Saskatchewan Cyclotron Facility

Activity & Achievement Report

April 2021 - March 2022

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Fedoruk Centre
SYLVIA FEDORUK CANADIAN CENTRE FOR NUCLEAR INNOVATION

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OPENING REMARKS

Message from the Chair

Tom Kishchuk,
Chair of the Fedoruk Centre Board of Directors

The Sylvia Fedoruk Canadian Centre for Nuclear Innovation operates the Saskatchewan Cyclotron Facility as a first-class scientific resource, making it accessible for researchers to advance life sciences with nuclear imaging methods. We are supporting growth of a multidisciplinary community of experts in our province, enabling Saskatchewan people to generate, interpret and apply knowledge from nuclear imaging for social and economic benefits.

Despite the challenges of the lingering COVID-19 pandemic, we made good progress in building nuclear research and innovation capacity in Saskatchewan. We delivered even more of the nuclear imaging agent, FDG, to Royal University Hospital than in the previous year, enabling diagnoses and treatment of more than 2,500 patients.

The Board of Directors is proud of the achievements of the Facility team and the accomplishments of the Saskatchewan research community they are supporting.

Message from the Facility General Manager

Dale Schick-Martin,

Saskatchewan Cyclotron Facility General Manager

Six years after initial commissioning, the Saskatchewan Cyclotron Facility has transitioned from an initial start-up phase into a resilient continuous operation. The number of agreements for user access almost doubled from 21 in March 2021 to 43 by March 2022 (including two private-sector clients). During the reporting period, there were three master supply agreements for delivery of FDG to hospitals in Saskatchewan, Alberta and Manitoba, plus one for the Western College of Veterinary Medicine. The Facility also manufactured radioisotope and radiochemical products for researchers, including FDG, $^{11}CO2$ and ^{89}Zr-oxalate. Other isotopes received and handled safely for researchers under the Facility license included ^{67}Cu, ^{99}Mo, ^{68}Ga and ^{225}Ac.

Facility workstations offer a wide range of specialized equipment, all accessible through user-access agreements. The Facility introduced a practice to introduce new users to the operation of specialized equipment at no charge to individual projects.

Many thanks to the Fedoruk Centre team, whose enthusiasm and cohesion are helping to build a reputation for the Saskatchewan Cyclotron Facility as a client-focused resource accessible to researchers across academia and industry.

The Saskatchewan Cyclotron Facility is Saskatchewan's sole producer of FDG (fluorodeoxyglucose), a radiopharmaceutical used in nuclear imaging to detect cancer.

