Fedoruk Centre
SYLVIA FEDORUK CANADIAN CENTRE FOR NUCLEAR INNOVATION

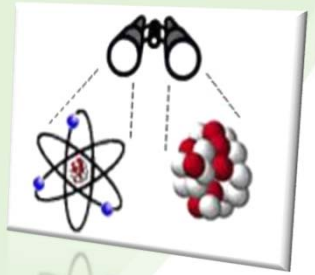
Saskatchewan Centre for Cyclotron Sciences: A New Multi-User Research and Production Facility

(AccApp '17)

Ghilt Boudreault
Facility Manager

Medicine.
Materials.
Energy.
Environment.

- Primarily a research facility
  - Novel radioisotopes / radiopharmaceuticals
    - Nuclear imaging (humans, animals, plants)



- Production facility
  - Drug manufacturer (approved radiopharmaceuticals)
    - Source of revenue – ROI

SCCS: relatively well equipped

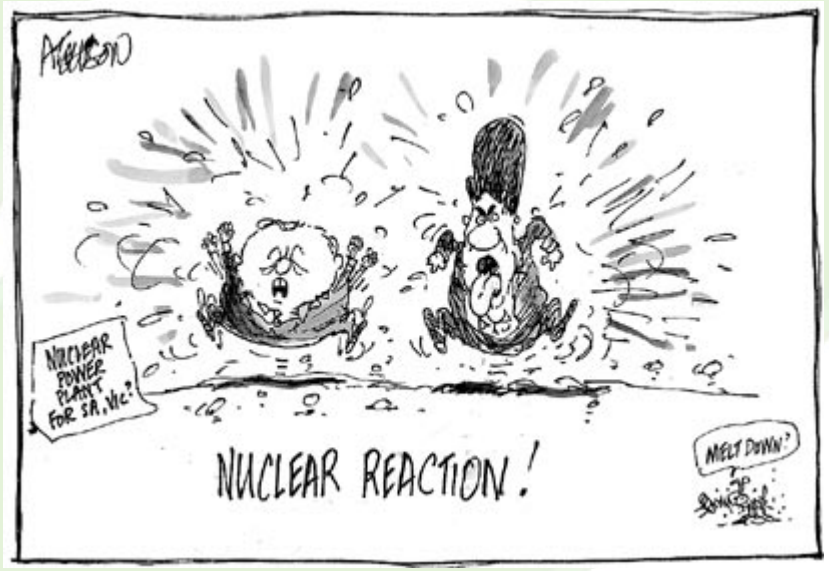
\+ strategically situated = Unique facility

Gives researchers in all branches of Life Sciences (Medicine, Veterinary Medicine, Agriculture, Environment…), thriving and wide-ranging at U of S, the opportunity to design, and ultimately produce, new drugs and probes

Nuclear energy

Radioisotopes

Radiation



- Nuclear technology
- Fire
- Electricity
- …

Tools

→ Proper vs improper use

Fire: Improper use

Fire: Proper use

Nuclear tools - applications

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Radioisotope power sources (heart pacemakers, beacons, satellites…)

Medical applications: diagnosis and therapy

Smoke detectors

Detection and analysis of pollutants

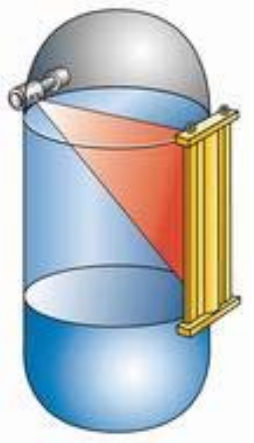
Leak detection

Material sciences – ion beam analysis, neutron activation

Thickness gauges

Food irradiation and blood irradiation

Leveling gauges



Sterilization of medical equipment

Electricity generation

Dating

Measurement of rate of wear of engines and plant and equipment

SCCS:

→ Facility owned by U of S
→ Operated by Fedoruk Centre
(Sylvia Fedoruk Canadian Centre for Nuclear Innovation)

Fedoruk Centre:

→ Established in December 2011 under the Canada Not-for-Profit Corporations Act
→ Wholly-owned subsidiary of U of S

Sylvia Fedoruk

(1927 – 2012)

Canadian physicist – medical physicist

(only woman doing medical physics research in Canada in the 1950s)

- Part of a team who did pioneering work in treatment of cancer using cobalt-60 radiation therapy
- The Cobalt 60 Therapy Unit was the first effective Cobalt Radiation Therapy machine for use on patients with cancer
- First cancer patient to use the Cobalt 60 Therapy Unit lived another 50 years and died only recently, well into her nineties!

- Later in her career, worked on developing the Dosimeter

- First woman member of the Atomic Energy Control Board of Canada (now CNSC)

- Chancellor of the University of Saskatchewan (1986-1989)

- Lieutenant Governor of Saskatchewan (1988 to 1994)

- Part of the winner team (Joyce McKee) of the first Canadian Ladies Curling Championship held in Oshawa, Ontario (1960)

- President of the Canadian Ladies Curling Association (1971 to 1972)

- As a member of the Joyce McKee curling team, was inducted into the Saskatchewan Sports Hall of Fame (1973)

- Inducted into the Canadian Curling Hall of Fame, as a builder

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VISION:

→ Placing Saskatchewan among global leaders in nuclear research, development and training through investment in partnerships with academia and industry for maximum societal and economic benefit.

→ Making positive impacts in 4 areas:

- Nuclear Medicine, Instruments and Methods
- Nuclear Techniques for Materials Research
- Nuclear Energy and Safety Systems (including Small Reactor Technology)
- Physical and Social Environment (management of benefits and risks of nuclear technology)

MAIN FOCUS SO FAR:

→ Building and bringing into operation SCCS on U of S campus

→ Creating the framework from which a successful, world leading and sustainable nuclear imaging research and teaching program can grow

→ Former animal husbandry facility on campus turned into a cyclotron facility

→ CPDC at McMaster University assisted with regulatory affairs and help establish an overall quality system

→ Overall cost for renovating, commissioning, and bringing into operation: $CAN25 million

- WD (Western economic Diversification)
- Innovation Saskatchewan
- Fedoruk Centre

Project calls:

→ Fedoruk Centre invites researchers, institutions, and partners to participate in building a community of expertise that will place Saskatchewan among global leaders in nuclear research and innovation

→ To date, the Board of Directors has allocated $5 million for project calls:

- > $CAN4 million has been committed to some individual projects (27)
- < $CAN1 million left for future calls for project proposals

Nuclear imaging:

→ $CAN3.45 million to establish 3 Fedoruk Chairs:

- Radiopharmacy
- Nuclear Imaging
- Nuclear Physics (Detection Technologies)

SCCS

Class II nuclear facility → Particle accelerator

→ TR24 cyclotron from ACSI

→ Accelerate protons up to 16-24 MeV (~22% of speed of light)

→ Personnel: trained as NEW (Nuclear Energy Worker)

Regulatory body: CNSC

(Canadian Nuclear Safety Commission)

→ Permit / commissioning

→ Inspections

→ Research applications submission

Production / drug manufacturing

→ Medical care: patient injection

→ GMP (Good Manufacturing Practices)

→ Strict and stringent rules / guidelines

→ Strong QA system

→ Clinical trials → License

Regulatory body: HC

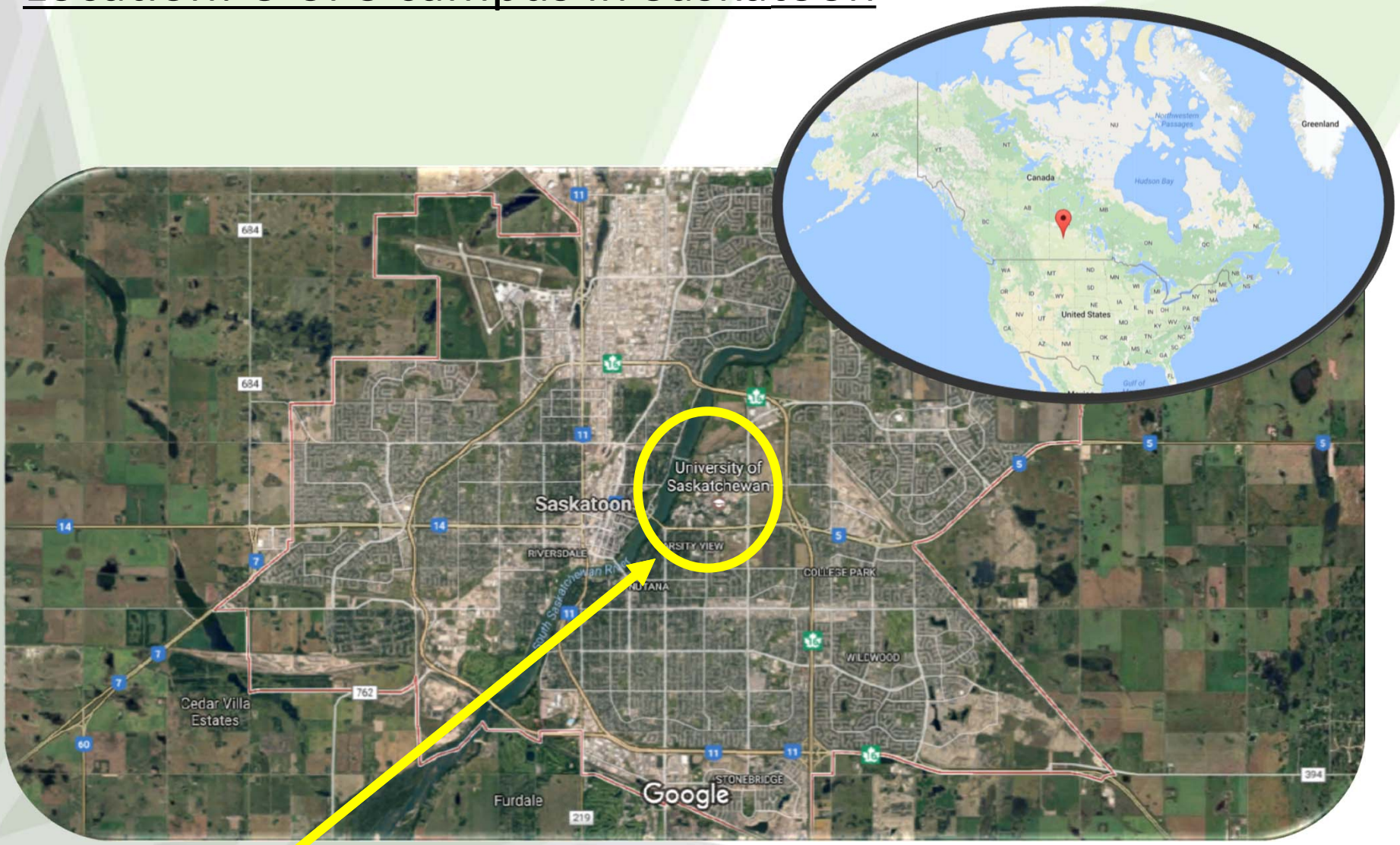
(Health Canada)

