Saskatchewan Centre for Cyclotron Sciences

Activity & Achievement Report

April 2020 - March 2021

Fedoruk Centre
SYLVIA FEDORUK CANADIAN CENTRE FOR NUCLEAR INNOVATION

CONTENTS

OPENING REMARKS

Message from the Chair

Tom Kishchuk,

Chair of the Fedoruk Centre Board

The Fedoruk Centre operates the Saskatchewan Centre for Cyclotron Sciences (SCCS) as a first-class scientific resource, making it accessible for researchers to advance life sciences with nuclear imaging methods. We have built and continue to grow a multidisciplinary community of experts, and manage facilities that enable Saskatchewan people to generate, interpret, and apply knowledge for social and economic benefits.

Although challenged by the lingering COVID-19 pandemic, the past year saw several achievements that contribute to building nuclear research and innovation capacity in Saskatchewan. The Saskatchewan Centre for Cyclotron Sciences is a shared resource for a growing community of researchers and a supplier of radiopharmaceuticals for Saskatchewan and regional hospitals. The Board is proud of the successes of the Fedoruk Centre and is confident that it's on track to realize our objectives.

Message from the Facility General Manager

Dale Schick-Martin,

Saskatchewan Centre for Cyclotron Sciences Facility General Manager

The Saskatchewan Centre for Cyclotron Sciences has transitioned from an initial start-up phase into a resilient continuous operation. Twenty-one agreements for user access, along with three master supply agreements covering Alberta, Saskatchewan and Manitoba's healthcare systems, demonstrate the maturity the facility has developed within the first five years of operation. We've established standard practices for engagement with industry, academia, government agencies and healthcare services. Our focus on providing a sustainable resource to Saskatchewan is demonstrating success with reliable product delivery, low frequency of facility outages and high-quality scientific outcomes from SCCS users.

Despite all the healthcare-related turbulence through the COVID-19 pandemic, there have been no disruptions to FDG production. My sincerest thanks to the Department of Medical Imaging and Nuclear Medicine at the Royal University Hospital, as well as the Fedoruk Centre team at the SCCS, for maintaining patient care throughout an immensely challenging time.

The Fedoruk Centre team's determination and enthusiasm have placed the SCCS in a position to support leaders in research and development. This report will provide evidence of the impacts that the facility and team have made possible.

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INTRODUCTION

The Sylvia Fedoruk Canadian Centre for Nuclear Innovation, Inc. (Fedoruk Centre) facilitates research that advances health, energy, science policy and environmental stewardship for the benefit of society—in Saskatchewan and worldwide.

The Value of Nuclear Methods

Nuclear methods are powerful tools to reveal new knowledge about materials that cannot be found easily by other ways. With nuclear methods, and radioactive isotopes in particular, specialists can detect and treat cancers and disease, develop new medicines and study the inner workings of life itself.

Our Main Activities

We Fund Projects

The Fedoruk Centre supports innovation in a wide range of nuclear topics through grants. These grants include funding for research connected to life sciences, radiochemistry, radioisotope production, and nuclear medicine, all of which can be supported by access to the Saskatchewan Centre for Cyclotron Sciences (SCCS). Applications are evaluated by an external panel of experts. To date, we have awarded more than $7.5M in grants, supporting 43 research projects led by Saskatchewan scientists.

We Invest in Program Partnerships

We partner with Saskatchewan institutions to strengthen academic research leaders and establish education programs. These partnerships help train highly qualified people and grow Saskatchewan's capacity to participate in nuclear science, technology, research and policy.

We Operate Facilities

The Fedoruk Centre operates facilities that house nuclear technology, including the SCCS, a world-class facility for radiopharmaceutical production and innovation in nuclear imaging.

The SCCS makes radioisotopes and radiopharmaceuticals for healthcare. The majority of these radiopharmaceuticals are delivered to the Royal University Hospital in Saskatoon for PET/CT scans. The SCCS also provides resources to support researchers from veterinary, agriculture, pharmacy, medicine, and physical science departments from various post-secondary institutions. We maintain the facility in a state of readiness for users to advance their work by accessing its capabilities.

We Provide Consultation and Promote Conversation

The Fedoruk Centre is a neutral, third party when it comes to nuclear research and technology, and can provide objective, unbiased information on the subject. We promote respectful public conversation about nuclear technology in Saskatchewan. We can provide advice on projects and policies related to the nuclear sector or provide expert testimony for the media.

SCCS Ownership and Operation

In March 2011, the Government of Saskatchewan, in partnership with the federal agency Western Economic Diversification and the University of Saskatchewan, announced funding for the creation of a ***cyclotron*** and ***PET/CT*** program in the province now known as the SCCS.

In 2013, the Fedoruk Centre accepted a responsibility to operate and manage the cyclotron and production facilities at the SCCS through an operating license agreement with the University of Saskatchewan (USask).

PET/CT scans are important tools for nuclear imaging. They can help detect, diagnose, and treat cancers and other diseases.

In 2018, the responsibility for operating the Innovation Wing of the facility was added to the Fedoruk Centre license agreement with USask.

A license to construct the cyclotron facility, issued by the Canadian Nuclear Safety Commission, became active in January 2014. The cyclotron facility was placed on the university campus, near the Royal University Hospital and the Western College of Veterinary Medicine. Commissioning began in October 2014.

A cyclotron is a type of particle accelerator. It produces radioactive isotopes that can be used for nuclear imaging.