INTRODUCTION

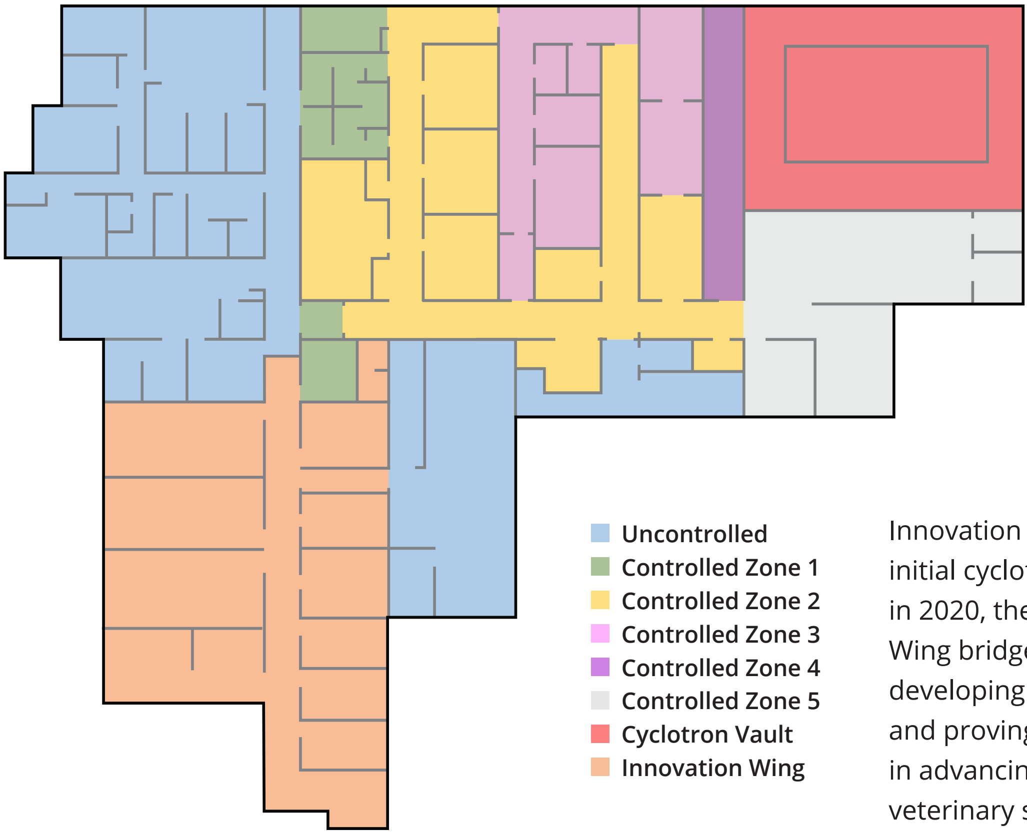
Facility Basics

The Sylvia Fedoruk Canadian Centre for Nuclear Innovation, Inc. (Fedoruk Centre) was established in 2011 to help place Saskatchewan among global leaders of nuclear research, development and training. The Fedoruk Centre invests in partnerships with academia and industry, funds research projects led by Saskatchewan scientists, partners with Saskatchewan institutions to establish new faculty in nuclear subject areas and operates the Saskatchewan Cyclotron Facility (the Facility). The Facility is owned by the University of Saskatchewan (USask) and operated under an Operating License Agreement with the University of Saskatchewan. Located at 120 Maintenance Road on campus, the Facility features a 24MeV cyclotron, hot cells, facilities to manufacture Health Canada-compliant radiopharmaceuticals, radiochemical research laboratories, facilities to host living specimens, and PET/CT scanners for nuclear imaging to advance life sciences and preclinical studies.

Timeline from Construction to Operation

With capital contributions from Western Economic Diversification Canada (WD), Innovation Saskatchewan (IS) and the Fedoruk Centre, the initial cyclotron and nuclear-substances laboratories were commissioned in 2014. In 2016, the Facility was licensed to manufacture the nuclear imaging agent FDG for PET/CT scanning of human patients. In 2018, funding from WD, IS and the Fedoruk Centre was used to renovate and equip the Innovation Wing attached to the initial cyclotron facility. Completed in 2020, the renovated Innovation Wing bridges the gap between developing nuclear imaging drugs and proving their effectiveness in advancing human medicine, veterinary science and agriculture.

Figure 1 - Floor plan of the Saskatchewan Cyclotron Facility



SAFETY

Licensing and Compliance

The Facility includes a TR24 cyclotron, labs for the safe handling of nuclear substances, equipment to manufacture and qualify radiopharmaceuticals for clinical applications in humans, and capacity to hold living specimens for preclinical research and other life sciences. These activities are regulated by the Canadian Nuclear Safety Commission (CNSC), Health Canada (HC), Public Health Agency of Canada (PHAC) and the University of Saskatchewan.

Key licenses and permits include:

- CNSC Class II Facility and prescribed equipment License
- CNSC Nuclear Substances and Radiation Devices (NSRD) License
- HC Drug Establishment License (DEL)
- PHAC Pathogen and Toxin License
- USask Biosafety Permit

In April 2021, the CNSC renewed the Fedoruk Centre's Class II Nuclear Facilities and Prescribed Equipment (Class II) Licence. This licence authorizes operation of the cyclotron and processing of nuclear substances. It is valid for a ten-year period. In November 2021, we were granted a Pathogen and Toxin License from the Public Health Agency of Canada, which allows the Facility to import, handle, store and dispose of Risk Group 2 materials.

Fedoruk Centre professional and technical staff work together to ensure compliance with all permits as well as the Canada Labour Code and Canadian Council on Animal Care guidelines.