→ License issuance

→ Inspections

Work at SCCS

Location: U of S campus in Saskatoon



U of S campus

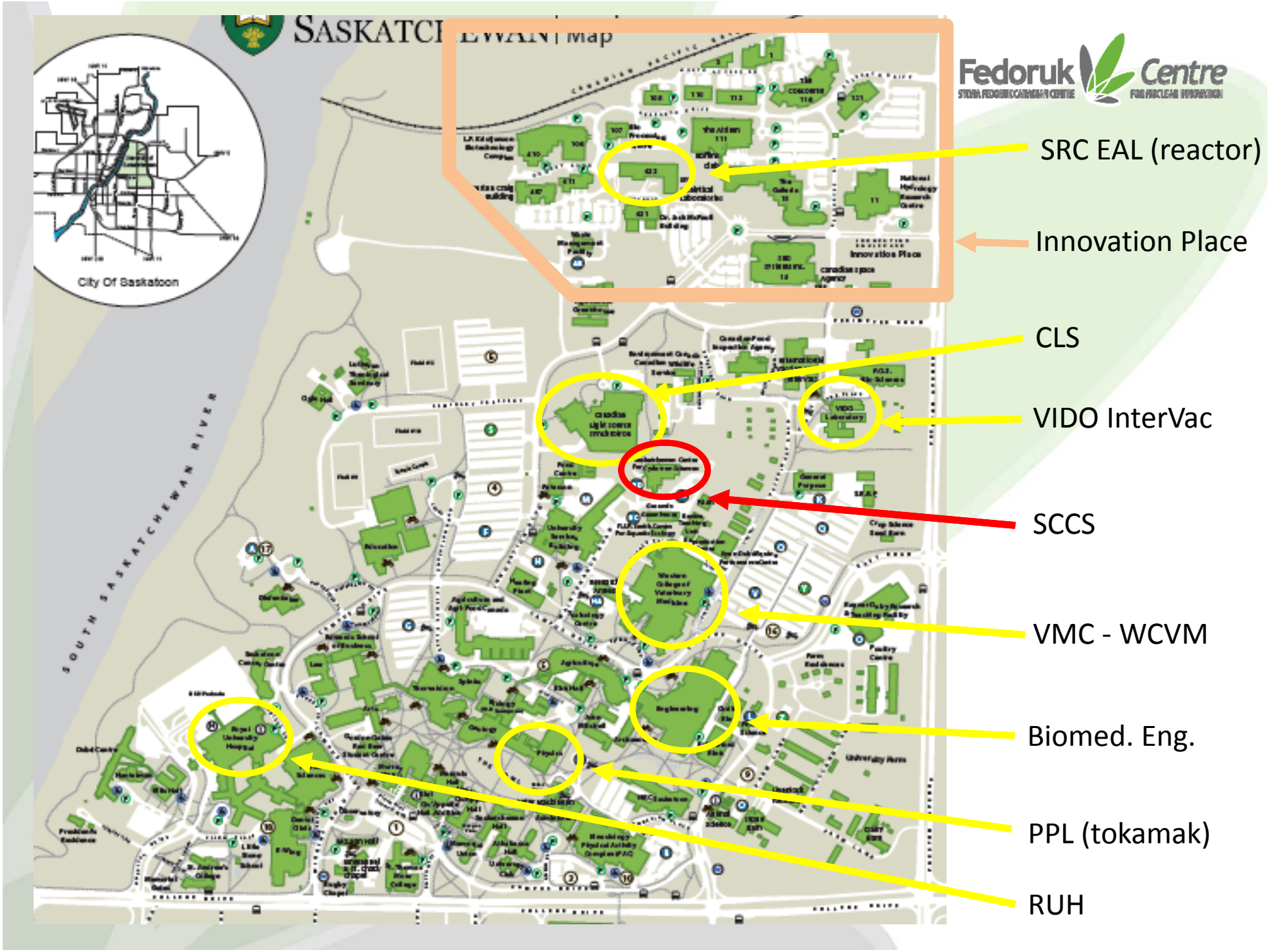
SCCS

SCCS: Strategically situated

→ U of S: Amazing concentration of resources on one campus which allows for advancing basic, translational and clinical research and commercialization of the drugs via collaborative work

→ Life Sciences at U of S: Thriving and wide-ranging

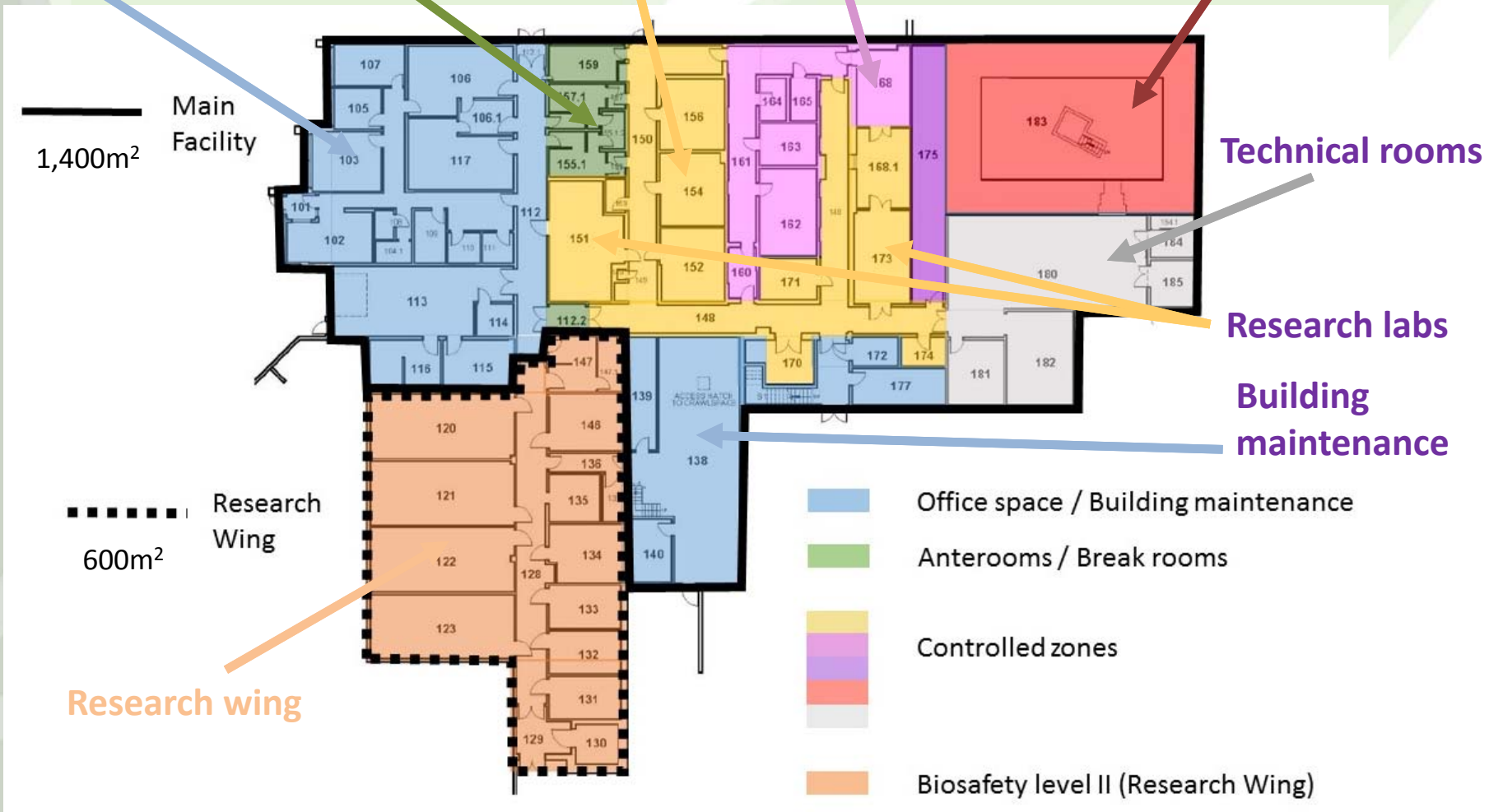
- Agricultural Biology
- Agricultural Economics
- Agronomy
- Anatomy and Cell Biology
- Animal Bioscience
- Animal Science
- Applied Plant Ecology
- Arts and Science Transition Program
- Biochemistry
- Biochemistry and Biotechnology
- Bioinformatics
- Biology
- Biotechnology, Microbiology and Immunology
- Combined Kinesiology/Education
- Crop Science
- Dentistry
- Diploma in Agronomy
- Environmental Science
- Exercise and Sport Studies
- Food and Bioproduct Sciences
- Global Health
- Health Studies
- Horticulture Science
- Medicine
- Microbiology & Immunology
- Nursing
- Nutrition
- Pharmacy
- Physiology & Pharmacology
- Psychology
- Resource Economics and Policy
- Resource Science
- Soil Science
- Veterinary Medicine


