The Design, Construction, and Commissioning of a Multi-Use Cyclotron Facility

S. Ho[1], M. Hutcheson, [1] D. Schick-Martin[1], M. Dalzell[2], and N. Alexander[2]
[1] Saskatchewan Centre for Cyclotron Sciences, Saskatchewan, Canada
[2]Sylvia Fedoruk Canadian Centre for Nuclear Innovation, Saskatoon, Saskatchewan, Canada
sara.ho@fedorukcentre.ca, matt.hutcheson@fedorukcentre.ca, d.schickm@fedorukcentre.ca, matthew.dalzell@fedorukcentre.ca, neil.alexander@fedorukcentre.ca

Abstract

The Sylvia Fedoruk Canadian Centre for Nuclear Innovation in Saskatchewan is in the process of commissioning the Saskatchewan Centre for Cyclotron Sciences that is to be used for both academic research and commercial radiopharmaceutical production. The hybrid nature of this facility comes with unique challenges in satisfying both the rigid demands of pharmaceutical production while providing the necessary flexibility for academic research. In order to meet these competing demands, the Fedoruk Centre has assembled a distinct combination of skill sets and areas of expertise to operate a facility with an interdisciplinary focus.

1. Introduction

The Sylvia Fedoruk Canadian Centre for Nuclear Innovation, established in 2011, is based at the University of Saskatchewan in Saskatoon. The Fedoruk Centre has a mandate to place Canada and Saskatchewan among global leaders in nuclear research, development and training [1]. This is to be accomplished through a combination of partnerships with both academia and industry, with an emphasis on social and economic benefit, expressed in the following goals: “(1)building nuclear expertise and capacity through the support to academic programs and research projects in partnership with industry, academic institutions and research organizations in nuclear medicine, materials research, energy and the environment; (2) enhancing innovation in partnership with the research community and industry; (3) engaging communities and increasing understandings of risks, benefits, and potential impacts of nuclear technologies.” [1]. The Fedoruk Centre is named after Saskatchewan researcher Sylvia Fedoruk, who was involved in development of cobalt-60 radiation therapy devices at the University in the early 1950’s [1].

A major step in achieving these goals is in the bringing online of a 24 MeV cyclotron facility that is slated for Good Manufacturing Practices (GMP) production of commercially available radiopharmaceuticals such as the PET (Positron Emission Tomography) imaging agent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) for Saskatchewan hospitals, as well as the ability to be heavily used by the surrounding research community.

2. Vision for the Facility

In March of 2011, funding from the federal and provincial governments was announced for a PET-CT (Positron Emission Tomography-Computed Tomography) scanner at Royal University Hospital in Saskatoon and the construction of a cyclotron on the University of Saskatchewan campus [1]. The physical proximity of these two sites allows for efficient use of cyclotron-produced radiopharmaceuticals. However, the vision for the cyclotron facility is much broader than providing ^{18}F radiopharmaceuticals to a local hospital, as this could have been achieved with a much smaller facility and a much less powerful cyclotron [1]. A 24 MeV cyclotron not only gives the capability to produce PET and SPECT (Single-Photon Emission Computed Tomography) tracers currently in clinical use, but is also able to produce more novel isotopes for research applications.

One of the first projects undertaken by the cyclotron team is to produce GMP grade ^{18}F-FDG for clinical use. ^{18}F-FDG is currently being used by the Medical Imaging Department at Royal University Hospital, but they are limited in their supply due to the need to ship the radiopharmaceutical over 2700 km. Once the facility is online and is able to produce ^{18}F-FDG under Health Canada's stringent GMP requirements, Royal University Hospital will have the flexibility of local ^{18}F-FDG and will not be limited by transportation hurdles.

The Advanced Cyclotron Systems Inc. (ACSI) TR-24 cyclotron is capable of utilizing solid, liquid, and gas targets, and therefore is capable of synthesizing a variety of radioisotopes including ^{18}F, ^{11}C, ^{13}N, SPECT and other exotic isotopes [1]. With many research groups already present at the University of Saskatchewan, the cyclotron has the potential to produce agents that are useful for research in medicine, pharmacy, veterinary medicine, agriculture, and other life sciences [1].