In 2021, the Canadian Nuclear Safety Commission renewed the Fedoruk Centre's licence for another 10 years.

Radiation Safety and Training

The safety of our employees, users and community is paramount in everything we do. Work with nuclear substances requires stringent safety measures and compliance with specific rules and regulations. Our radiation protection program guides all safety protocols at the Facility. This includes biannual Facility inspections and an Occupational Health and Safety Committee that meets quarterly.

Staff and users are trained and qualified as Nuclear Energy Workers (NEWs). Everyone is expected to conduct their work in a manner that ensures radiation exposures are below administrative limits established by the Radiation Protection Program, respecting the principle of ALARA (As Low As Reasonably Achievable) and well under CNSC regulatory limits for NEWs.

Table 1 - Nuclear Energy Worker (NEW) Statistics

Metric	2019	2020	2021	Regulatory Limit
Number of individuals newly trained and qualified as Nuclear Energy Workers (NEWs)		23	14	
Number of NEWs monitored at the Facility	49	65	45	N/A
Maximum Effective Whole-Body Dose for an individual NEW in the calendar year (mSv)	2.04	1.10	1.65	50
Maximum Equivalent Extremity Dose for an individual NEW in the calendar year (mSv)	27.80	17.81	40.44	500

Figure 3 - Fedoruk Centre operations and production technologists ensure the Facility is maintained in a state of readiness for user access

Production of FDG and Other Isotopes

The Facility manufactures the nuclear imaging agent fluorodeoxyglucose (FDG) for daily delivery to the PET/CT scanner at Royal University Hospital (RUH) in Saskatoon. Production typically begins at 4:00 a.m. each morning with proton-irradiation of an ^{18}O-enriched water target to generate the positron-emitting isotope ^{18}F. This is followed by chemical processing and testing for quality control. FDG is delivered to RUH by 8:00 a.m. for use in patient diagnoses.

In 2021-2022, the Facility team delivered 236 FDG batches to RUH. This included 23 extra-delivery days to reduce the PET scan patient waitlist. The Facility also provided 47 deliveries of FDG to the Western College of Veterinary Medicine and 34 batches of FDG to hospitals in Alberta and Manitoba.

Additional radioisotopes produced at the Facility for researchers included Carbon-11, Nitrogen-13, Fluorine-18, Copper-64 and Zirconium-89. A multi-year comparison of isotope production for research (Table 2) reflects curtailed user access during the COVID-19 pandemic through 2020 and into 2021. While 2021 production appears slightly lower than the 2019 benchmark, the first few months of the year continued to be severely impacted by the pandemic. The latter part of the year, however, nearly made up for the deficit, suggesting growing demand to work with isotopes produced by the Facility.