SASKATCHEWAN | Map
City Of Saskatoon
SOUTH SASKATCHEWAN RIVER
Fedoruk Centre
SRC EAL (reactor)
Innovation Place
CLS
VIDO InterVac
SCCS
VMC - WCVM
Biomed. Eng.
PPL (tokamak)
RUH

U of S through the year

All kinds of students to be seen on campus…

SCCS: main facility and research wing layout



SCCS: staff

- 1 Facility Manager
- 1 QA Manager
- 1 Safety and Compliance Officer
- 1 Research Wing Coordinator
- 1 Cyclotron Engineer
- 1 Senior Production Technologist – QA Designate
- 3 Production Technologists
- 1 Administrative Assistant

- 1 Clinical Research Coordinator (College of Medicine)

= team of 10-12 + U of S cleaning/service/maintenance staff

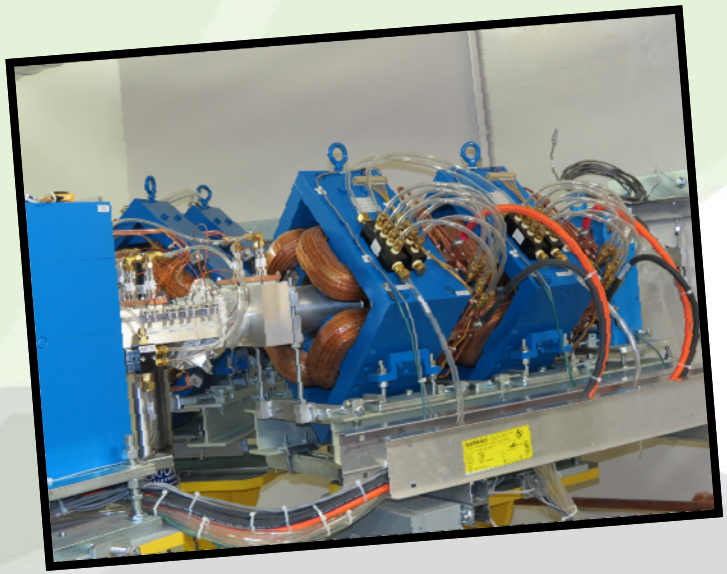
+ over 25 affiliated researchers/facility users

(including 4 top-level radiopharmacists/radiochemists)

SCCS main facility

→ Cyclotron: ACSI high-current TR-24 model
(with expanded injection and RF systems)

- Variable energy: 16 (approximately) to 24MeV
- Beam current: up to 500μA extracted (all energies)
- 1× split beamline: → 2× beamlines (doublet quads and X-Y steering on each)
- Room for a second split beamline to be added in future
- 2× 3-port target selectors (one fixed to cyclotron, one terminating a beamline)
- Dual bombardment possible



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→ Targetry available

Modular targets allow for reconfiguration of the target selectors (all ports have access to water and helium cooling):

- 3× ACSI F-18, 100µA water targets (used in GMP production of ^{18}F-FDG);
  - 2 on cyclotron: - 1 for daily productions
    - 1 held as spare, mounted and ready to be used
  - 1 dismounted: for decay and maintenance
  - Remark: may be used to make ^{13}N in a limited capacity
- 1× ACSI C-11, 40µA gas target
- 1× ACSI 90° solid target (coin) holder; can operate up to 70µA (coin target may have a lower maximum depending on material) [On order; not yet installed]
- 1× ACSI high-current solid target station (500µA maximum current to target) complete with automated pneumatic transfer system to processing hot cell
  - Remark: Dedicated solid target station allows high current bombardments and an automated transfer system to maximize production yields
  - Remark: 7° solid target station; can operate up to 500µA (specific target may have a lower maximum depending on material)

Note: 2 port locations are still unoccupied

→ cGMP clean rooms and production labs

- 4× Comecer Grade C mini hot cells [BBS2-V-75]
- 1× Comecer Grade A (with laminar flow) dispensing hot cell [MIP1-1P 1330 LAF] (with Grade B prechamber)
- 1× pair of Tru-Motion telemanipulator arms [TM2748 10L]
- 2× GE FASTlabs FDG synthesizers
- 1× Capintec dose calibrator [CRC-55T]
- 2× PBI SPA microbial air samplers [SAS Super 180]
- 3× Lasair non-viable particulate monitors [1× 5100] [2× 310C]
- 2× Millipore bubble point gauges (Millex Integrity Tester) [SLTest000]

→ QC labs

- 1× Agilent GC with headspace sampler
  - GC System [7890B]
  - GC Headspace Sampler [7697A]
  - GC Injector/Autosampler [G4513A]
- 1× HPLC with UV detector and flow count detector
  - Waters separations module [Alliance e2695]
  - Waters UV/VIS detector [2489 UV/VIS Detector]
  - Eckert & Ziegler flow count detector (for HPLC) [B-FC-1000]
- 1× Capintec dose calibrator [CRC-55T]
- 2× Charles River endotoxin readers [Endosafe PTS]
- 1× Binder lab oven [FED115]
- 1× Mott fume hood [Mott7428000]
- 2× TLC
  - Eckert & Ziegler TLC scanner [B-AR2000-1]
  - Eckert & Ziegler TLC add-on to HPLC (Mini-Scan with Flow Count)
- 1× Mettler Toledo analytical balance [XPE205DR]
- 1× Mettler Toledo top loading balance [MS30025]
- 1× Panasonic fridge/freezers [MPR414-F]
- 2× Panasonic incubators [MIR-154]

→ Research labs

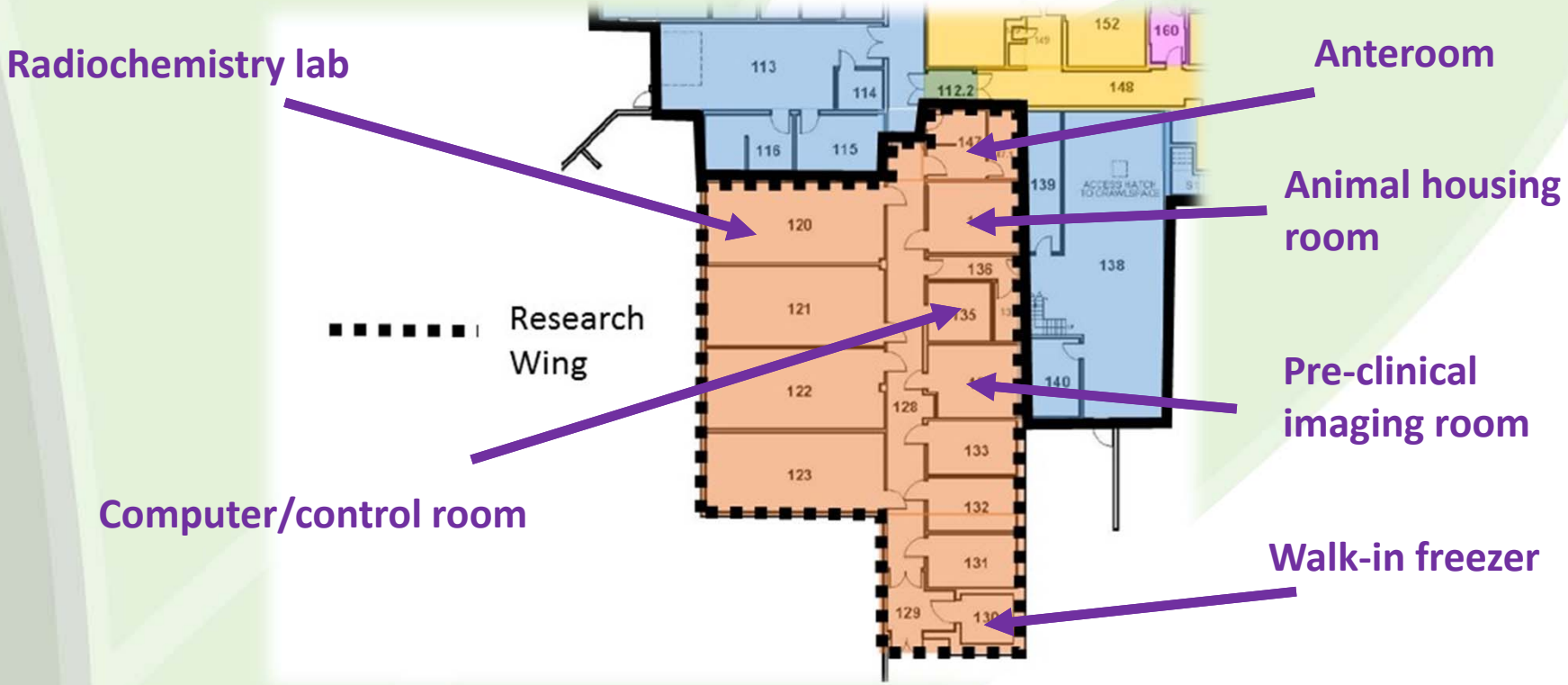
- 4× Comecer Grade C mini hot cells [BBS2-V-75]
- 2× Comecer Grade C dispensing/processing hot cells [MIP1-1P 1330]
- 1× pair of Tru-Motion telemanipulator arms [TM2748 10L]
- 1× Eppendorf thermomixer
- 1× ThermoFisher centrifuge and rotor (with purification accessories)
- 1× UPLC/HPLC and radiation detector
  - ThermoFisher Vanquish UPLC/HPLC
  - Eckert and Ziegler radiation detector for HPLC
- 1× Fisherbrand hot plate stirrer
- 1× Trasis mini AIO synthesizer
- 1× Panasonic fridge/freezers [MPR414-F]
- 1× Capintec dose calibrator [CRC-55T]