The Saskatchewan Centre for Cyclotron Sciences is intended to accommodate many different research laboratories and projects, as well as room for future expansion. In addition to the lab space set aside for the GMP testing of ^{18}F-FDG, there is space in the clean zone of the facility allocated for blood cell or human tissue labelling, and for compounding of other radiopharmaceuticals. There is also space within the facility for a radiopharmacy and for future expansion and development of laboratories, including a micro PET-CT scanner and facilities for plant or small animal scanning. The segregation of the facility into a clean zone and regulated laboratories allows for the preparation of radioisotopes in sterile conditions, making them suitable for clinical use.

The Centre is designed to be supported in its research activities and endeavours by investments by the Fedoruk Centre for research positions at Saskatchewan universities [3]. There are plans and searches currently underway for faculty positions and research chairs at both the University of Saskatchewan in the fields of nuclear imaging and nuclear chemistry/radiopharmacy, and at the University of Regina in nuclear physics focused on detector development [3]. These positions will help provide guidance and direction to research endeavours undertaken at the Centre, as well as contribute to core cadre of researchers who will use the facility.

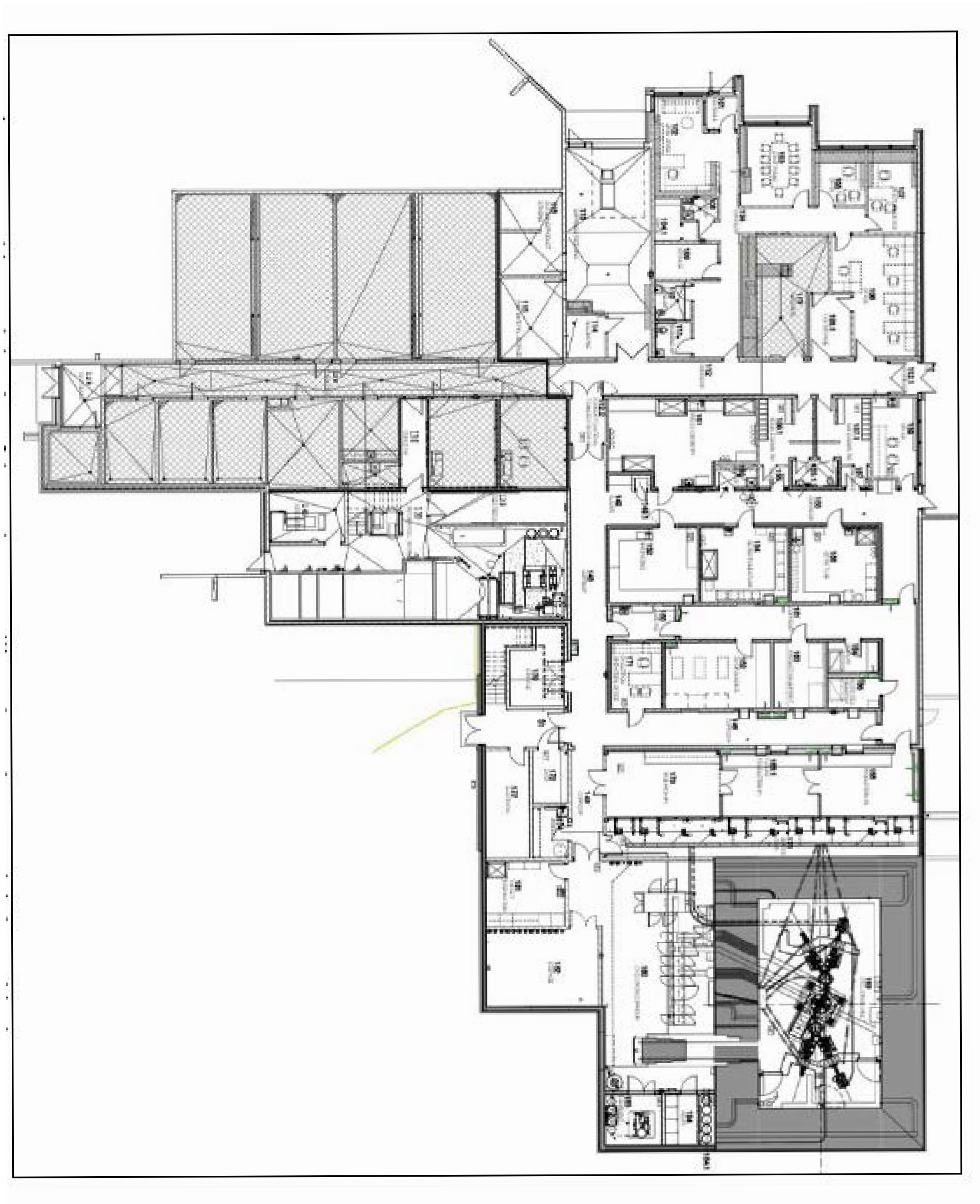

Figure 1-Floorplan of Saskatchewan Centre for Cyclotron Sciences

2.1 The ACSI TR-24 Cyclotron

The cyclotron at the heart of the facility is a 24 MeV TR-24 cyclotron produced by Advanced Cyclotron Systems, Inc., of Richmond, British Columbia. The acquisition of the cyclotron itself was a very large step for the University and for nuclear research in the province; Saskatchewan is among one of the final provinces to possess a cyclotron [4]. In a news article published in November of 2014, the radiopharmacist with the Saskatoon Health Region, Humphrey Fonge, is quoted as saying:

“This is going to blow out the amount of research opportunities the province is going to be having, the university is going to be having. We are actually one of the last provinces to get a cyclotron. But the nice thing is, we got the Ferrari. So we got one of the best cyclotrons at any academic institution. Depending on the amount of research done, it will rank us somewhere in the top 10 per cent of institutions that have similar facilities” [4].

Figure 2-View of the cyclotron and beamline from the vault entrance

The TR-24 cyclotron is equipped with a Y-shaped beamline ending in two end-stations; one with a solid target and the other equipped with a multiplex target selector. There is also a back-up set of targets that are available for PET products. There is room for expansion of the cyclotron and the addition of a second beamline and targets to further enhance production.

Figure 3-Quadrupole magnets on the cyclotron's beamline

The ACSI TR-24 cyclotron is particularly suited to GMP production of ^{18}F due to particular characteristics of the water targets [5]. The Havar foils that are used in the liquid targets manufactured by ACSI for ^{18}O water bombardment are assembled with a thin layer of niobium that is thought to reduce the amount of water-based radicals produced during bombardment. This results in a purer product and actually optimizes the radiochemistry that is performed on the ^{18}F in the synthesis of the FDG [5]. This theorized capability of the TR-24 cyclotron is advantageous for GMP production, since it results in a product with fewer impurities and more consistent performance [5].