Number of PET-CT scans at RUH

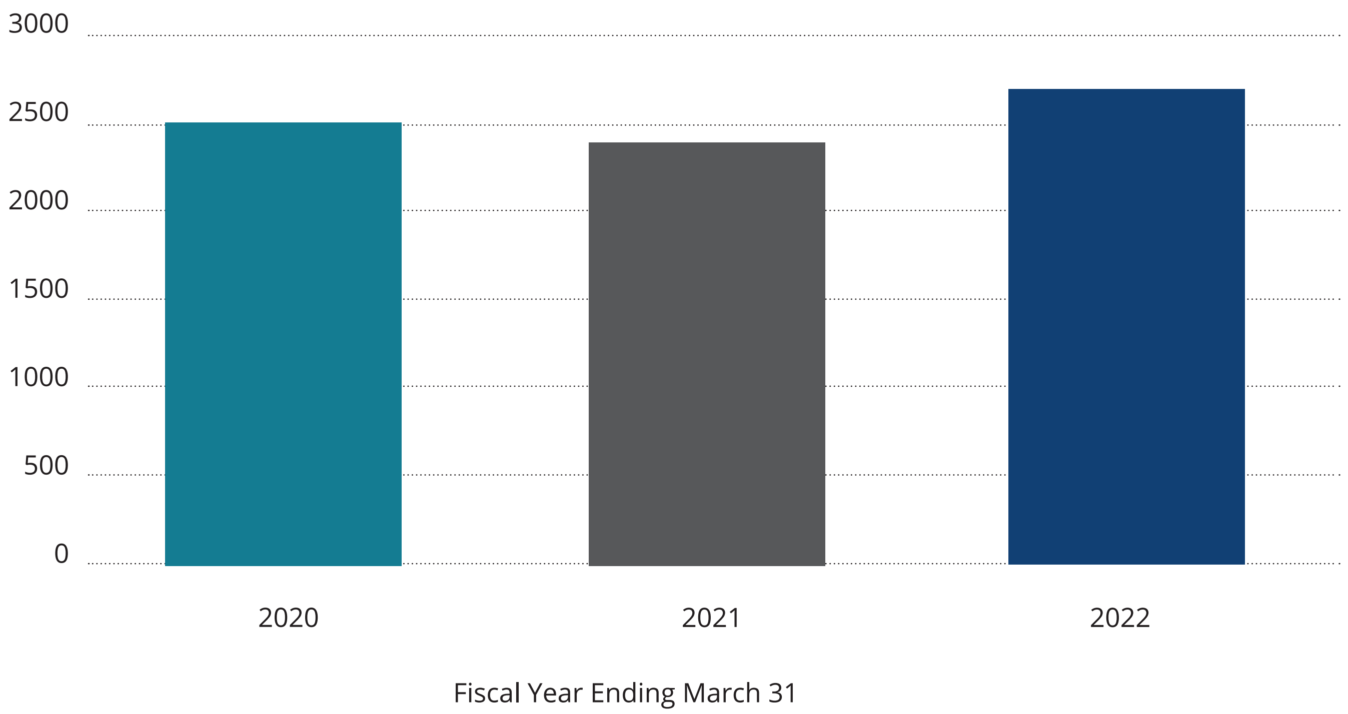


Figure 4 – Number of patient PET/CT scans at RUH with FDG produced by the Facility

Table 2 – Number of Isotope Batches Produced at the Facility for Researchers

Isotope	Calendar Year		
	2019	2020	2021
^{11}C	45	25	41
^{13}N	0	0	3
^{18}F	101	42	83
^{64}Cu	12	10	0
^{89}Zr	28	31	29
^{68}Ga	0	0	3

Several other isotopes were received and handled safely for researchers under the Facility license, including Copper-67, Molybdenum-99, Gallium-68, Indium-111, Lutetium-177 and Actinium-225.

CAPABILITY AND PERFORMANCE

Infrastructure Upgrades

In April 2021, an Ortec gamma spectrometer was installed and commissioned to identify radionuclides and evaluate purity.

An automated solid target transfer system from ARTMS Inc. was installed and commissioned during the reporting period. This QUANTM Irradiation System™ allows high-activity solid targets to be retrieved from the cyclotron vault without exposing staff.

The storage space for decay of radioactive waste was renovated to add shielding, capacity and improvements.

Products

The Facility has produced the isotope ^{89}Zr and supplied it to users sporadically for over two years.

This capability has allowed the Fedoruk Centre to participate in a Collaborative Research Project with the International Atomic Energy Agency, and work with leading ^{89}Zr producers from around the world. In September 2021, method developments increased the yield from 1-2 GBq to the range of 3-3.5 GBq per production run.

Trends

Operational performance indicators are used to reveal trends in demand for user access, success in maintaining a state of readiness for access, and reliability of equipment, including the cyclotron itself. Production days can be lost by an outage of the cyclotron or other Facility outage . The COVID-19 pandemic strongly curtailed user access, leading to a disruption of academic and industrial research and development activities. This persisted through 2020 and into 2021.

Table 3 – Trends in Facility Performance Indicators

Performance Indicator	Fiscal Year Ending March 31		
	2020	2021	2022
Workstation availability – ready for user access (percentage of total time)	90.3%	95.8%	97.0%
Workstation occupancy by users (percentage of available time)	36.1%	14.7%	15.3%
Unplanned outages of cyclotron (days)	9	4	5
Unplanned outages of Facility production (days)	9	5	6

Figure 5 - Fedoruk Centre Operations Technologist at cyclotron power system.