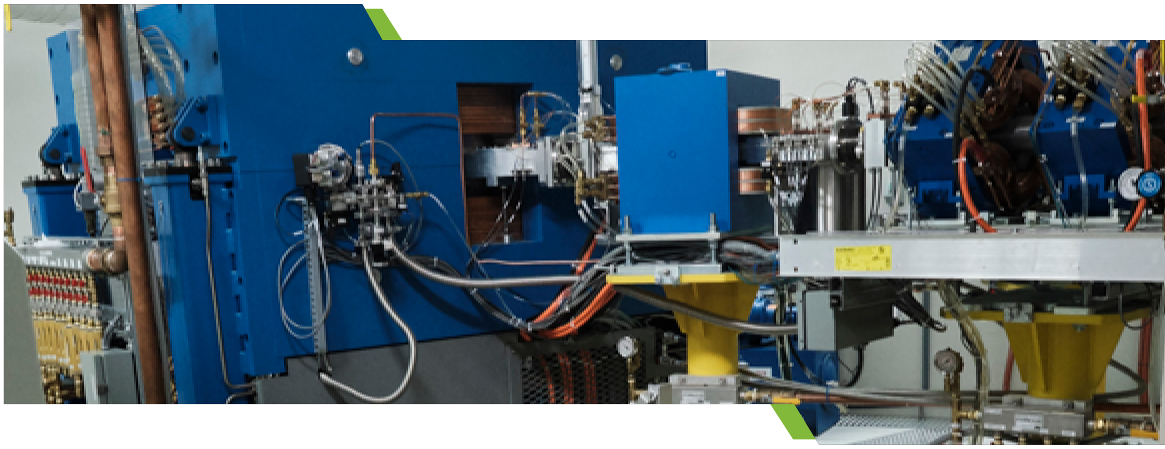

Fig 1: 24 MeV cyclotron in the Saskatchewan Centre for Cyclotron Sciences, operated by the Fedoruk Centre at the University of Saskatchewan.

OUR COMMITMENT TO SAFETY

The safety of our employees, users and community is paramount to everything we do. Work with nuclear substances requires stringent safety measures and compliance with specific rules and regulations. Our top priorities are to keep our workforce healthy, our workplace safe, and to minimize the impact our operations have on the environment. These priorities are essential to our reputation of excellence in supporting scientific research, innovation and healthcare with nuclear methods.

We operate a Class II Nuclear facility licensed by the Canadian Nuclear Safety Commission, and we follow all applicable environmental and regulatory requirements.

Our production processes are compliant with Good Manufacturing Practices as certified by Health Canada. And of course, we follow the policies from the Canada Labour Code and the University of Saskatchewan on general safety, biosafety and animal ethics.

To read more about the specific things we do to keep the facility and its user safe, see the "Safety and Compliance Details" Appendix on page 20.

SASKATCHEWAN CENTRE FOR CYCLOTRON SCIENCES (SCCS)

Our Key Activities

At the Saskatchewan Centre for Cyclotron Sciences, specialized equipment and labs allow our community of experts to conduct research and innovation with nuclear imaging, therapies, ***radioisotope*** production and radiochemistry.

While there's a wide variety of work, these are our main activities:

1. *We produce a reliable supply of the radiopharmaceutical **"FDG"*** for diagnostic imaging in regional hospitals.

2. *We offer access to specialized equipment.* Our cyclotron, specialized workstations and expert staff are accessible by researchers from academia and industry to conduct studies in ways that cannot be accomplished elsewhere.

3. *We support a community of experts.* Scientists and researchers from all over the world are welcome to access the facility to advance their innovative programs.

4. *We support specialists* with a wide spectrum of interests, including nuclear medicine, instruments, imaging, radiochemistry and the advancement of ***life sciences*** through nuclear imaging methods.

Each chemical element has a specific number of protons in its atomic nucleus. However, an atomic nucleus might have more or less neutrons than the number of protons. Elements with different numbers of neutrons are called isotopes. Some isotopes are stable, and others are radioactive, called radioisotopes.

FDG stands for fluorodeoxyglucose, a radiopharmaceutical needed for PET/CT scanning.

The life sciences include all studies of living things, including plants, animals and humans, with applications in agriculture, the environment, human medicine and veterinary medicine.

Snapshot of Our Achievements from April 2020 to March 2021

Supply of Radiopharmaceuticals	• *310 FDG deliveries with 99% delivery success rate (during the calendar year 2020)* • *2412 patients received PET imaging scans at the Royal University Hospital (during the reporting period)* • *One new investigational Active Pharmaceutical Ingredient: Zirconium-89 Oxalate*
Production of Radioisotopes	• *Routine supply of Zr-89, F-18, C-11, N-13 responding to demand from researchers*
New Capacity	• *One new workstation available for gamma spectroscopy*
Building Resilience	• *We strengthened resilience of production and operation by acquiring equipment and technical staff to cover unplanned outages*
Access to State-of-the-Art Capabilities	• *24 workstations available for access* • *21 new user access agreements* • *95% workstations ready for access*
Training	• *23 new Nuclear Energy Workers trained*
Safety	• *Tungsten shielded containers acquired* • *Upgraded radioactive waste decay room*

OUR ACHIEVEMENTS

Achievements in Radioisotope Production

1

We produced a reliable supply of radioisotopes for PET/CT scans.

This reporting period, 2412 patients in Saskatchewan received imaging scans to diagnose and treat cancer with FDG made at the cyclotron facility. Even though our support for research activities was temporarily limited because of COVID-19, there were no disruptions to FDG supply for regional hospitals. Before we began producing FDG in 2016, local hospitals had to bring it in from other parts of Canada, which can be expensive and prone to supply issues. Now, Royal University Hospital and other regional hospitals can rely on our supply of quality-assured FDG to help them detect and diagnose cancers and other diseases.

2

We made radioactive substances to support research in life sciences.

We also make additional radioisotopes for radiopharmaceutical and life science research. In some cases, the quality of our isotopes and compounds is high enough for marketing across Canada as a drug, well beyond what is required for initial clinical trials. This means that new medical treatments can be developed using isotopes made right here in Saskatchewan.

Beyond our routine production of F-18 we produced C-11, Cu-64 and Zr-89.

See Table 1 showing the impact of COVID-19 in reducing researcher activities and demand for isotopes from the SCCS.

Table 1: SCCS Manufacturing Metrics

Radionuclides Produced at the cyclotron facility (Batches per Calendar Year)		
Isotope	**2019**	**2020**
Carbon-11	51	26
Copper-64 (targets from Price lab)	12	10
Zirconium-89	34	27

3

We developed facility space to make “cold kits” for medical use.

In 2021, the Fedoruk Centre committed to create a designated workstation for ***cold kit*** production. The new workstation will enable users to manufacture the non-radioactive compounds for nuclear medicine procedures and treatment. This has the potential to improve access to nuclear medicine procedures and treatment of cancer in Saskatchewan.

Cold kits are the non-radioactive components of radiopharmaceuticals. They're shelf-stable and can be kept safely at hospitals.

Achievements in Offering Specialized Research Equipment

1

We maintained the facility in a state of readiness with high reliability.