→ Miscellaneous

- Hand/foot monitors
- Survey meters
- …

SCCS: research wing

Note: partially renovated



→ $CAN1.72 million for molecular imaging equipment (from the Fedoruk Centre)

- Preclinical imaging equipment (microPET)
- Plant detection system (PhytoPET)
- Radiochemistry equipment

→ Animal housing room

- 1× Ventilated rack system for mice/rats
  - Can accommodate 128 small cages (up to 4-5 mice per cage → capacity of 500-600 mice) or 64 large cages (rats)
  - Connected to emergency power (in case of power cut)
- 1× Biosafety cabinet
- 1× Infrared heating lamp
- 1× Light timer switch

→ Preclinical (animal) imaging room

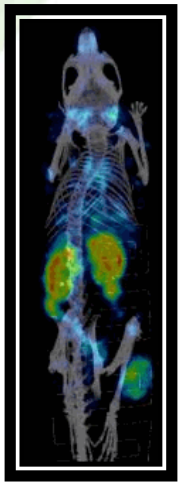
- 1× MILabs VECTor^{4}CT scanner (tri-modality PET/SPECT/CT scanner)
  - True simultaneous SPECT and PET images down to sub-mm resolution in mice
  - 4D movies of pharmaceutical interaction with tissue, time resolution of few sec
- 1× Benson Medical Industries mobile anesthetic system
- 1× PhysioSuite monitoring system for mice and rats
  - Warming pad
  - Temperature sensors
  - MouseSTAT and pulse oximeter sensors
- Few warming pads with water pump

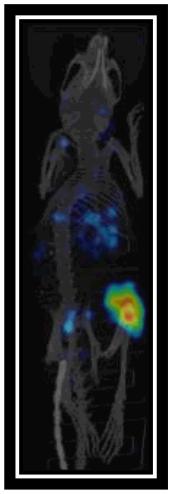
→ Computer/control room

- 1× Acquisition super-fast computer
  - Fast 1× 4 Core Intel CPUs
  - 2 GB internal memory
  - 180 GB hard disk for operating system (Microsoft Windows Professional)
  - 1 TB hard disk for user data
- 1× Reconstruction super-fast computer
  - Fast workstation with 2x 16 Core CPUs
  - 64 GB internal memory
  - 120 GB hard disk for operating system
  - 6 TB disk array for user data
  - 24" LCD screen, Microsoft server 2008
- 1× MILabs advanced software package for data acquisition and image reconstruction
  - List-mode data acquisition (multi-isotope SPECT and/or PET imaging, retrospective gating, easy scan time and dose)
  - Batch-mode reconstruction functionality
  - Corrections for attenuation, scatter, resolution loss, and distant dependent sensitivity

- 1× Professional PMOD software (data processing, visualization, and quantitative analysis)
- Data format: DICOM 3.0, Interfile, ACR/Nema, Analyze, and NIfTI
- Reconstruction time: 3 minutes to 1 hour, depending on voxel size and scan area
- Minimal voxel size for SPECT collimator:
  - 0.125 for XUHR-M
  - 0.2 mm for UHR-M
  - 0.4 mm for GP-M, UHS-M and XUHS-M
  - 0.8 mm for UHR-RM, GP-RM
  - 1.6 mm using the GP-MSA
- Minimal voxel size for high energy SPECT/PET collimator:
  - 0.4 mm using the HE-UHR-M
  - 0.4 mm using the HE-UHR-RM
- Other characteristics:
  - Remote access
  - Live monitoring of animal
  - Multiple isotope imaging
  - Dynamic imaging

^{111}In - DOTA – SUM149 – 24h post injection





^{89}Zr - NIMO - MB468 – 168h post injection

→ Radiochemistry lab

- 1× Perkin Elmer automatic gamma counter [2480 Wizard]
- 1× HPLC with UV, fluorescence and radio-TLC detector
  - Waters bioseparations module [2796]
  - 2× Waters Dual I absorbance detector [2487]
  - Waters Multi I fluorescence detector [2475]
  - Lablogic radio-TLC detector [Scan-ram]
  - Automatic fraction collection
- 1× Balance [OHAUS ex423]
- 1× Water bath
- 1× Sonicator
- 2× Thermomixer
- 2× Centrifuge
- 1× Fridge (4°)
- 1× Freezer (-20°)
- 2× Berthold contamination monitor [LB 124]
- 1× Dose calibrator

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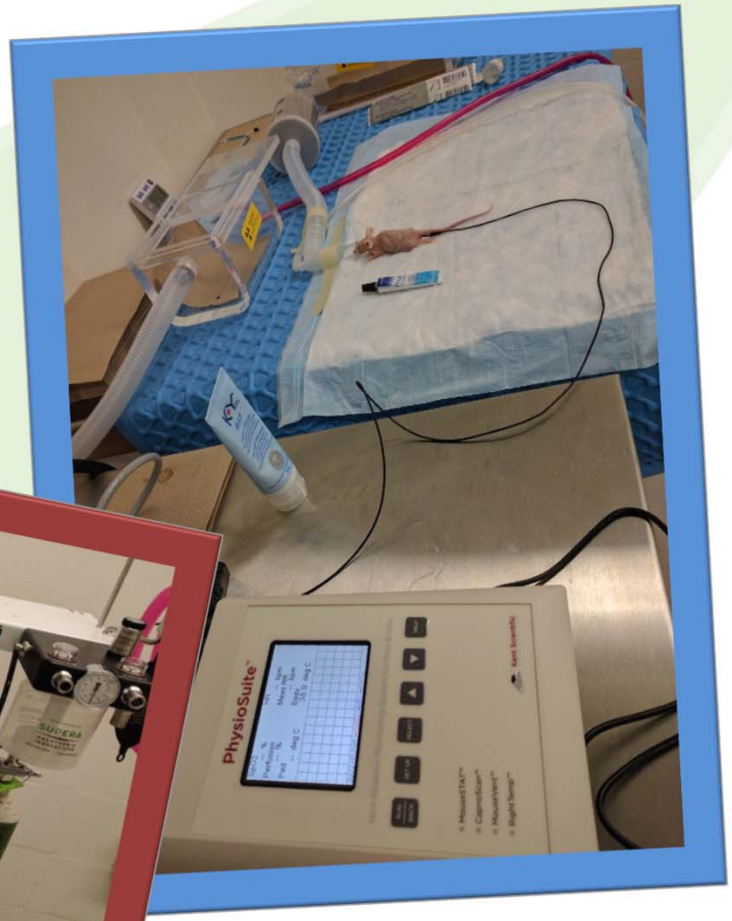

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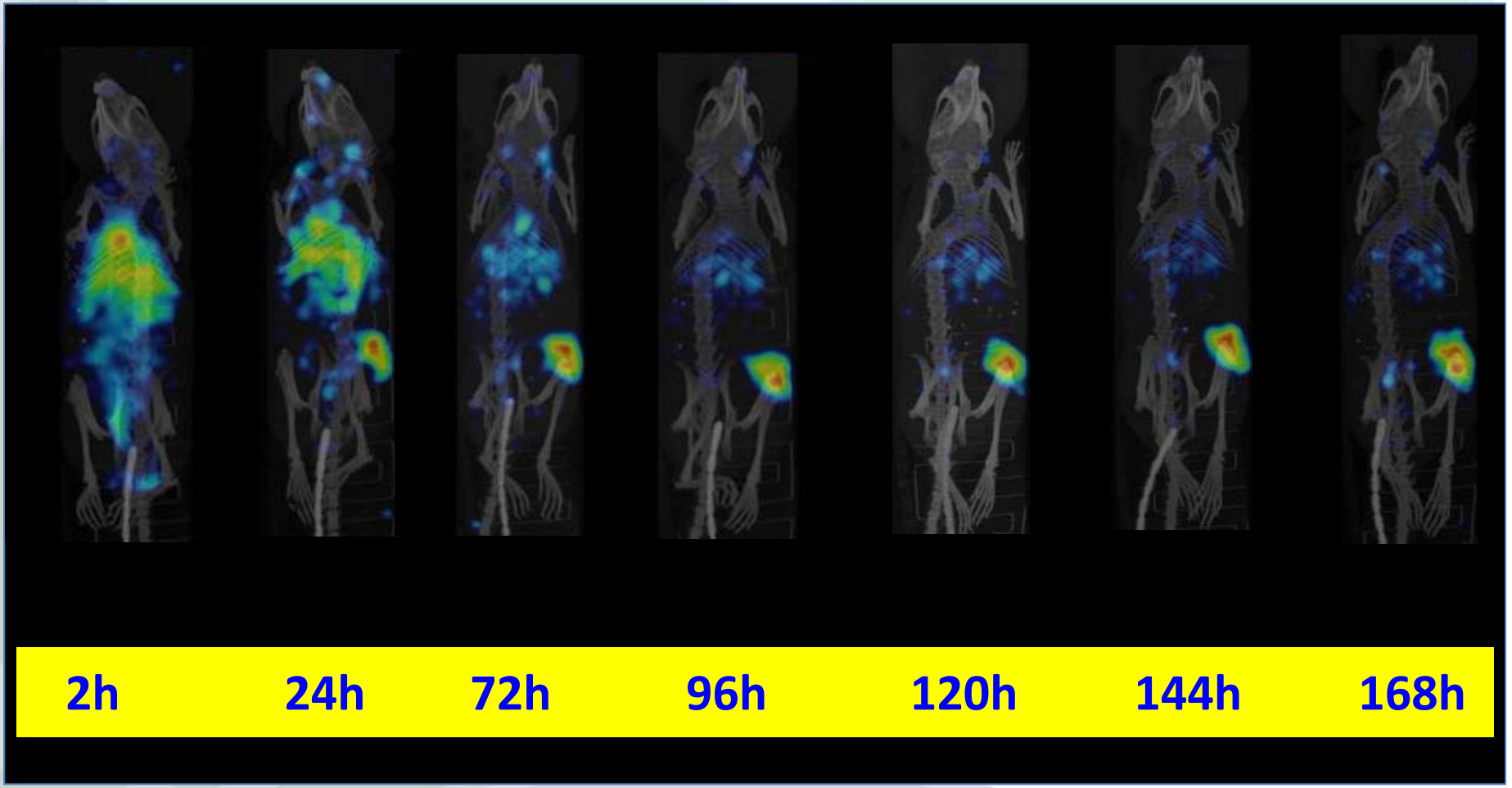
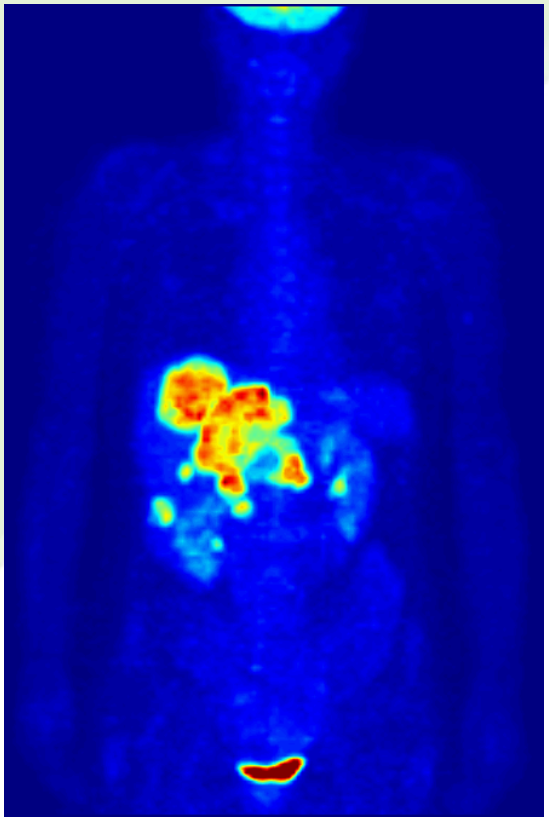
Summary : ^{89}Zr - NIMO – MB468