USER INNOVATIONS

User Access

The Fedoruk Centre offers researchers and students from academia and industry access to Facility workstations to advance their programs of innovation in nuclear imaging, therapies or life sciences. Workstation access is arranged through our website **https://fedorukcentre.ca/our-offering/cyclotron-lab-services.php**

The Fedoruk Centre and USask signed 13 new agreements for academic user access in 2021-2022 and three user access agreements with industry clients for proprietary research. Actual Facility access enabled 10 individual research leaders and their teams to occupy Facility workstations for about 10,000 hours in total.

Trends of user access to the Facility to advance their research programs are revealed in Table 4. During the reporting period, six individuals accessed the Facility for other purposes, such as tours or training.

Figure 6 – Fedoruk Centre Research Officer operating a micro-PET/CT scanner for preclinical imaging.

Table 4 – Users Accessing the Facility to Perform Research

User Type	Fiscal Year Ending March 31		
	2020	2021	2022
Industry Researchers	5	3	6
Faculty Researchers	10	4	3
Post-doctoral Research Associates	20	10	14
Graduate Students	18	11	18

User-Driven Research

The table below highlights public domain research led by USask scientists with support from the Facility in 2021-2022.

Table 5 – Examples of research led by USask scientists during the reporting period

Project Title or Description	Project Leader
Effects of Space Radiation (exposure of mice to ionizing radiation)	Dadachova
Production of ^{68}Ga-PSMA (relates to prostate cancer)	Fonge
Radiolabelled Imaging Agents for Cancer in Mice	Fonge
PET Imaging Pancreatic Cancer	Price
Multi-Centre Development of Radionuclides	Price
Detecting Responses to Anti-cancer Therapies	Geyer
3’-^{18}F-ABA: a PET Probe to Image ABA Transport in Plants	Phenix
General Proofing of a System to Separate ^{11}C for Plant Imaging	Siciliano
Wheat and Lentil Root Carbon Allocation in Soils	Lamb
^{225}Ac and ^{67}Cu for Cancer Theranostics	Fonge
Radioimmunotherapy for Cancer and Multiple Sclerosis	Dadachova
Imaging Carbon and Nitrogen Fixation by Biological Soil Crusts	Stewart
Radiosynthesis Targeting Alphasynuclein (Parkinson’s Disease)	Krol
Commercialize New Imaging Agents with Zirconium-89 NimotuzumAb	Geyer
Nitrogen fixation and Root System Carbon Allocation	Lamb
Synthesis of Carbon-11 Toluene	Siciliano

USER HIGHLIGHTS

University of Saskatchewan Professor Ron Geyer

Molecular Imaging Research for Clinical Applications

The Centre for Biologic Imaging Research and Development (C-BIRD) was established at the University of Saskatchewan to translate laboratory findings in molecular imaging and radio-immunotherapy into clinical research. C-BIRD's core competencies create a vertically integrated structure that enables the development and translation of imaging probes and therapeutics from pre-clinical to human clinical trials under "one roof."

C-BIRD has engineered an antibody, which recognizes the cancer-specific marker epidermal growth factor receptor (EGFR), to develop a ^{89}Zr-nimotuzumab conjugate for positron emission tomography (PET) to non-invasively image lung and colorectal cancers, as well as the infrared IRDYE800CW-nimotuzumab conjugate for precise lung tumor resection during image-guided surgery.

The ^{89}Zr-nimotuzumab antibody imaging probe will allow for effective therapy planning by enabling non-invasive visual diagnosis and molecular characterization of tumors to differentiate sub-types of cancers and track their response to therapy in real-time. It will also enable patient stratification by identifying those who could benefit from molecular-targeted therapies.

The infrared IRDYE800CW-nimotuzumab imaging probe binds to the EGFR tumour marker to define the tumor and its borders through fluorescence in real time, allowing surgeons to accurately resect the tumor and significantly reduce cancer recurrence. During the clinical trial, IRDYE800CW-nimotuzumab imaging drug proved successful in illuminating the tumor and differentiating it from the surrounding benign tissue.