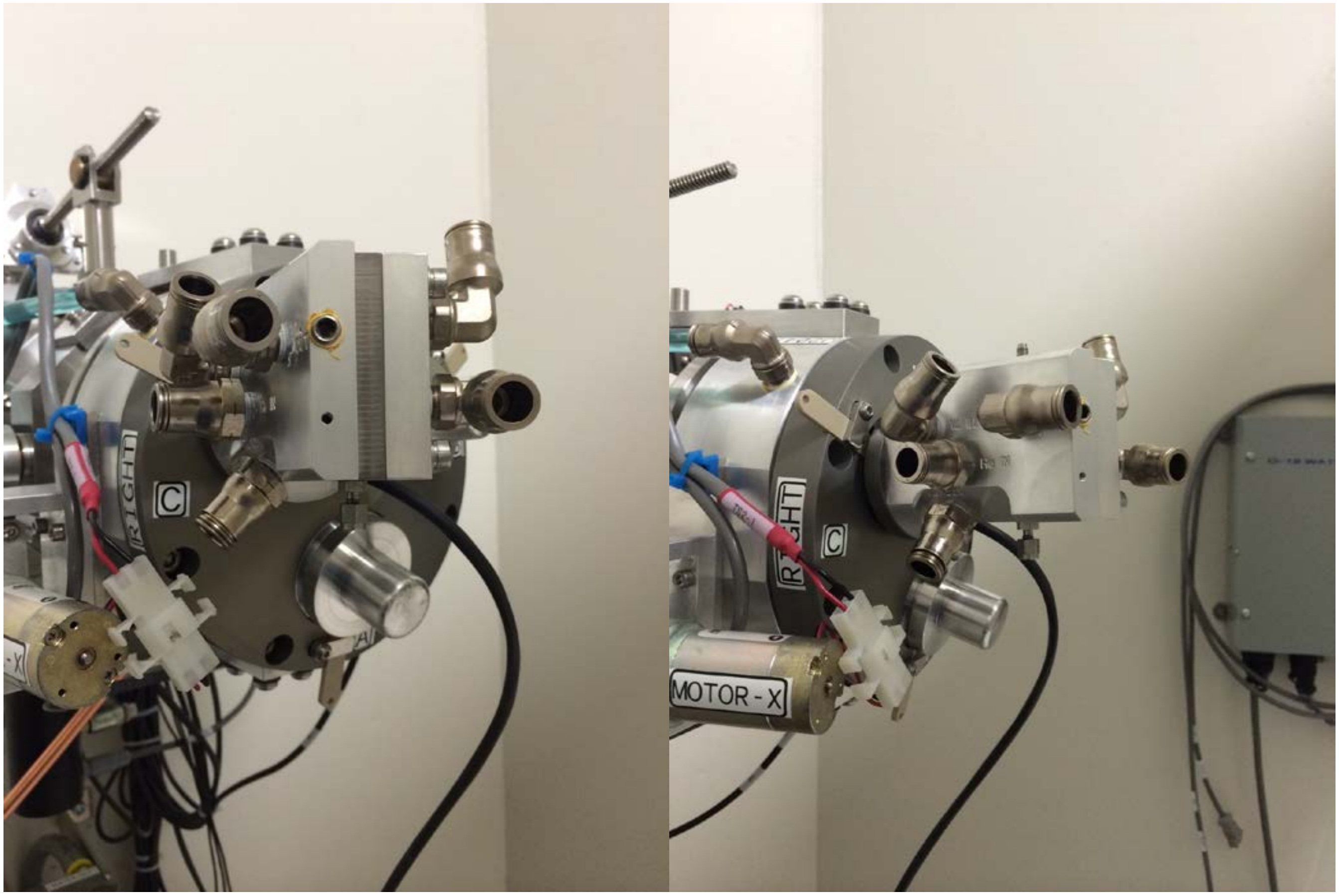

Figure 4-Target selector with mounted liquid target (not plumbed)

2.2 Challenges of a Multi-Use Facility

One significant challenge of having a multi-use facility is meeting the controlled standards that exist in the Health Canada GMP regulations that govern the premises, equipment, personnel, sanitation, raw materials testing, manufacturing control, quality control, packaged materials testing, finished product testing, records, samples, stability, and sterile product information for radiopharmaceuticals [6]. These rigorous standards have implications for the structural design of the building in everything from ventilation systems, types of paint and flooring, to the type of air filtration that is used, implications for how the facility is managed and controlled, and how tightly the use of equipment is managed [6]. The fact that the cyclotron facility will house several different laboratory spaces, can create a variety of radioisotopes, and will be utilised by different research groups creates a logistical challenge for keeping the GMP-critical areas controlled. The GMP-critical areas are required to undergo their own set of commissioning and validation, as well as the nuclear commissioning that is required of the entire site.

The complexity of GMP standards is something that is relatively new to cyclotron-based isotope production of Positron Emitting Radiopharmaceuticals (PER) [7]. ^{18}F-FDG is classified as a PER and is regulated by an Annex to the Good Manufacturing Practices [7,8]. PERs have additional complications due to their short half-lives and the hours-long lifespan of product, and therefore require different treatment as far as Quality Control testing and Final Product Release than typical GMP pharmaceuticals[8]. The speed of the decay and limited time of use allow for certain Quality Control tests to be completed in a retrospective manner.