Our medium energy TR-24 cyclotron can produce a wide range of isotopes. The cyclotron facility is equipped with a chain of ***hot cells*** and clean spaces for the development and manufacturing of radiopharmaceuticals. It's the only cyclotron in Saskatchewan, and our staff take care of it so it's always research-ready for users. This year, our workstations were fully ready for access 95.8% of the time, up from 90.3% the previous year. Research using nuclear substances requires access to specialized tools and equipment.

A hot cell is a shielded containment chamber that allows people to handle radioactive substances safely.

On top of the cyclotron, we offer specialized workstations, including:

- *nuclear imaging equipment (SPECT, PET, CT)*
- *radioanalytical instruments (radio HPLC, TLC, GC)*
- *hot cells and clean spaces*
- *synthesis unit*
- *equipment for radiochemical processes*
- *equipment for analyzing bio-distributions*
- *equipment for pharmacological and pharmacokinetic studies*
- *space to house living plants and animals*

With the equipment we have available, and support of technical or scientific staff, researchers are advancing cutting-edge innovations in the life sciences.

2

Our staff introduced training for new Facility users.

We take pride in our culture of continuous improvement and client service. Our goal is for all users, experts or not, to be able to design and implement their research projects successfully. We stay current with the evolving technology of the isotope, radiopharmaceutical and nuclear imaging industry, so we can enable their research and support their work to reach new heights of innovation.

Not every researcher who uses our facility is an expert in nuclear methods or familiar with a cyclotron. Some work in other fields, and need occasional access to our technology and know-how to advance their research. Others may have knowledge of nuclear methods but are less familiar with the specific equipment at the SCCS, or they are mainly present to mentor students in a hands-on learning experience. With our support, everyone can be comfortable and safe working with the equipment.

We provide specialized training for individuals to achieve designation as Nuclear Energy Workers (NEWs) and keep dose records for NEWs working in the SCCS. We kept dose records for 49 NEWs in 2019 and 65 NEWs in 2020.

See Table 2 in the Appendix - Safety and Compliance on page 20 for a breakdown of these numbers.

Our goal is for all users, experts or not, to be able to design and implement their research projects successfully.

3

We established Canada's first-ever plant imaging workstation—the Phytosuite.

The Phytosuite lets researchers study plant metabolism and soils in real-time. This has the potential to provide useful information to agricultural sciences and help breed enhanced crops with higher productivity. The Phytosuite uses an innovative system of nuclear imaging that can image the uptake of radioactive tracers in plants. It uses the BioPETx instrument developed at the University of Regina, and chambers to control the plants' environment and safely house them after uptake of radioactive tracers. The Phytosuite is a cutting-edge resource for environmental and biological research.

This year, we built a new shielded transport line that can send carbon dioxide [C-11]CO_2 and nitrogen gas [N-13]N_2 right from the cyclotron to the Phytosuite. The Canadian Nuclear Safety Commission approved the project in July 2020, and the C-11 line is now fully operational. It runs from the cyclotron, through the hot cells, up to the second floor in our mechanical space, and down to the Phytosuite.

Table 3: Radionuclides used in Research conducted at the SCCS

Table of Radionuclides (Units of GBq, Summed Over the Calendar Year)		
Isotope	**2019**	**2020**
Actinium-225	0.4	0.2
Bismuth-213	1.2	0.8
Carbon-11	279.1	137.7
Copper-64	8.8	5.6
Copper-67	4.7	69.7
Fluorine-18	70.6	29.0
Gallium-68	2.6	3.6
Iodine-131	0.2	0
Indium-111	0.8	0.2
Lutetium-177	0.4	0.3
Molybdenum-99	0.9	0
Technetium-99m	257.9	8.3
Zirconium-89	10.1	8.0

4

We expanded capabilities to bring isotopes from other producers to support researchers.

Some researchers have specific needs to handle isotopes that are not readily available at our facility. However, isotopes can't just be ordered and delivered to any lab or institution. We have specialized capabilities and a license for receiving and handling these isotopes. This capability is a valuable resource for Saskatchewan researchers, enabling them to access controlled materials for their projects. In 2020-2021 we amended our license to include two new isotopes, and increased our handling capacity for eight isotopes.

See Table 3 for a complete list of radionuclides used at the SCCS.

Achievements in Growing Our Community of Experts

1

We supported a growing community of experts.

In 2020-2021, we signed 21 new user-access agreements and three new supply agreements. In 2020, the users (scientists that are accessing the workstations and capabilities at the SCCS) published 23 articles in peer-reviewed journals and conference proceedings. The publications show the high quality of research led by scientists from Saskatchewan universities, supported by access to our specialized facilities and expertise.

See the list of publications, beginning on page 32 in the appendices.

Achievements in Enabling Research and Innovation

1

Our facilities supported pre-clinical research.

We have the specialized equipment that researchers need to conduct pre-clinical trials at our facilities. Specifically, researchers can perform ***in vitro*** and ***in vivo*** experiments to develop new therapeutic molecules and imaging agents by accessing state of the art imaging equipment, cell culture laboratory and vivarium which are all maintained in state of readiness for the user access by our experienced staff.

In vitro experiments are more commonly understood as "test tube" experiments. For in vitro experiments, researchers study microorganisms, cells, and molecules in labware like petri dishes or test tubes.

In vivo experiments study an entire living organism, like an animal or a human, instead of just a few cells.

a) New treatments for multiple sclerosis.

Professor Ekaterina Dadachova (USask, College of Pharmacy) and her research team are currently doing a pre-clinical study on a new approach to the treatment of Multiple Sclerosis (MS). Dr Dadachova is using our labs and equipment to develop radiopharmaceuticals and radioimmunotherapy as potential new treatment options. As the rates of MS in Saskatchewan are some of the highest in the world, Dr Dadachova's work is especially interesting locally, while aiming to improve health care worldwide.

"Our hope is that these clinical trials will help to bring new therapeutics to patients."
- Dr Dadachova

See page 24 of the Appendix - Details of Selected Research Highlights for more.

b) New tools to understand lung inflammation.

Dr Gurpreet Aulakh (USask, Western College of Veterinary Medicine) and her research team are currently working on new imaging tools and protocols to detect and treat lung inflammation caused by various diseases. Dr Aulakh has developed a robust animal imaging program, and has trained graduate and undergraduate students in advanced and novel imaging of innate immune cells in lungs. The findings of this work are expected to offer exciting new information for other drug researchers, radiochemists, veterinarians, doctors and patients.