"The development and success we have achieved with the imaging probes would not have been possible had it not been for the core competencies and expertise at the Fedoruk Centre. We have worked collaboratively with Fedoruk Centre staff to produce ^{89}Zr for routine production and for our clinical trial. Their good manufacturing facilities were imperative in the manufacture of both imaging drugs," said USask Professor Ron Geyer.

"We look forward to further collaborating with the Fedoruk Centre to advance these imaging drugs to the next regulatory phase. We are also hoping to work with the Fedoruk Centre on a new phase II clinical trial for an Alzheimer's disease therapeutic and to facilitate the production of an imaging drug to implement Alzheimer's disease PET diagnostics in Saskatchewan."

COMMERCIAL SUPPLY OF COPPER-67 FOR RESEARCH AND THERAPY

Canadian Isotope Innovations Corp. (CIIC) is a Saskatoon-based start-up that is pioneering the production of medical isotopes with electron accelerators. Over the past several years, CIIC has developed a new method for making Copper-67 (^{67}Cu), an isotope many researchers need for the development of new cancer therapies. CIIC uses an accelerator at the Canadian Light Source and the hot-cell processing facilities at the Saskatchewan Cyclotron Facility in its novel production process.

In 2021-22, CIIC became one of only two global commercial suppliers of ^{67}Cu for research and therapy, with sales to Canada, the US and Europe. CIIC is continuing to explore other isotope production options with electron accelerators through access to the specialized capabilities of the Facility.

Dr. Mark DeJong, Chief Technology Officer of Canadian Isotope Innovations Corp.

Figure 7 – Technician from Canadian Isotope Innovations Corp. at a Facility workstation.

University of Saskatchewan Professor Chris Fenix

Distribution of Abscisic Acid (ABA) in Living Plants

The diverse research group of USask Professor Chris Phenix includes students and staff with expertise in chemistry, biochemistry and molecular imaging, all focus on developing new chemical tools to study biological processes in plants, animals and humans.

One of their most interesting and potentially impactful projects resulted in a new radiotracer for imaging the distribution of abscisic acid (ABA) in plants. ABA is a plant hormone that plays a central role in regulating growth and development, while also enabling plants to tolerate environmental stressors such as drought, frost and infection. Emerging evidence has also established ABA as a key signalling molecule in humans. It is currently under investigation for treating diabetes, obesity and other diseases of the immune system.

Despite intense scientific interest in ABA's role in plant biochemistry over the past 50 years, the distribution and transport of ABA in various crops (such as canola) is not well understood. To address this gap, Dr. Phenix and his collaborative research team have developed ^{18}F-ABA, a powerful new radiotracer capable of imaging ABA flow in living plants. Industry and academic partners are interested in employing ^{18}F-ABA to develop smarter crops with enhanced drought tolerance as well as to guide the design of next-generation agrochemicals to improve crop performance.

"In 2021-2022, our team validated ^{18}F-ABA as a radiotracer that accurately reflects ABA transport and metabolism in canola. We also uncovered a possible new way to utilize ABA to treat metabolic disorders in humans," said USask Professor Chris Phenix.

Figure 9 – Professor Phenix showing research associate Morshed Chowdhury how to use the Facility tele-manipulators for remote handling of radiopharmaceuticals.