Current radioisotope production

→ ^{18}F-FDG

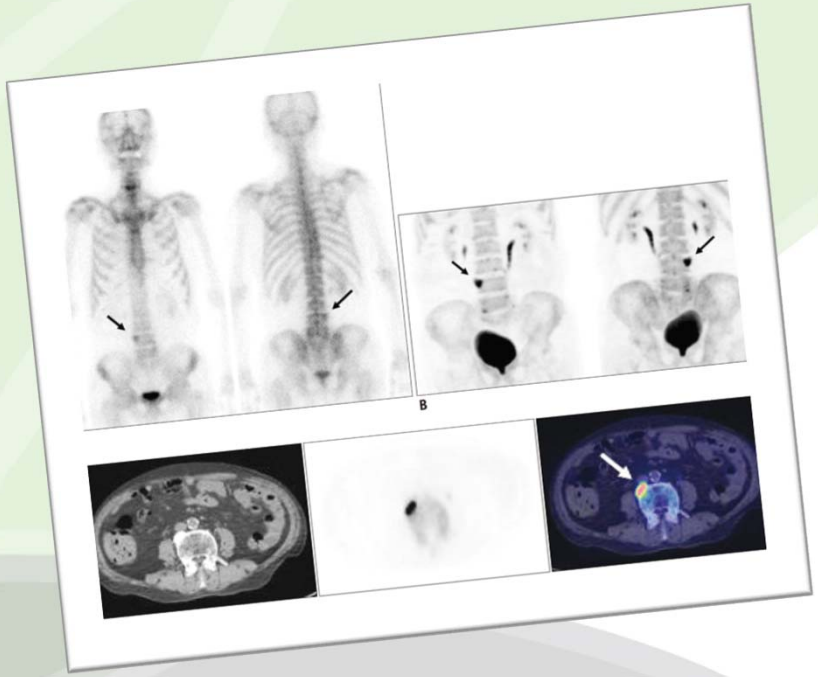
- Proton beam at 16MeV on ^{18}O-enriched water – $^{18}O(p,n)^{18}F$
- Cancer diagnosis
- Reliable daily supply to RUH on campus since June 2016
- Marketing authorization (NOC) since January 2017
- Back-up supply to Foothills Nuclear Medical Centre in Calgary since July 2017
- Trying to reach out to other customers → logistic is a challenge



Projects in the pipeline

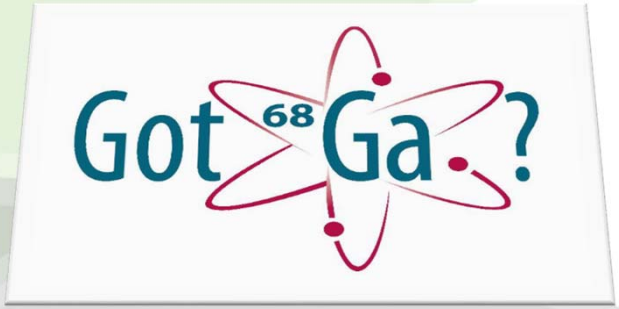
→ Implementing ^{18}F-NaF productions

- ^{18}F is already produced on site
- NaF synthesis: easy and straightforward
- Interesting candidate for bone scan



→ ^{68}Ga produced using cyclotron

- Some interesting ^{68}Ga-radiolabeled complexes candidates
  - ^{68}Ga-DOTATOC for NET (Neuroendocrine Tumor) investigations
  - ^{68}PSMA (Prostate-Specific Membrane Antigen) for prostate cancer investigations
- At present: use of new generation of ^{68}Ge/^{68}Ga generators
  - Expensive
  - To be renewed after 10 months
  - As time goes by quality decreases (more radionuclidic impurities)
- Plan: produce ^{68}Ga using the cyclotron
  - Use conventional ^{18}F water target
  - Load target with ^{68}Zn-enriched solution
  - Shoot proton beam below 12.3MeV (to avoid production of ^{67}Ga)



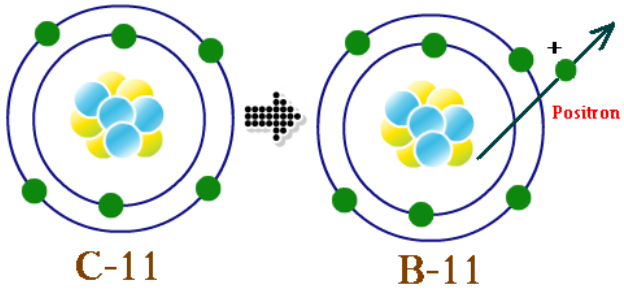
→ ^{64}Cu

^{64}Cu

- Biological distribution in small fish (no imaging)
- Low yields: < 1mCi (37MBq)
- Plan: produce ^{64}Cu using the cyclotron
  - Shoot proton beam on ^{nat}Ni metal foil (500µm, Ø 10mm)
  - Irradiation: 15µA, 3h, below 15MeV (beam stopped in foil)
  - Cheap, no target recycling
  - Final product: in a NaCl saline solution

