETT VI is (then) TRIUMF Director Erich Vogt (left, with suit) and Associate Director Brian Pate (right, with sweater).

With the availability of production and labeling FDG with F-18, a means of transporting the tracer to the hospital, and a scanner to image with, TRIUMF was set to begin an imaging program by early 1983. Initially, FDG PET was developed to perform human functional studies of the brain, *in vivo*. Thus, the cameras being used during these early days were designed to optimize brain imaging. It was not until the mid 1990s that FDG begin to be used in the diagnoses of cancer, principally in Europe and the US.

Establishing a brain research program required recruiting neurologists and psychiatrists. The challenge was that the large number of interested parties were, for the most part, clinicians, not researchers. The attempts at acquiring funding from the MRC (the CIHR predecessor) acknowledged the strength of the physical infrastructure while pointing out the weakness in the proposed

Fig. 2 Erich Vogt, Brian Pate, and Lloyd Detwiller, UBC Health Sciences Centre administrator, standing next to the radiopharmaceutical-transporting pneumatic pipeline to be installed between TRIUMF and UBC.

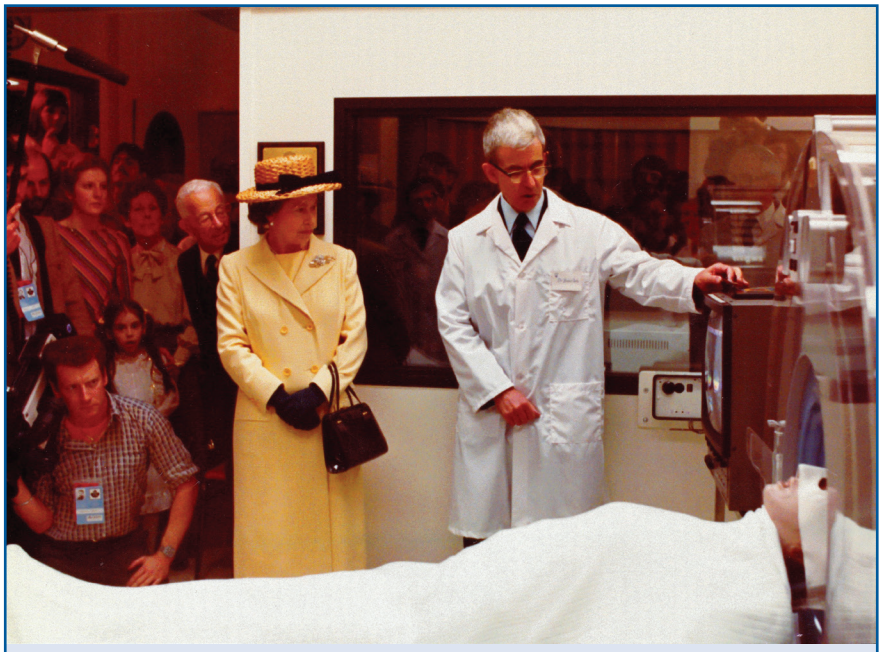

Fig. 3 Brian Pate showing off the PETT VI to Queen Elizabeth II in 1983 during the opening of the UBC Brain Research Center.

brain studies. Things changed in 1981 with the recruitment of Donald Calne, a world-renowned Parkinson's disease research scientist, who arrived emphatically stating that he intended to use PET as his primary tool for understanding the origins, progression and complications of Parkinson's disease (PD).

Our first PET scan with FDG was on a normal subject, one of the participating neurologists, on February 24, 1983. Just over two weeks later, Her Majesty, the Queen of Canada, came to UBC to participate in the opening of the UBC Brain Research Center (see Fig. 3). This included PET scanning and Canada's first clinical MRI scanner (acquired through the efforts of Laurie Hall who was an NMR expert in addition to his research in carbohydrate chemistry) at the Koerner Pavilion, UBC Hospital.

Later that year a new tracer, ^{18}F-fluorodopa, first developed at McMaster University, was introduced to the UBC program by the PET chemists. This L-Dopa analog allowed for the study of the dopamine system in PD patients.

With the support of (then) TRIUMF Director Erich Vogt and Bob Miller (VP Research, UBC), Tom Ruth became PET Director in 1989 after Brain Pate stepped down in late 1987 to pursue PET studies of dopamine metabolism in non-human primates. During the one-year gap between Brian's stepping down and Tom's assuming the role of PET Director, Andy Eisen served as the Acting Director during the search for a Full Time Director.

During the first 15+ years numerous studies were performed to demonstrate preclinical changes in the dopamine system that lead to PD. In addition, we were able to observe that asymptomatic patients progress to PD, that early signs of compensation can be detected, that singular events can cause PD, and that there exist clusters of PD, all of which led to the "event" hypothesis.