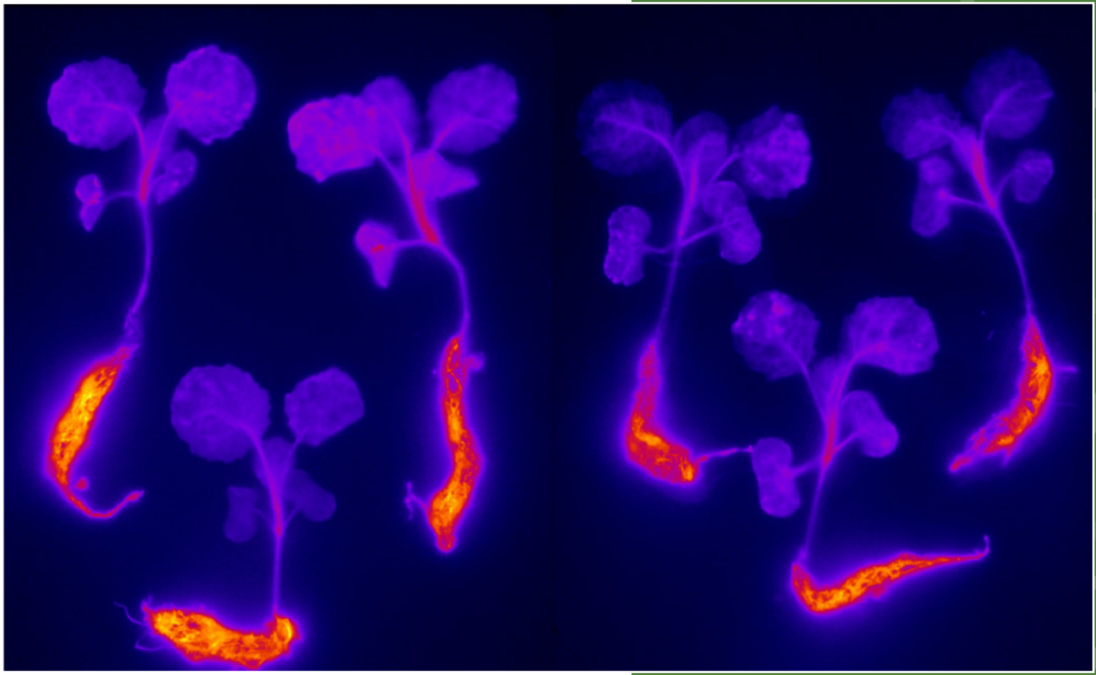


Figure 8 – The transport of ABA from roots to shoots in canola plants under well-watered conditions (left) vs. drought conditions (right).

The project is made possible by routine access to the cutting-edge isotope production facilities, radiochemistry equipment and imaging suites located at the Saskatchewan Cyclotron Facility.

Next steps are to optimize PET imaging methods and develop improved image data analysis to enable quantitative measurements of ABA transport rates in different canola cultivars under environmental stressors like drought. Such information could then be applied to identify specific plant genetics with improved drought tolerance and to identify next-generation agrochemicals to optimize ABA biochemistry for improved drought tolerance. In parallel, we will continue to investigate how ^{18}F-ABA can help inform new treatments for metabolic disorders in humans.

The Facility is quickly emerging as a world-class resource enabling USask researchers to develop “made in Saskatchewan” next-generation radiopharmaceuticals with significant potential to impact crop, animal and human health sciences.


FASTlab

PUBLICATIONS ARISING FROM FACILITY ACCESS (2021)

1. Aulakh GK, Maltare S, Khanh LNP, Singh B.
   CD34 Protein is Expressed in Murine, Canine, and Porcine Lungs
   Can J Vet Res. 2021: **85**(3): 161-169 (2021)
   PMID: 34248259

2. Aulakh GK, Maltare S, Singh B.
   Lack of CD34 Delays Bacterial Endotoxin-induced Lung Inflammation
   Respir Res. 2021: **22**:69 (2021) DOI: 10.1186/s12931-021-01667-2

3. Bernhard W, Barreto K, El-Sayed A, Gonzalez C, Viswas RS, Toledo D, Casaco A, DeCoteau J, Fonge H, Geyer CR
   Pre-clinical Study of IRDye800CW-nimotuzumab Formulation, Stability, Pharmacokinetics, and Safety
   BMC Cancer 21(1): 270 (2021) DOI: 10.1186/s12885-021-08003-3

4. Bocking T, Johnson L, Singh A, Desai A, Aulakh GK, Singh B.
   Research Article Expression of Surfactant Protein-A and D, and CD9 in Lungs of 1 and 30 Day Old Foals
   BMC Vet Res. 17(1): 236 (2021) DOI: 10.1186/s12917-021-02943-5

5. Broqueza J, Prabaharan CB, Andrahennadi S, Allen KJH, Dickinson R, MacDonald-Dickinson V, Dadachova E, Uppalapati M.
   Novel Human Antibodies to Insulin Growth Factor 2 Receptor (IGF2R) for Radioimmunoimaging and Therapy of Canine and Human Osteosarcoma.
   Cancers (Basel). **13**(9): 2208 (2021)