We have found that the way to achieve a balance between GMP production and research flexibility is to bring together a unique interdisciplinary blend of talents to make the cyclotron facility as versatile as possible. The staff has a set of varied backgrounds including: cyclotron engineering, installation and repair; nuclear medicine and radiopharmaceutical production in a hospital setting; and GMP Quality Control and analytical chemistry of conventional pharmaceuticals. The partnership and collaboration that exists between the University of Saskatchewan, University of Regina and the Fedoruk Centre creates a powerful synergy--the universities can provide the expertise and the vision for research endeavours, and the Fedoruk Centre provides staff with the technical knowledge and skill to aid the researchers in producing and synthesizing isotopes or tracers that will aid them in their given fields of expertise. It is also envisioned that the facility will also be utilized by industry and researchers from outside of Saskatchewan, in partnership with the provincial user community. The Saskatchewan Centre for Cyclotron Sciences is intended to be a collaborative facility, where the Fedoruk Centre technical staff work alongside researchers to aid them in meeting their research goals. This goal will also be supplemented by the experience of the researchers working as part of the nuclear imaging programs being developed at the University of Saskatchewan and at the University of Regina [3].

In order to establish a cyclotron facility that is capable of meeting the requirements of GMP regulations for PERs and the differences in the production of radiopharmaceuticals with a short half-life compared to traditional pharmaceutical production, the Fedoruk Centre looked to find other Canadian expertise. The Fedoruk Centre has established a long-term partnership with the Centre for Probe Development and Commercialization (CPDC) at McMaster University in Hamilton, Ontario. The CPDC has a long-standing history of producing PET isotopes, and is assisting the Fedoruk Centre team with regulatory affairs, establishing an overall quality system, and overall production and testing of ^{18}F-FDG [1]. This relationship with an established PET isotope supplier with expertise in the nuances of clinical trials, automated production, and the engineering required to operate a cyclotron is allowing the Fedoruk Centre to adopt an already-proven system of production of ^{18}F-FDG, and provides a foundation for the potential GMP production of other tracers.

3. Conclusion

The Saskatchewan Centre for Cyclotron Sciences is the result of an interdisciplinary attempt and coming together of many different areas of expertise to achieve the goal of establishing a site in Saskatchewan that is sustainable and capable of meeting both research and commercial radiopharmaceutical production goals.

4. References

[1] Alexander, N., Root, J. H., Chad, K., Bereznai, G., & Dalzell, M. T. (2014). The Sylvia Fedoruk Canadian Centre for Nuclear Innovation: advancing knowledge through partnerships. The 19th Pacific Basin Nuclear Conference.

[2] Sylvia Fedoruk Canadian Centre for Nuclear Innovation (2013). *Saskatchewan's Future in Nuclear Innovation: Strategic Plan 2020.* http://www.fedorukcentre.ca/docs/SK_FutureInNuclearInnovation.pdf

[3] " Fedoruk Centre funds nuclear medicine research leaders at Saskatchewan universities." News release, October 30, 2014, Saskatoon, SK, Canada. http://www.fedorukcentre.ca/news/news-releases/nr20141030-nuclear_imaging.php

[4] Charlton, J. (2014, November 29). "'We got the Ferrari': Meet Saskatchewan's $25 million, 25-tonne radioactive research machine." *The Star Pheonix* , pp. E2-E3.

[5] Johnson, R. R., Watt, R., Kovac, B., Zyuzin, A., Van Lier, E., Erdman, K. L., et al. Advances in intense beams, beam delivery, targetry, and radiochemistry at advanced cyclotron systems. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*,261, 1-2,2007, 803-808.

[6] Health Canada . (2009, March 11). Good Manufacturing Practices (GMP) Guidelines GUI-0001.

[7] Lougheed, Tim. "Uncertainties shroud medical isotope supply", *CMAJ: Canadian Medical Association Journal.* 184, 11, 2012. E567

[8] Health Canada. (2006, March 30). Annex to the Good Manufacturing Practices Guidelines. *Good Manufacturing Practices (GMP) For Positron Emitting Radiopharmaceuticals (PERs) Guide-0071*.