In the early 1990s, Dick Johnson, serving as Head of the Life Science Program within the Science Division, worked with EBCO Industries to build a small cyclotron suitable for hospitals. The TR13 prototype (see Fig. 4), built with TRIUMF support, utilized localized shielding so that it could be placed in an open area within a fenced safety zone, obviating the need for a special shielded vault. The TR13 cyclotron allowed the PET program to schedule their productions runs according to the needs of the medical program. In addition, the cyclotron opened the possibility to produce C-11 radiotracers.

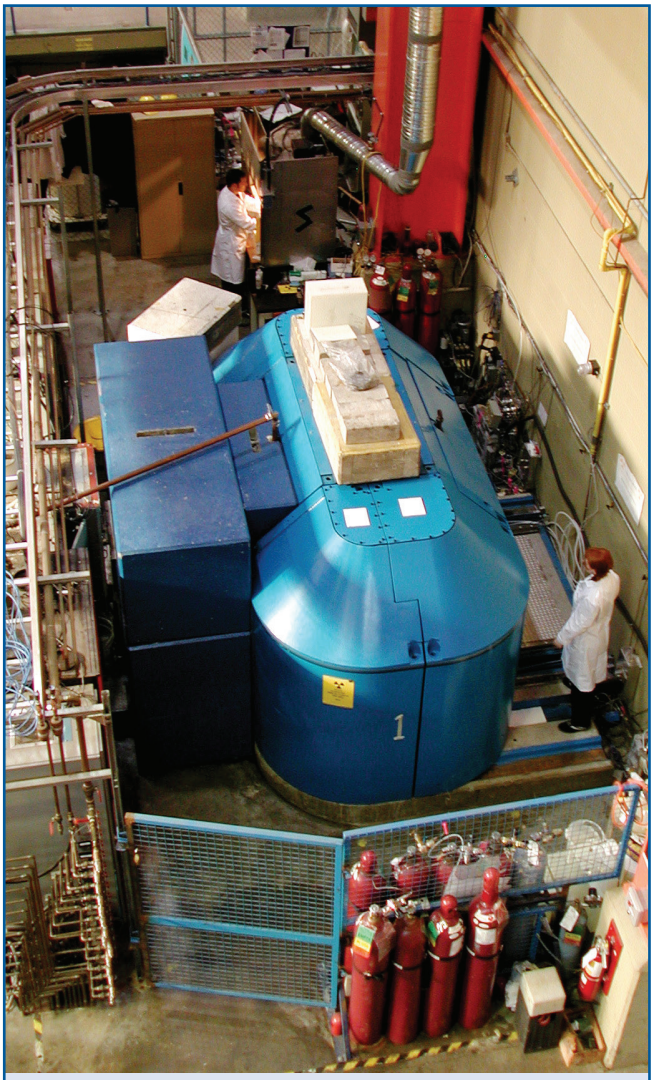

Fig. 4 Overhead view of the TR13 medical-isotope cyclotron at TRIUMF.

The tracers developed were ones that had been previously published elsewhere. The unique aspect of the UBC/TRIUMF PET program was applying them to address significant fundamental questions in the living human brain, especially as related to Parkinson's disease. The availability of C-11 tracers provided the opportunity to explore the dopamine system in a very dramatic fashion. The leadership of the Parkinson's disease program changed hands in the 1990s with Jon Stoessl leading the research efforts. All told, the UBC/TRUMF PET program in Movement Disorders became a recognized world class effort.

While the PET program was moving forward with gusto, collaborations were established amongst local university researchers which demonstrated that radiotracers could be used to address questions in a variety of fields. Probably the most successful collaboration was with Tony Glass, a Botanist at UBC, who made use of $^{13}NO_3^-$ to investigate nitrogen incorporation in various plant systems. Over the next 20 years Tony and his colleagues published nearly 50 papers using ^{13}N, fifteen of which each had more than 100 citations.

Other studies involved the pulp and paper industry with Mark Martinez, a Chemical Engineer at UBC, who used the PET scanner to monitor the settling of ^{18}F-labeled pulp fibers**.** He devised a mathematical term that he called the *Crowding* number which related to the quality of paper. These studies determined the optimal conditions for operating a paper mill**,** optimizing the tradeoff between cost efficiency and environmental safety. Mark's further work explored the mathematics of fluids undergoing sudden expansion, a phenomenon observed in many industrial processes. Recently, Mark has been helping develop heat transfer models to better understand the operation of gas targets for radioisotope production.

UBC oceanographer Maite Maldonado used isotopes of Cu to study the use of copper by phytoplankton in iron-poor regions of the ocean, work impacting the study of CO_2 sequestration in the oceans. She brought radioactive copper on sea cruises to enable the investigation of copper uptake in various regions of the North Pacific Ocean.

Also, in the 1993, John Vincent, Tom Ruth and Mike Cackette published a process for the production and isolation of Sr-82 that has been adopted by a number of centers for the production of Sr-82 for use in supplying $^{82}Sr/^{82}Rb$ generators. Rb-82 is used in cardiac PET studies.