6. Broqueza J, Prabaharan CB, Allen KJH, Jiao R, Fisher DR, Dickinson R, MacDonald-Dickinson V, Uppalapati M, and Dadachova E
   Targeting IGF2R on Canine-Patient-Derived Osteosarcoma Tumors in Mice and Radiation Dosimetry in Canine and Pediatric Models
   Radioimmunotherapy Pharmaceuticals 15(1): 10 (2021) DOI: 10.3390/ph15010010

7. Dadachova E.
   Melanin - Protecting and Enhancing the Earliest Life on Earth: Comment on "Insoluble organic matter in chondrites: Archetypal melanin-like PAH-based multifunctionality at the origin of life?" by Marco d'Ischia et al.
   Phys Life Rev. **38**: 127-128 (2021) DOI: 10.1016/j.plrev.2021.05.006

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   Overcoming Drug Resistance in Osteosarcoma and Pancreatic Adenocarcinoma with Radioimmunotherapy
   In: A. FREYWALD AND F. J. VIZEACOUMAR (Eds.) Biological Mechanisms and the Advancing Approaches to Overcoming Cancer Drug Resistance. V. 12. Academic Press: 261-271 (2021)

9. Dadachova E.
   Potential Use of Radiolabeled Antibodies for Imaging and Treatment of COVID-19
   J Nucl Med. **62**(7): 1020 (2021)

10. Duda JAB, Kaur M, Aulakh GK
    Visualizing Lung Cellular Adaptations during Combined Ozone and LPS Induced Murine Acute Lung Injury
    J Vis Exp. 169 (2021) DOI: 10.3791/62097

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 ^{225}Ac-labeled CD33-targeting Antibody Reverses Resistance to Bcl-2 Inhibitor Venetoclax in Acute Myeloid Leukemia Models
 Cancer Medicine 10:1128–1140 (2021).
 https://doi.org/10.1002/cam4.3665

12. Hui J, Aulakh GK, Unniappan S, Singh B.
 Localization of Nucleobindin2/Nesfatin-1-Like Immunoreactivity in Human Lungs and Neutrophils
 Ann Anat. 2021 May 31: 151774 (2021)
 DOI: 10.1016/j.aanat.2021.151774

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14. Mamet, SD; Jimmo, A; Conway, A; Teymurazyan, A; Talebitaher, A; Papandreou, Z; Chang, Yu-Fen; Shannon, W; Peak, D; Siciliano, SD
 Soil Buffering Capacity Can be Used to Optimize Biostimulation of Psychrotrophic Hydrocarbon Remediation
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 Lung inflammation from repeated exposure to LPS and glyphosate
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16. Pandher U, Kirychuk S, Schneberger D, Thompson B, Aulakh G, Sethi RS, Singh B
 Pulmonary Inflammatory Response from Co-exposure to LPS and Glyphosate
 Environ Toxicol Pharmacol. 86: 103651 (2021)
 DOI: 10.1016/j.etap.2021.103651

17. Raheem SJ; Schmidt BW; Solomon VR; Salih AK; Price EW
 Ultrasonic-Assisted Solid-Phase Peptide Synthesis of DOTA-TATE and DOTA-linker-TATE Derivatives as a Simple and Low-Cost Method for the Facile Synthesis of Chelator–Peptide Conjugates
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18. Sharma SK; Glaser JM; Edwards KJ; Khozeimeh Sarbisheh E; Salih AK; Lewis JS; Price EW
 A Systematic Evaluation of Antibody Modification and 89Zr-Radiolabeling for Optimized Immuno-PET
 Bioconjugate Chem 2020: **32**(7): 1177-1191 (2021).
 https://doi.org/10.1021/acs.bioconjchem.0c00087

Sylvia Fedoruk Canadian Centre for Nuclear Innovation Inc.

303-111 Research Drive
Saskatoon, SK, Canada S7N 3R2
Phone: 306-966-3377

fedorukcentre.ca

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SYLVIA FEDORUK CANADIAN CENTRE FOR NUCLEAR INNOVATION