"The data obtained from the proposed experiments will enhance our understanding of mechanisms of lung inflammation induced with low dose exposure to ozone. The fundamental data may, at some point, influence environmental policies in Canada."
- Dr Aulakh

See page 23 of the Appendix for more details.

2

We introduced a new clinical-grade investigational compound for medical imaging and cancer treatment research.

In August 2020, the Fedoruk Centre submitted a master file (MF) to Health Canada describing the manufacturing process of an investigational active pharmaceutical ingredient (API) form of [Zr-89] zirconium oxalate. Previously, the Zr-89 oxalate produced at the SCCS was only suitable for research purposes in pre-clinical or non-clinical studies. This master file is a common reference for all parties interested in pursuing a Canadian clinical trial using Zr-89 oxalate manufactured at the SCCS. Clients can use our produced Zr-89 oxalate in clinical studies with the reassurance that the manufacturing process is reliable and consistent.

In October 2021, researchers administered their first dose of a new nuclear-imaging drug made in our facility to a human patient. Zr-89-NimotuzumAb is being developed in Saskatchewan for targeted imaging of specific cancers. It's one of the first Saskatchewan-made nuclear imaging agents for clinical trials. The Centre for Biologic Imaging and Research and Development (CBIRD) team at the University of Saskatchewan began this work in September of 2019. The study opened the potential to provide radioactive compounds manufactured at the SCCS for evaluating their response on certain cancers for patients around the world.

3

We supported work on a clinical trial for prostate cancer imaging.

In December 2020, the first patient in a new clinical trial received a dose of a new nuclear imaging agent targeting prostate cancer. The trial uses the radiochemical Ga-68 chloride to make the nuclear imaging agent [Ga-68]Ga-PSMA (prostate-specific-membrane-antigen). Produced with support from our facility, the nuclear imaging agent was administered to a patient at the Royal University Hospital (RUH) in Saskatoon. The diagnostic scan was the first of its kind in the province of Saskatchewan, beginning a clinical trial with humans. Since then, a total of 11 patients have received scans. If successful, this could be a new way to more accurately diagnose and treat prostate cancer in the future.

"The overarching goals of [the] research program are to improve early detection of a variety of cancers"

4

We enabled researchers to improve molecular imaging and radiotherapy drugs.

Dr Price (USask, Chemistry) and his research team are currently using our facility to create new molecular imaging and radiotherapy drugs. These drugs will improve how we detect, diagnose, and treat a range of diseases like cancers or bacterial infections. In the future, advancements in nuclear imaging could help doctors around the world give more accurate, comprehensive care to patients. The ***automated synthesizer*** in the SCCS, essential for this work, has been readily available to the team.

A machine that performs chemical mixing of radioactive tracers without the need for manual handling of the materials.

"The overarching goals of [the] research program are to improve early detection of a variety of cancers using molecular imaging techniques such as fluorescence and positron emission tomography (PET) imaging, and then to treat them using theranostic "smart drugs" that harness therapeutic radioactive metals or potent anticancer drug. Once injected, these "smart drugs" can selectively seek out cancerous cells by binding selectively to diseased cells that present specific receptors or biological processes."
- Dr Price

See page 26 of the Appendix - Details of Selected Research Highlights for more.

5

Researchers advanced the understanding of plant metabolism and soil structures with nuclear imaging methods at the Facility.

Dr Steven Siciliano (USask College of Agriculture and Bioresources) is using our facility to create new systems that help us better understand the inner workings of plants and soil. He and his team have developed new ways to purify and synthesize nuclear products made at our facility. These innovative advancements will help other researchers design more accurate experiments in the future. Dr Siciliano's work has already been used to study the arctic biocrust, and to assess mines for restoration. Applications of this work could be invaluable for environmental remediation and agricultural technologies.

See page 27 of the Appendix - Details of Selected Research Highlights for more.

Appendices

APPENDIX

Safety and Compliance Details

As noted before, safety is a top priority for everyone at the Fedoruk Centre. Here are some specific ways we keep everyone safe.

Safe by Design

The radioisotope laboratory is specially designed to let researchers work safely with nuclear substances. Specialists, whether staff or users, separate materials from the cyclotron targets and prepare them for use in radiopharmaceuticals or experiments. Much of the work with nuclear substances is done by our staff using remote arms inside lead-shielded chambers called "hot cells" or behind lead-shielded workstations to minimize their radiation exposure.

Radiation Protection Program

The Fedoruk Centre's radiation protection program guides all the safety protocols at the SCCS. The program includes an Occupational Health and Safety Committee that meets quarterly to discuss safety concerns, plan solutions and monitor protocols. They also conduct facility inspections twice a year.

In alignment with CNSC (Canadian Nuclear Safety Commission) regulations, the Fedoruk Centre maintains a Public Information and Disclosure Program to make sure that information about the Saskatchewan Centre for Cyclotron Sciences related to health, safety and security of the people and the environment is effectively communicated to the public.

The total radiation dose to staff and users is closely and constantly monitored. We make sure the levels are below the administrative limits established through the Radiation Protection Program. This is based on the ALARA (As Low As Reasonably Achievable) principle that the total radiation dose is well under regulatory limits for all Nuclear Energy Workers.

See Table 2 for details.

Table 2: SCCS Nuclear Energy Worker (NEW) Statistics by calendar year

Nuclear Energy Worker (NEW) Statistics			
Metric	**2019**	**2020**	**Regulatory Limit**
Number of Nuclear Energy Workers (NEW) Monitored at Facility	49	65	N/A
Maximum Effective Whole-Body Dose for an individual NEW in the calendar year (mSv)	2.04	1.10	50
Maximum Equivalent Extremity Dose for an individual NEW in the calendar year (mSv)	27.80	17.81	500

Type II Compliance Inspection

In August 2020, the Canadian Nuclear Safety Commission conducted a remote Type II compliance inspection. It focused on licensed activities associated with cyclotron operation, isotope production and nuclear handling and packaging. The inspection included discussions with staff and users, review of prescribed records and observations provided through photos, videos and live streaming of the facility and activities performed on a routine basis. The CNSC found the radiation safety program at the Fedoruk Centre to operate as expected and commented on the evident maturity of the program for a facility that has been operating for such a short time. Although non-compliances were found during the inspection, none would affect the overall effectiveness of the Radiation Protection Program.