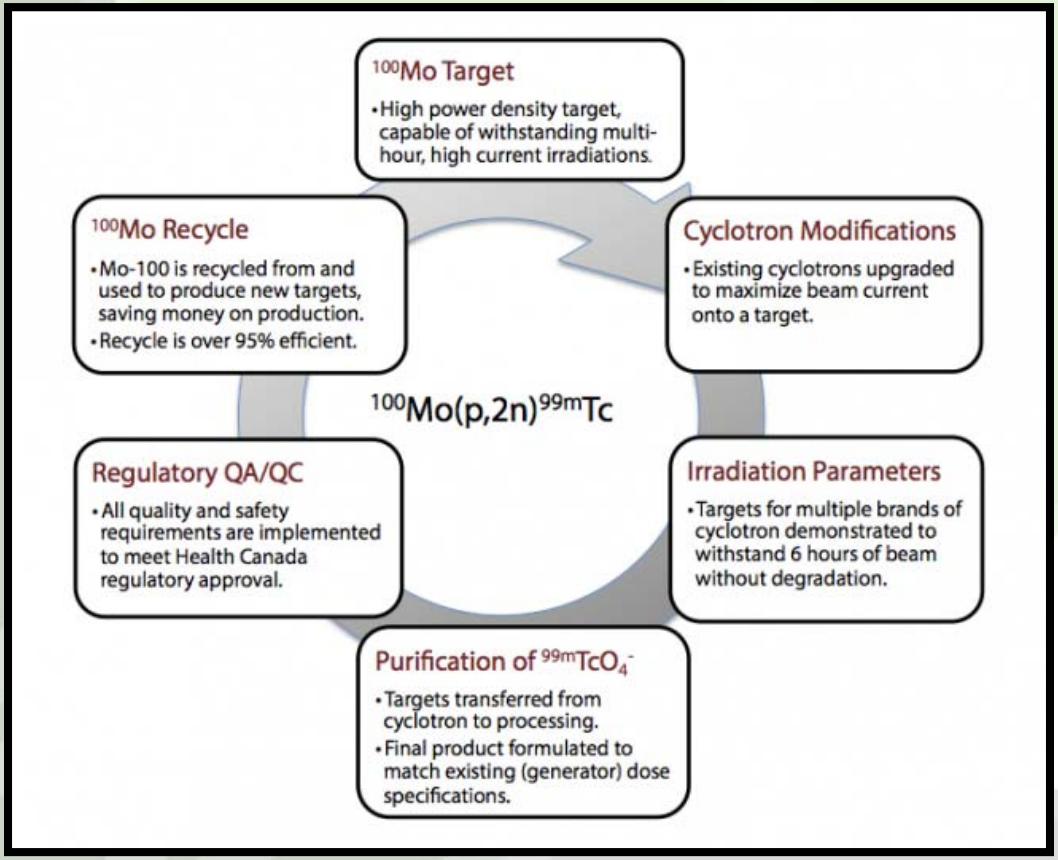
→ ^{11}C

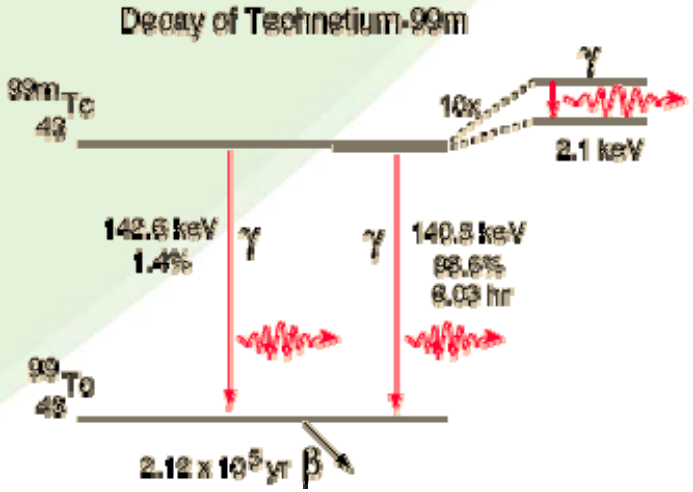
- Mainly for plant imaging
- Gas target



→ ^{99m}Tc

- Facility has all necessary equipment (solid target station…)

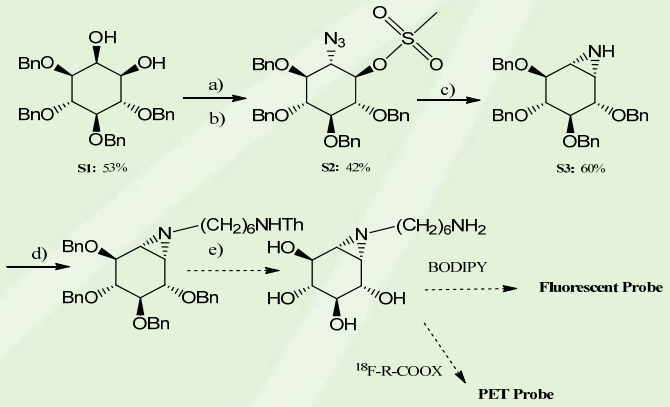




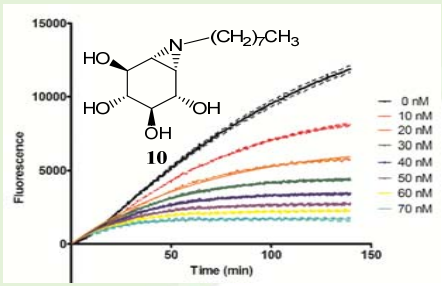
→ Development of new ^{18}F-based PET probes

- Design and synthesis of probe candidates
- Imaging the activity of enzymes important to human health
- ^{18}F-labeled versions of the compounds for microPET imaging studies
- Clinical translation

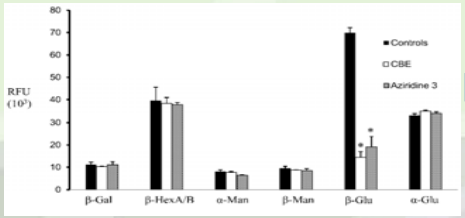
Design and Synthesis of Probe Candidates



Kinetic Evaluation



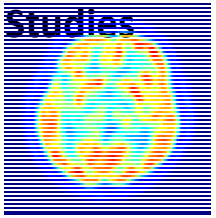
Cell Assays to Evaluate Specificity



Labeling @ SCCS Cyclotron

MicroPET Imaging Studies

Clinical Studies



→ ^{89}Zr-Nimo antibody radiolabeling project: C-BIRD

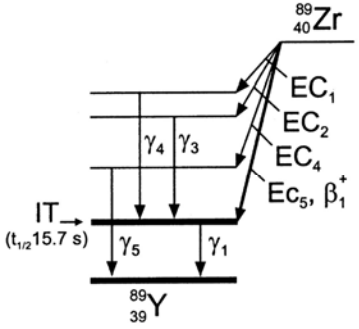
Nimotuzumab: anti-EGFR antibody

→ imaging agent for EGFR-positive cancers

- ^{89}Zr solid target (coin) holder design and tests
- ^{89}Zr coin solid target + energy degrader tests
- ^{89}Zr-Nimo radiolabeling
- Pre-clinical validation
- Clinical trials
- Manufacturing (^{89}Zr-Nimo)

} Started November 2016 (^{89}Zr ordered from Sherbrooke)

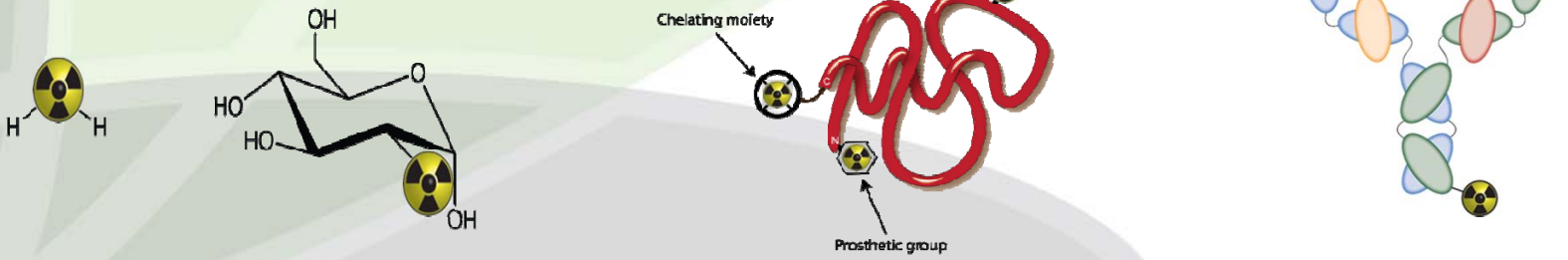
^{89}Y(p, n)^{89}Zr



Transition		Energy (MeV)	Abundance (%)
β+	1	0.897	22.6
EC	5		77.0
γ	1	0.909	99.9
	3	1.657	0.10
	4	1.713	0.77
	5	1.744	0.13

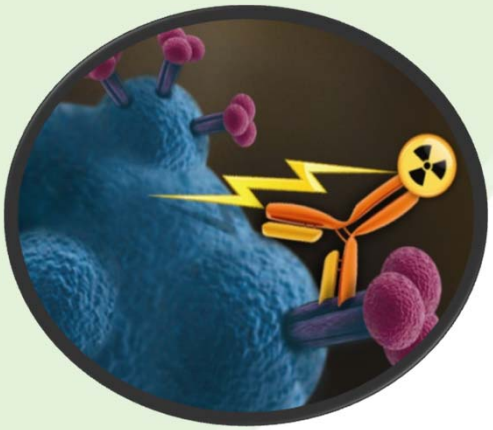
→ Novel chelators for labeling peptides and antibodies with radiometals

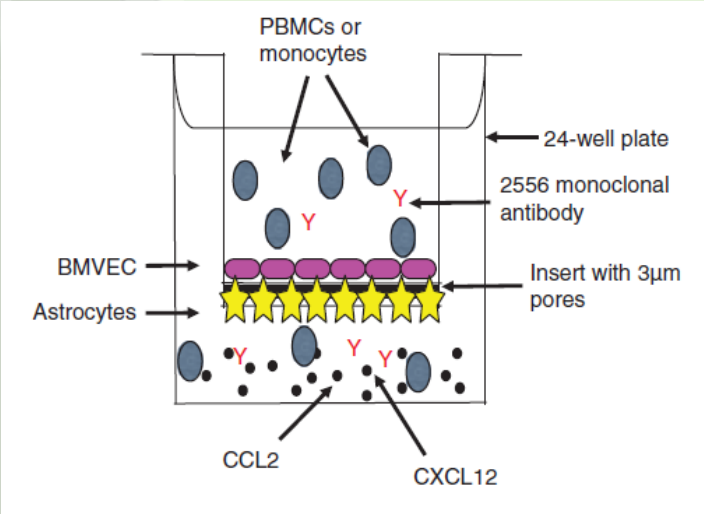
- Chelators in radiochemistry: Harnessing radioactive metals to image and treat cancer and severe multidrug-resistant bacterial infection
  - Over-abundant use of antibiotic drugs over the past few decades: multi-drug resistance has been observed in an increasing number of bacteria and is emerging as a global threat to health
  - Infectious disease a growing part of molecular imaging
  - Molecular imaging probes can be “tweaked” for use as radiotherapeutics
- New chelators
  - Increase stability of exiting radiometal-based drugs
  - Improve efficacy of all existing and new drugs that use a specific radiometal
- New applications
  - Develop existing bacteria imaging agents to improve targeting
  - Transform into radiotherapeutics