During this period, the TR13 was used to support the University of Alberta PET program before they acquired their own cyclotron, which involved shipping F-18 to Edmonton once a week. Even with the long transit time (8-10 hours including clearing transport requirements), they were able to begin their clinical program in cancer research and diagnoses.

Throughout the 1990s and early 2000s the Life Science program was organized within the Science Division Headed by Jean-Michel Poutissou who provided support and guidance for all aspects of the Life Science endeavors. As part of the succession plan, Paul Schaffer was recruited to assume the leadership of the Life Science program in 2010. The (then) Director Nigel Lockyer created a Nuclear Medicine Division, which was then led by Paul.

Collaborations with the Chemistry Departments at UBC and SFU led to many graduate student theses based on new techniques in the development of radiotracers. The principle UBC Chemistry professors were Chris Orvig (metal chelates), Steve Withers (β-Glucosidase inhibitors), David Perrin (Boron, silicon facilitated fluorinations), and at SFU with John D'Auria (Tracers for ISAC, Mass Separator), David Li (microfluidics), Tim Storr (fluorination of large molecules, click chemistry), Rob Britton (aqueous photocatalytic fluorinations of amino

acids), and David Vocadlo (^{18}F — cerebrosidase inhibitors for Alzheimer's research). Each of these collaborations involved students at all levels of training. And for nearly 30 years, the PET group involved Coop students from the University of Victoria Chemistry Department. Many of these students went on to pursue graduate studies at one of the TRIUMF member universities.

Probably the most significant non-UBC PET collaboration developed was with the BC Cancer Agency in helping to establish their clinical PET program. This relationship established a working plan for the design of a PET facility, the writing of a grant proposal to establish a Chair in Functional Imaging, the recruitment of a lead Clinician Scientist to fill that chair, the delivery of FDG to the Cancer Agency while their program was being expanded, and the assistance with establishing the research laboratories for radiochemistry and the GMP facility (see Fig. 5). Francois Benard became the Chair and has since established a strong cancer research imaging program. This relationship has continued with TRIUMF serving as a back-up for when the Cancer Agency cyclotron is down for maintenance.

This close relationship led to a collaboration to develop a cyclotron approach to the production of Tc-99m. Following the worldwide shortage of ^{99}Mo/^{99m}Tc caused by outages at the two largest reactor producers (NRU at Chalk River and the HFR in the Netherlands), the Government of Canada put out a series of Request for Proposals for which TRIUMF and the BC Cancer Agency teamed up to lead one effort. Leadership for the various grants rotated between Ruth, Benard, and Schaffer. The success of this effort resulted in NSERC awarding the team the Brockhouse Award for interdisciplinary research, honouring team leaders Ruth, Schaffer, Benard, Anna Celler (UBC Radiology), Mike Kovacs (Lawson Health Research Institute in London) and John Valliant (Centre for Probe Development and Commercialization in Hamilton).

Fig. 5 (from left) Ken Buckley, Christine Takhar, Kathleen Genge, Mike Adam, Salma Jivan, Tom Ruth, and Paul Schaffer in the newly-commissioned GMP lab in 2016.

In an additional research effort to address the Mo-99 shortage, a team led by the late John D'Auria and Tom Ruth sought to improve the specific activity of neutron capture Mo-99 by performing post-irradiation mass separation. This effort built on the success of a graduate student Suzanne Lapi, whose thesis explored mass separation of Re-186 as a means to increase specific activity of this potential therapeutic radionuclide.

The Division's latest research thrust is into the production of alpha emitting isotopes for therapy. The use of the TRIUMF ISAC facility made it possible to prepare $^{210/211}$At and ^{211}Rn to create a ^{211}Rn/^{211}At generator. Now the focus has extended to include ^{225}Ac.

For nearly 30 years the Life Science program operated with just two TRIUMF faculty, Mike Adam and Tom Ruth. Then Paul Schaffer was hired and the program became its own Division. With this new status, more personnel have been appointed. Conny Hoehr is pursuing targetry research, Valery Radchenko has expertise in actinium production and applications, and Monika Stachura is involved in Metallo-Biochemical studies.

There are many, many individuals over the years that have contributed to the success of the program. That said, there are two individuals that provided expertise and dedication over the years, Salma Jivan, a magician chemist who could make just about anything, and Ken Buckley (since retired) who has worn many hats from cyclotron manager, PET camera manger (these two at the same time), program manager for the Tc-99m project, and then Deputy Division Head for Life Sciences.

The Life Science program is poised to install a new cyclotron, the TR24, which will expand the isotope production capabilities, forming the center of the new Institute for Advanced Medical Isotopes (IAMI) program (see Fig. 6). The IAMI program led by Paul Schaffer reflects the continued support of TRIUMF management. In fact, TRIUMF's ability to reinvent itself and expand programs has been due to the continued support of its Directors over the years, most recently with the latest Director, Jonathan Bagger.

Fig. 6 Concept rendering of the new Institute for Advanced Medical Isotopes (IAMI) at TRIUMF. Construction of the new building began in spring 2019.