License Amended

In November 2020, the CNSC Nuclear Substances and Radiation Devices (NSRD) License was amended to include the new laboratories in the Innovation Wing (IW) and the increase to the maximum permissible limits of certain radionuclides to align with the room classification levels.

Tungsten Pigs

In February 2021, the Fedoruk Centre purchased ten tungsten shielded containers, called "pigs" into which vials of radioactive liquids can be placed for safe handling and transportation. The use of high-density tungsten helps to reduce the radiation field by 25 – 44 percent, depending on the nuclear substance inside. This allows for larger shipments of FDG to out-of-province hospitals as it requires less material than lead to provide the same level of shielding. It guarantees minimum radiation exposure and aligns with ALARA goals in the workplace for staff and users when moving and storing nuclear substances at the facility.

Good Manufacturing Practices for Patient Safety

For radiopharmaceutical manufacturing, we are operating in compliance with Good Manufacturing Practices (GMPs), Quality Assurance (QA) and Quality Control (QC) policies and procedures (Quality Management System (QMS)) to align with regulations and current practices.

We have also developed Standard Operating Procedures (SOPs) to maintain compliance with all environmental and regulatory requirements associated with the operation of being a licensed drug establishment and Class II Nuclear Facility.

Functional Designation	→	Document Type	→	Document Number
e.g. PR		e.g. SOP, CA, MBR		e.g. 0002
e.g. **PR**-SOP-0002		e.g. PR-**SOP**-0002		e.g. PR-SOP-**0002**

Fig 2: Flow diagram from the SCCS document control Standard Operating Procedures (SOPs) part of the facility Quality Management System.

Good Pharmacovigilance Practices

In 2020, Health Canada conducted a Good Pharmacovigilance Practices audit and gave us a "C" rating. This grade confirms the establishment complies with the Food and Drugs Act and associated regulations with respect to Good Pharmacovigilance Practices.

Building Resilience

In September 2020, an additional Gas Chromatography (GC) system was qualified for GMP use. With this instrument, all major Quality Control equipment now has redundancy, ensuring resiliency for FDG delivery to regional hospitals.

Table 4 features the manufacturing and Quality Management System (QMS) indicators that are collected by calendar year for the overlapping reporting period.

Table 4: Cyclotron Facility Manufacturing and Quality Assurance (QA) Metrics

Manufacturing and QA Metrics (Calendar Year)		
Indicator	**2019**	**2020**
Total committed deliveries	348	310
Delivery success percentage	95.1%	99.0%
Total product complaints	3	0
Total Out-of-Specification Investigations	14	10

APPENDIX

Details of Selected Research Highlights

The following research project experiences have been offered by some of our users. We're happy to include them as examples of the important work made possible by our specialized facilities and staff.

Development of Nuclear Imaging Tools for Pre-clinical Evaluation of Lung Inflammation: Sequential PET-CT Imaging in the Swine and Murine Models

Dr. Gurpreet Aulakh
USask Assistant Professor and Fedoruk Chair on Veterinary Nuclear Imaging,
Western College of Veterinary Medicine

A spectrum of life-threating lung diseases impact veterinary and human patients of all age groups. Rising health care costs (>$12 billion/year) reflect the gap in our understanding of the lung inflammatory response and underscores the need to develop an efficient pre-clinical strategy for evaluation of specific lung inflammation diagnostics and therapeutics.

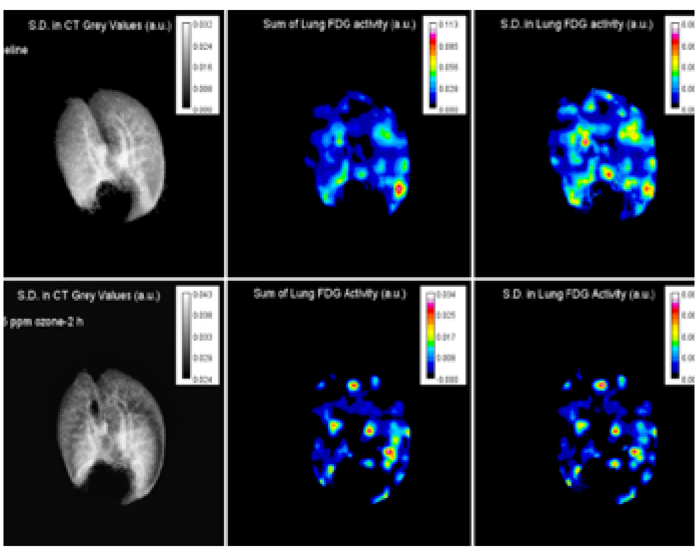

Fig 3: Murine Lung Micro PET-CT for the total lung (or SUM) and Standard Deviation (or S.D.) of FDG Activity before (at baseline), shown in the upper image panels and after acute (2 h) exposure to low-dose (0.05 ppm) ozone, shown in the lower image panels.

The long-term goal of our lab is to develop novel imaging tools and protocols for detection and/or mitigation of deleterious inflammatory response during lung diseases. Over the past four years, our lab has developed novel animal models of lung inflammation, nuclear imaging protocols and sensitive lung function read-outs (please refer to Figure 3).

Our team is utilizing their recently standardized combined ozone and LPS induced dual-hit model to understand the acute lung capillary leak, leukocyte recruitment (Gallium labelling), the lung metabolic status (FDG labelling) and endothelial surface complex V ATP synthase expression (Zirconium conjugated angiostatin), using sequential nuclear imaging in rodents (at Cyclotron Facility) and swines (WCVM PET-CT).

The project aims to bridge knowledge gaps in the field of lung inflammation research to build capacity for pre-clinical testing of future therapeutics in pigs. Second, the project will build upon and utilize the University of Saskatchewan's unique expertise and infrastructure for angiostatin radioisotope production and nuclear imaging to investigate lung inflammation. It is anticipated that the generated knowledge-base will create translatable knowledge for drug discovery researchers, radiochemists, practicing veterinary and human physicians, as well as patients.