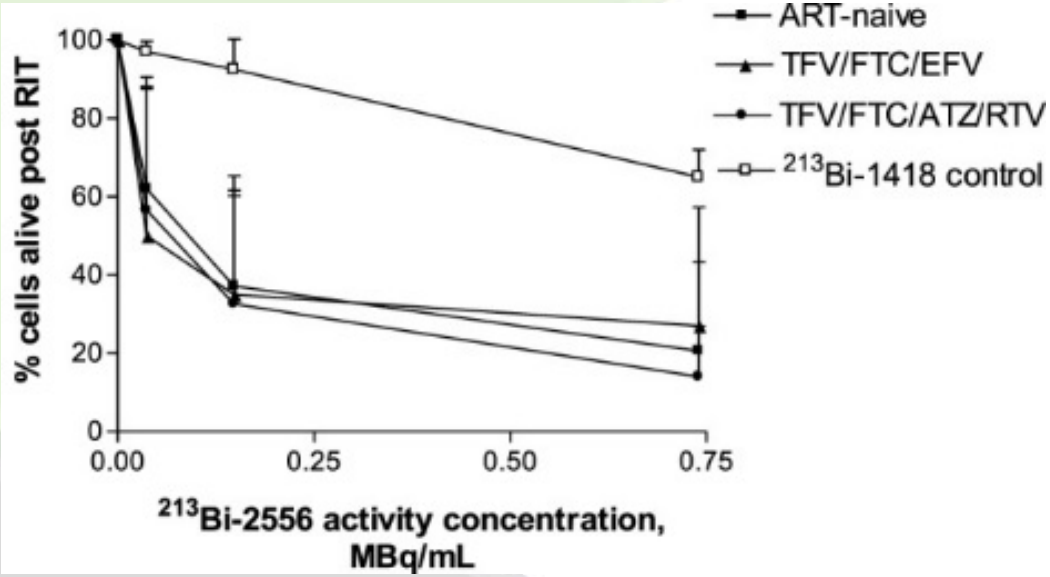


→ New approaches to radioimmunotherapy

- Of cancers: melanoma, osteosarcoma
- Of infections: opportunistic fungal infections







PhytoPET: Positron Emission Tomography for Plants

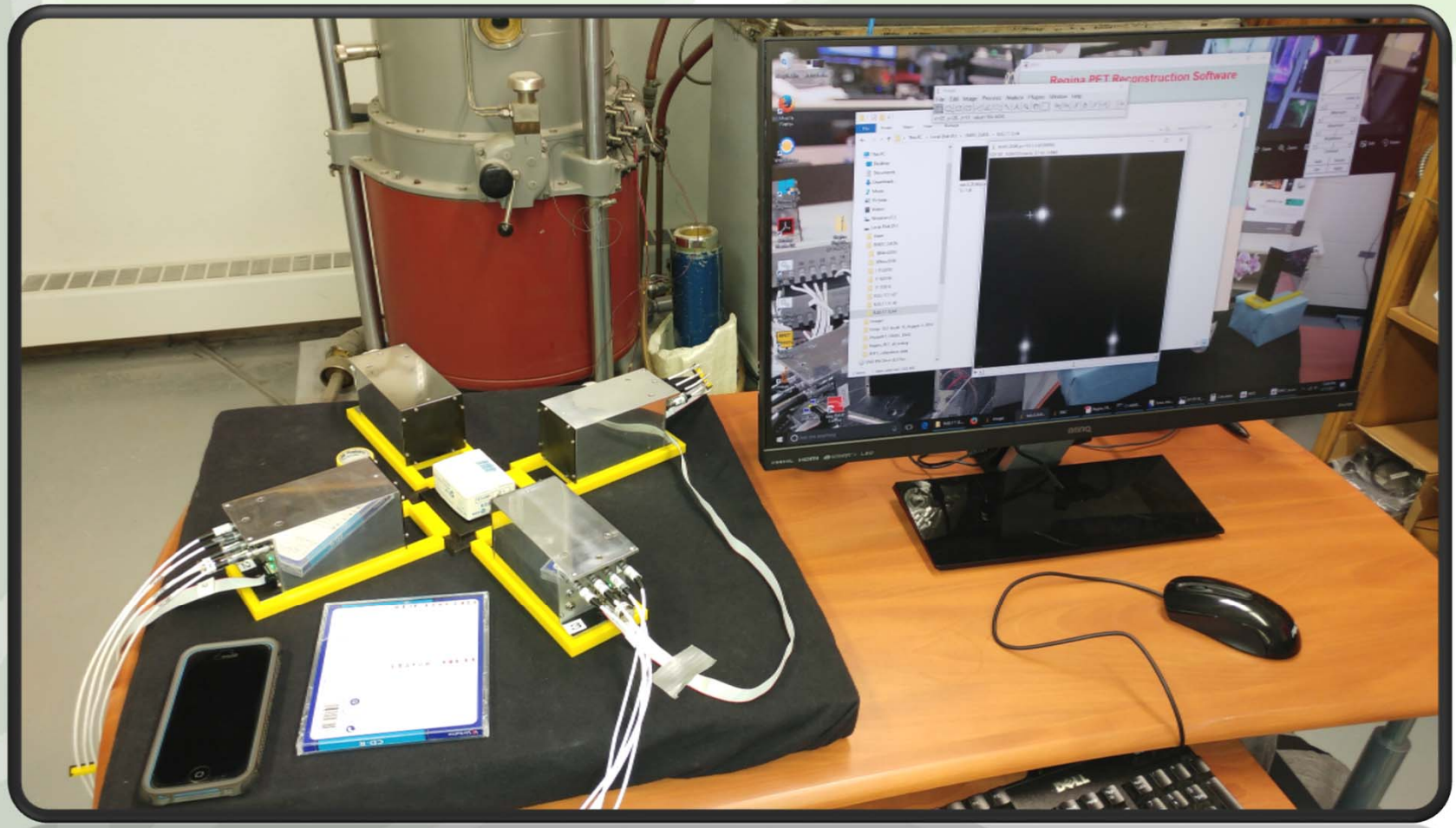
(collaboration with U of R)

→ First of its kind in Canada

→ Study biological processes in plants

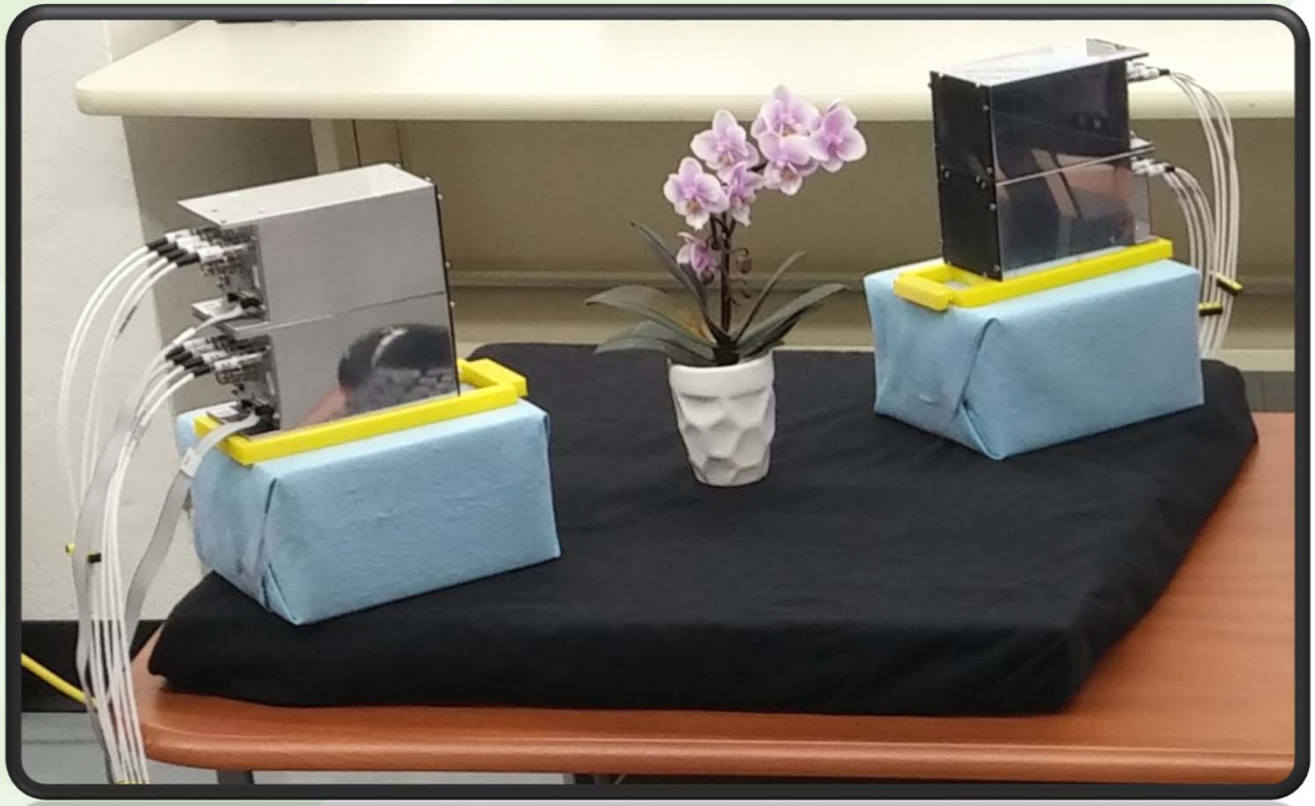
- Will provide insights that can be used to develop new crop varieties and breeding
- Will allow us to address climate change issues (increased levels of carbon dioxide…)
- Will allow us to study interaction between roots and beneficial microbes in the soil
- Will help optimize response to environmental stresses like:
  - higher temperatures
  - drought
  - declining water level
  - infection or insect attack

- Currently has 4 detector heads (more can be added)
- Detector area: ~6x6 cm^2
- Spatial resolution of fully 3D-reconstructed PET images <2mm (with sealed ^{22}Na point source and optimal geometry)