Researchers:

Dr. Aulakh is the Fedoruk Chair in Human and Animal Imaging and an Assistant Professor at the Western College of Veterinary Medicine at the University of Saskatchewan. She is a lung pathobiologist, pharmacologist and imaging expert. She collaborates with Dr. Fonge, whose research program is focused on development of novel radiopharmaceuticals, Dr. Ambros, who is a board-certified veterinary anesthesiologist, and Dr. Jaswant Singh, who specializes in quantitative 3D analyses of confocal, ultrasound and computed tomography datasets.

Radioimmunotherapy as a novel approach to treatment of multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) affecting roughly 14.5 Canadians per 100,000 as of 2016. With one of the highest rates of MS in the world, an estimated 93,500 Canadians are affected. Furthermore, Saskatchewan has the highest incidence of MS among the Canadian provinces – 18.6 cases per 100,000 population (2). Currently, there are no effective treatments that can stop or reverse the damage done to the CNS by MS. Thus, finding principally new approaches for treatment of MS is relevant and urgent.

We proposed to selectively eliminate chronically stimulated immune cells implicated in experimental autoimmune encephalomyelitis (EAE), a relevant animal model of MS, using a targeted radioimmunotherapy (RIT) approach with anti-PD-1 antibodies armed with radionuclides. We hypothesized that by reducing the population of chronically stimulated T cells with RIT, EAE symptoms might be significantly reduced and disease progression slowed. We have put forward the following milestones:

1. To conjugate anti-PD-1 antibodies and fragments to DOTA chelating agent and using in vitro techniques, evaluate the preservation of their immunoreactivity towards PD-1.

Professor Ekaterina Dadachova
Fedoruk Chair in Radiopharmacy,
USask College of Pharmacy and Nutrition

2. To evaluate the ability of radiolabeled anti-PD-1 antibodies or fragments to ameliorate disease in EAE, a mouse model of MS.

3. To assess the safety of radiolabeled anti-PD-1 antibodies or fragments in vivo in the EAE mouse model.

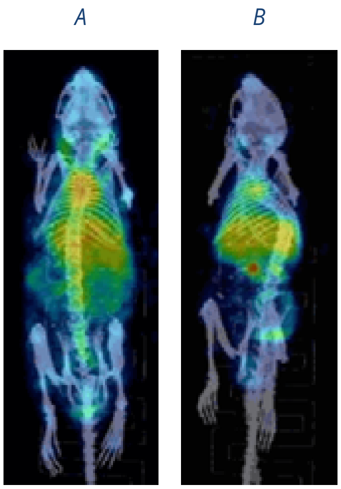

Fig 4: 1 microSPECT/CT images of C57Bl6 mice with EAE at 48 hrs after administration of:

A – 111in-labeled anti-PD-1 antibody;

B – 111In-labeled control antibody.

This project is carried out in partnership with the Office of the Saskatchewan Multiple Sclerosis Chair Professor Michael Levin, the Cameco Multiple Sclerosis Neuroscience Research Center and the Saskatoon City Hospital Foundation.

Since the beginning of the project in April 2021, we have already accomplished Milestone 1 by demonstrating that anti-PD-1 antibodies can be radiolabeled with 225Actinium and 177Lutetium radionuclides without loss of immunoreactivity for PD-1 and they are stable in human serum for several days. We have also just completed Milestone 3 by evaluating several doses of 225Ac-labeled anti-PD-1 antibodies in mice with EAE and showing that these doses do not produce systemic toxicity in mice.

As part of Milestone 3, we also imaged the mice with EAE with microSPECT/CT (Fig.4) and observed different uptake of the anti-PD-1 antibody (Fig.4A) and control antibody (Fig.4B) in the thoracic area, lymph nodes and the brain, which attests to the specificity of anti-PD-1 antibody in EAE model. The work on Milestone 2 is currently ongoing.

We expect the results of this project to demonstrate the great potential of RIT to treat MS, so this approach could be used in the future in the Canadian population in general, and in people of Saskatchewan in particular. Performance of this project allows us to train HQPs in radiolabeling, radioimmunotherapy, neuroscience, nuclear imaging, and toxicity evaluation. Such expertise is sought after in pharmaceutical research in academic, industrial and government laboratories and will contribute to the future professional employment of the trainees.

Researchers:

Dr. Ekaterina Dadachova is a Professor and Fedoruk Chair in Radiopharmacy, Department of Pharmacy and Nutrition, University of Saskatchewan. Dr. Michael Levin, MD who is the Saskatchewan Multiple Sclerosis Clinical Research Chair at the University of Saskatchewan is Dr. Dadachova's Co-PI on this project.

Dr. Eric Price
USask Assistant Professor and Canada Research Chair in Radiochemistry

Using Clever Chemistry to Enhance Radioactive Drugs for Imaging and Treatment of Cancer

Dr. Price has a strong interest in using chemistry to solve pressing issues in animal and human health by making new molecular imaging and radiotherapy drugs that can be used to improve the detection, staging, and treatment of a range of diseases such as cancer and severe bacterial infections. His growing multidisciplinary research program is creating new chemical tools and improving existing chemical methods to advance molecular imaging and radionuclide therapy. One of their most promising projects (partially funded by the Fedoruk Centre) is seeking to use clever chemistry to trick the human body into metabolizing radiopharmaceuticals in a more favorable way.

The Price Lab has invented and synthesized a new molecule that can be chemically inserted into many different peptide-based radiopharmaceuticals. Essentially, they have created a new amino acid that can be seamlessly inserted into peptides to modify their chemical structures and their physical properties. The goal of these peptide modifications is to reduce uptake and retention in the kidneys and other healthy tissues, which is a known limitation of many peptide-based radiopharmaceuticals.

After several years of intense research efforts in the chemistry and radiochemistry labs, the team feels they are very close to a big breakthrough. Pictured below are Shvan Raheem and Moralba Dominguez Garcia, who are trainees of Dr. Price performing preclinical experiments to demonstrate the effectiveness of these new molecules. Recent results have been very promising, and the team is preparing to submit a patent filing and a scientific manuscript for peer-reviewed publication. If successful, this

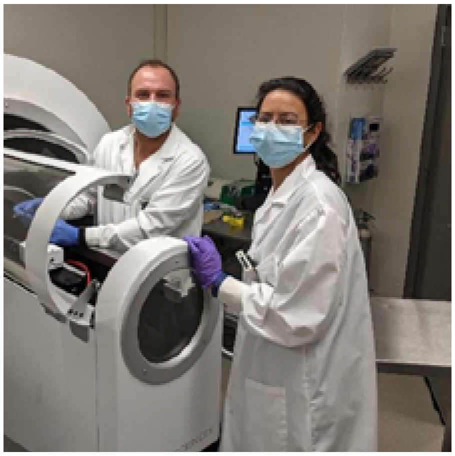

Fig 5: Shvan Raheem and Moralba Dominguez Garcia—members of Dr. Price's team.

new chemical technology could be applied to next-generation radiopharmaceuticals to help detect and treat a variety of cancers here in Saskatoon at the Royal University Hospital, and potentially worldwide.

The team is grateful for the SCCS and funding support from the Sylvia Fedoruk Canadian Centre for Nuclear Innovation.

Researchers:

The Price Lab is based out of the University of Saskatchewan's Chemistry Department, but heavily utilizes the cyclotron and radiochemistry labs at the Saskatchewan Centre for Cyclotron Sciences (SCCS). The team is led by Dr. Eric Price, an Assistant Professor of Chemistry and a Canada Research Chair in Radiochemistry at the University of Saskatchewan in the Chemistry department (College of Arts and Sciences).

Dr Steven Siciliano
USask Professor,
NSERC/FCL Industrial Research Chair in In Situ Remediation and Risk Assessment

Director, CREATE Human and Ecological Risk Assessment Program

An Undisrupted View: Proofing and Applications of Radioactive Gas Production

Carbon and nitrogen play vital roles within many systems, from the cycling and storage of nutrients and pollutants in our biological ecosystems to the metabolism of various organic molecules within our own bodies. Positron emission tomography (PET) imaging offers a non-invasive means to learn how target compounds are incorporated into biological systems, what factors regulate the compound's uptake and utilization, and who in the system is using it.

In our lab, these questions are shaped by our multidisciplinary interests in agriculture, soil science and plant biology. Some of these questions include what microbial or plant species are actively fixing the radioactive carbon and nitrogen tracers, how the fixed compounds are being used by the active plant or microbial species within the sample and how active microbial fixers respond to different soil remediation treatments. As such, we have built a new automated purification/ synthesis system to purify gaseous radioactive products such as [^{11}C]C-carbon dioxide and [^{13}N]N-nitrogen produced by the Sylvia Fedoruk Canadian Centre for Nuclear Innovation as well as synthesize [^{11}C]C-methane.

Our goal in proofing out the automated system's gaseous product purification is to dose soil and plant samples with the purified radioactive tracers, locating where and to what degree the tracers are being fixed within the samples. Pinpointing these regions of interest will allow researchers to tailor their experiments when answering specific questions about the samples and improve our understandings of agricultural and soil remediation techniques.

To date, we have proofed our homemade radio-purification and synthesis system's ability to purify [^{11}C]C-carbon dioxide and [^{13}N]N-nitrogen from crude radioisotope production runs with over 99% product purity. These purified tracers have since been applied in preliminary studies of artic biocrusts and will be used to assess mine closure site restoration and improved suitability of these sites for primary plant colonizers in the near future. [^{11}C]C-methane was successfully synthesized in high purity (>99%) with current efforts geared towards applying the radiotracer as a means of assessing the methanogenic and methanotropic communities involved in the biodegradation of hydrocarbons. What's more, the newly synthesized [^{11}C]C-methane will serve as an intermediate in the synthesis of [^{11}C]C-methylating agents and allow us to make a wider range of tracer molecules for PET imaging.

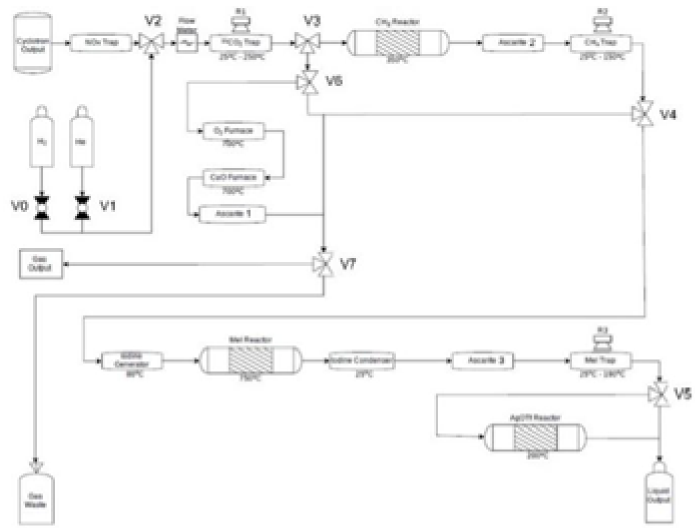

Fig 6: Schematic Diagram of 11C Purification/ Synthesis System biocrust work.

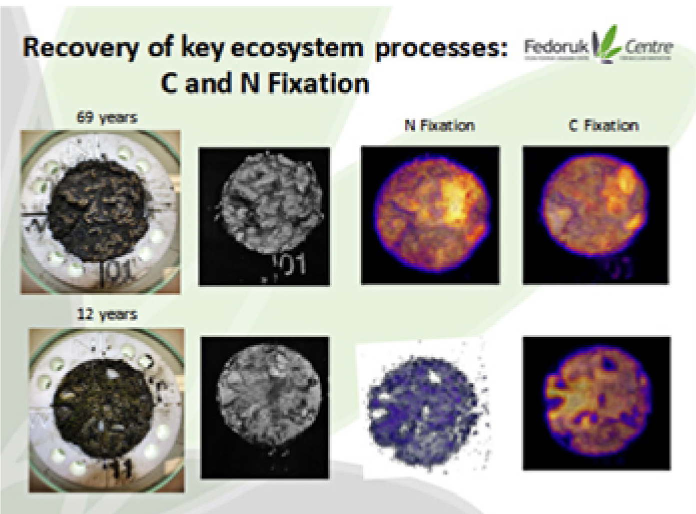

Fig 7: Summary images capturing the arctic biocrust work presented at NuclearFACTS 2021.

Researchers:

Dr. Steven Siciliano is a Professor in the College of Agriculture and Bioresources at the University of Saskatchewan and is the NSERC/FCL Industrial Research Chair in In Situ Remediation and Risk Assessment. He is also a Director of the CREATE Human and Ecological Risk Assessment Program. The research collaborators include Dr. Katherine Stewart, Associate Professor, Department of Soil Science, College of Agriculture and Bioresources, USask; Dr. Eric Lamb, Associate Professor, Department of Plant Science, College of Agriculture and Bioresources, USask; and former PDF at USask Dr. Michael Schmidt, Research Soil Scientist, USDA.

APPENDIX

Timeline of the SCCS

2013 – Construction Begins

The Fedoruk Centre accepted responsibility for operating the cyclotron and its associated nuclear-substances laboratories, compliant with Canadian Nuclear Safety Commission (CNSC) and Health Canada regulations.

2014-2015 – Establishing Operation and an Initial Program

In 2014, the University of Saskatchewan (USask) and the University of Regina submitted a proposal to the Fedoruk Centre to consider an investment to create a Saskatchewan-based interdisciplinary program for nuclear imaging.

In 2015, the University of Saskatchewan, University of Regina, and Fedoruk Centre established the Nuclear Imaging Program (NIP) through a tri-party agreement. The program built upon existing research and development capabilities in medical and life sciences. The program aimed to increase Saskatchewan's capacity in nuclear imaging tools and techniques, with applications to life sciences in plants, animals and humans.

The Fedoruk Centre invested $5.2 million of funding over five years to the NIP, establishing three Research Chairs, a clinical research coordinator position, and equipment for the then-new cyclotron facility for the safe conduct of radiochemistry research and nuclear imaging of small animals. The universities made additional cash and in-kind contributions valued at $3.7M.

2016 – FDG Production Begins

In June 2016, the Cyclotron Facility completed the cyclotron commissioning and began manufacturing the radiopharmaceutical fluorodeoxyglucose (FDG) for sale to regional hospitals for use in PET scanning. A quality program was also established to comply with radiological and health regulators. Since then, FDG manufacturing has quickly ramped up to support PET/CT scanning at RUH. By 2020-2021, more than 2400 Saskatchewan patients each year have been scanned using locally-produced imaging agents to diagnose and treat cancer.

2018 – Developing the Cyclotron Facility Innovation Wing

In 2018, the University of Saskatchewan and the Fedoruk Centre agreed that the Fedoruk Centre would assume responsibility for the Innovation Wing. Management of the entire facility, including the cyclotron, nuclear substance laboratories, GMP manufacturing area and laboratories for nuclear imaging, research and innovation in life sciences is now delivered under the license and authority of a single operator, the Fedoruk Centre.

Besides simplifying compliance with CNSC and Health Canada licenses, this adjustment also opened the door for funding from Innovation Saskatchewan, Western Economic Diversification and the Fedoruk Centre to jointly support a $4.2 million project to renovate and equip the Innovation Wing. The renovation added laboratories suited for nuclear imaging, radiochemistry and housing of living specimens, and fully equipped the space to accommodate the facility's growing number of users and their diverse needs. The renovation project was completed by March of 2020.

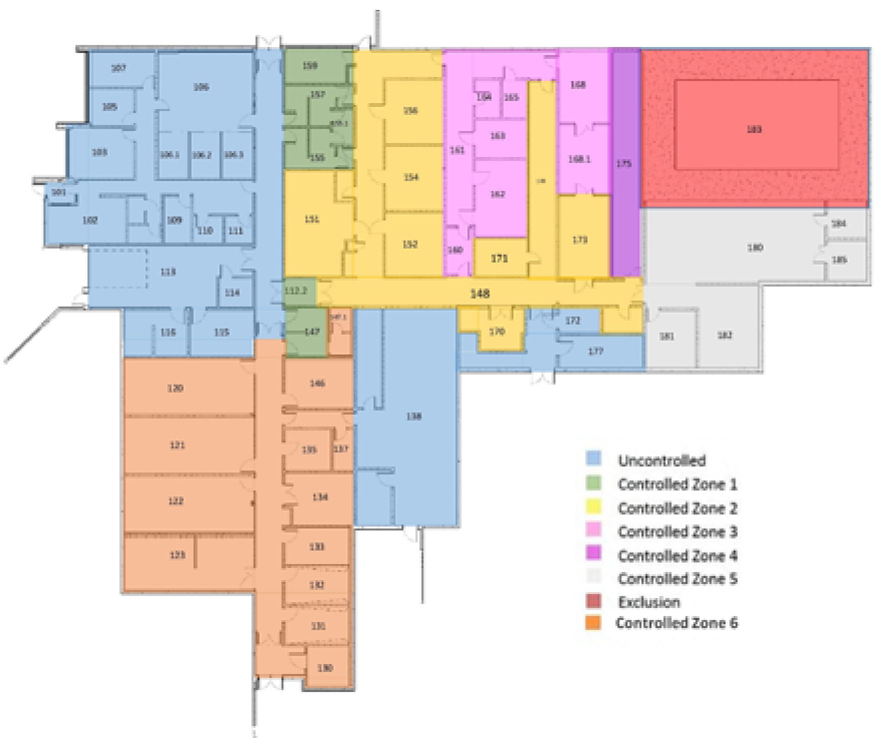

Fig 8: Cyclotron Facility floorplan showing the Innovation Wing as Controlled Zone 6.

2020-Today – Facilitating Research Programs and Projects

The Fedoruk Centre funds research projects led by Saskatchewan-based scientists in nuclear subject areas. Some of these research projects benefit from access to the workstations at the SCCS. Although the funding phase of the NIP Agreement concluded at the end of June 2020, program achievements endure and include:

- Establishing researchers continuing to develop new knowledge and know-how of nuclear imaging applicable to the diagnosis and treatment of a multitude of diseases such as neurological disorders and cancers in humans and animals.

- Attracting researchers to develop highly innovative plant research, targeting the eventual development of crops with superior productivity in the face of increased stress from climate change.

- Creating a cluster of researchers sharing a top-quality scientific resource and generating outcomes that attract more users and new collaborations, ever broadening and deepening the social and economic impacts of nuclear medicine, molecular imaging and isotope production.

- Completing the tool-kit at the cyclotron facility to ensure reliability of production and adding new products to the portfolio of isotopes, radiochemicals and radiopharmaceuticals for research and applications in healthcare.

- Strengthening Saskatchewan's capacity for respectful conversations about nuclear science and technology, including the benefits of nuclear imaging tools and applications in health and global food security.

Publications

PUBLICATIONS

By accessing the SCCS, researchers published the following in 2020.

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