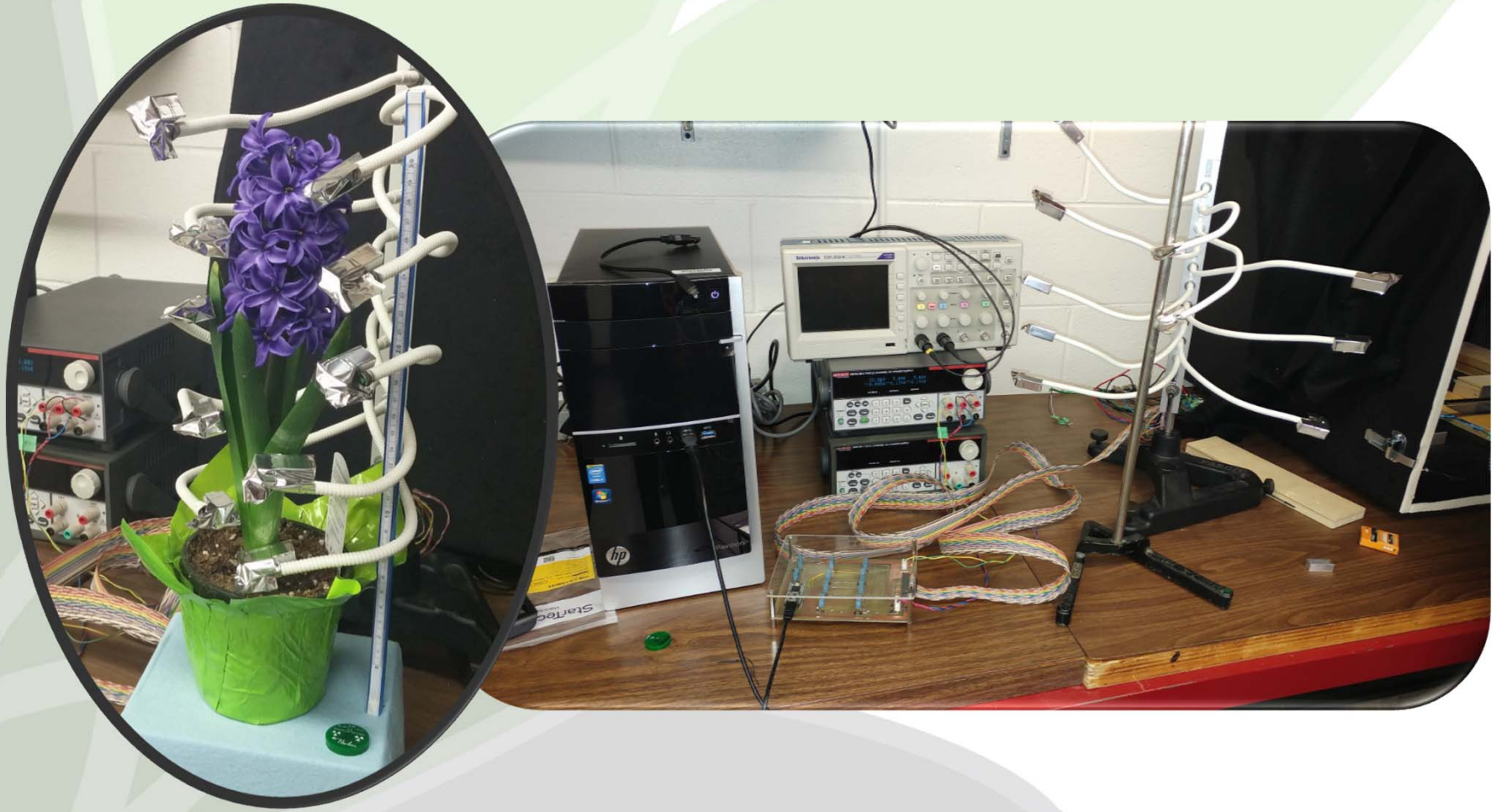
Modular system: fully adjustable detection geometry designed to accommodate various plant imaging scenarios:

- roots
- individual leaves
- whole plant



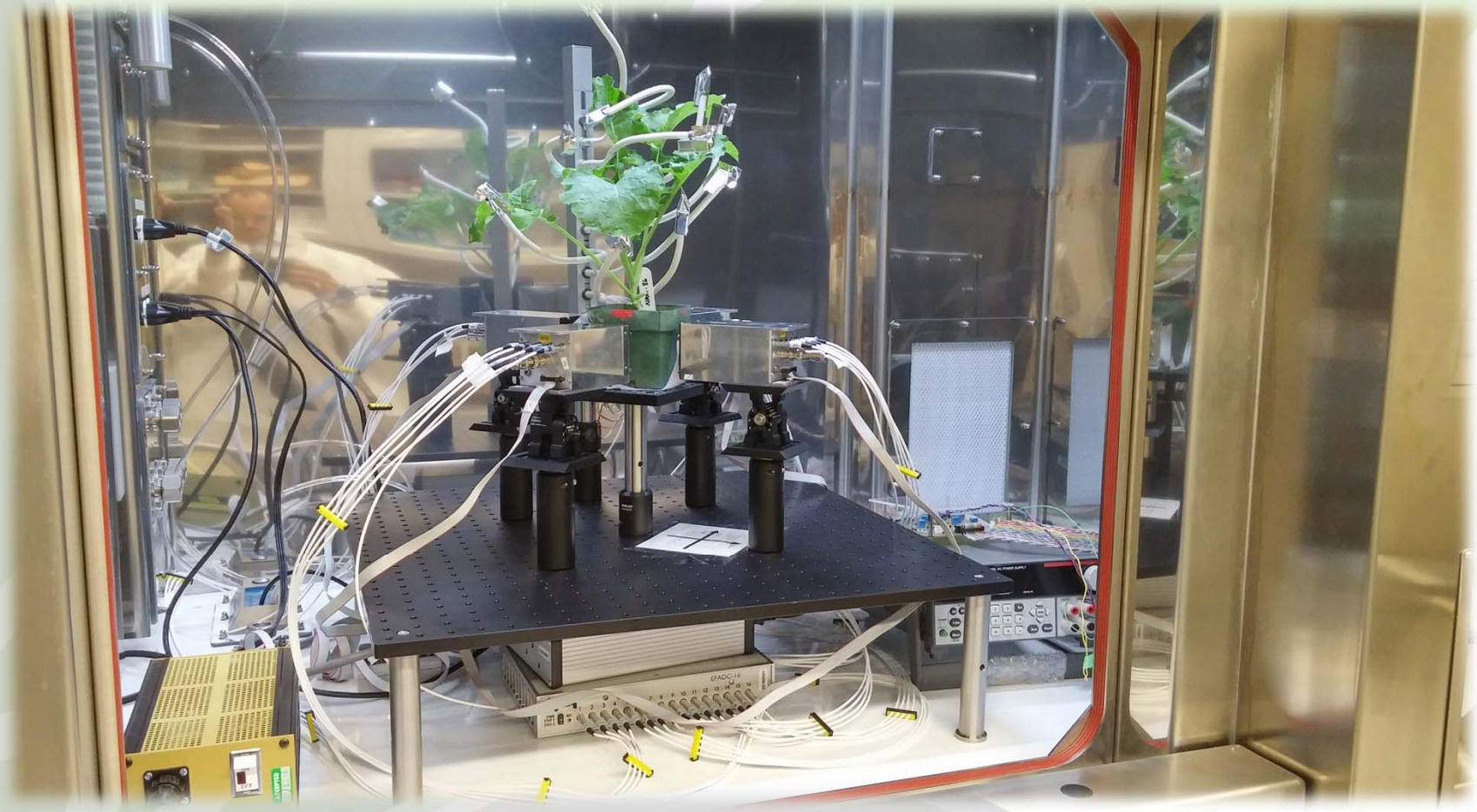
PhytoCount: Radiation counting system for high-throughput scanning of plants

- Novel, multi-channel radiation-counting detection system
  - Allows high-throughput scanning of radio-labeled molecule uptake and kinetics in plants

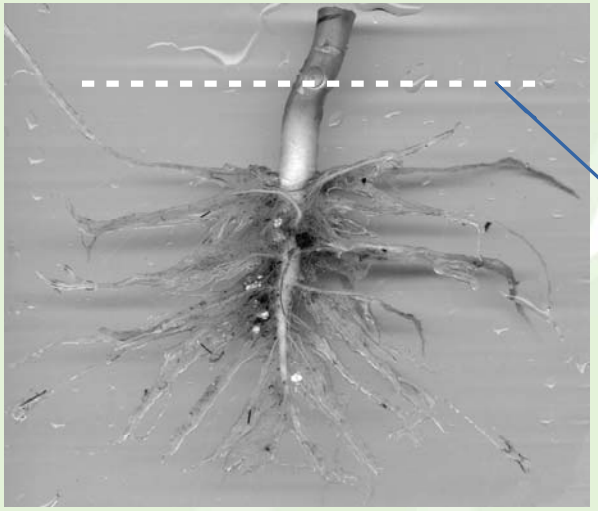


Plant imaging system mounted in a hot cell in main facility (only for 1 week, June 12-16)

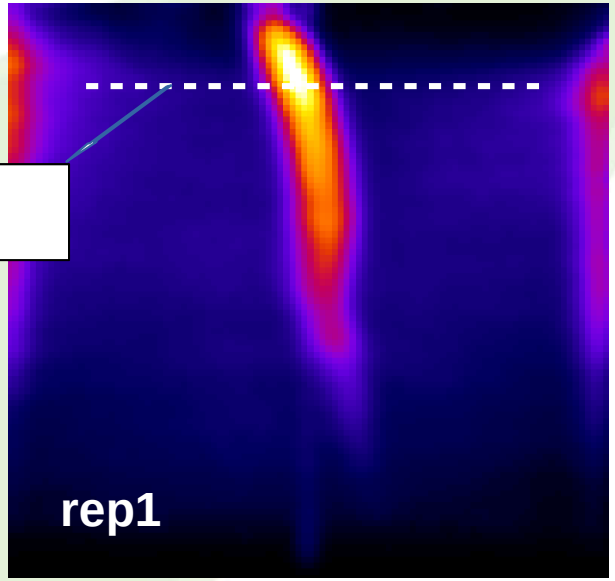
- Imaging roots and monitoring transport of glucose (FDG)

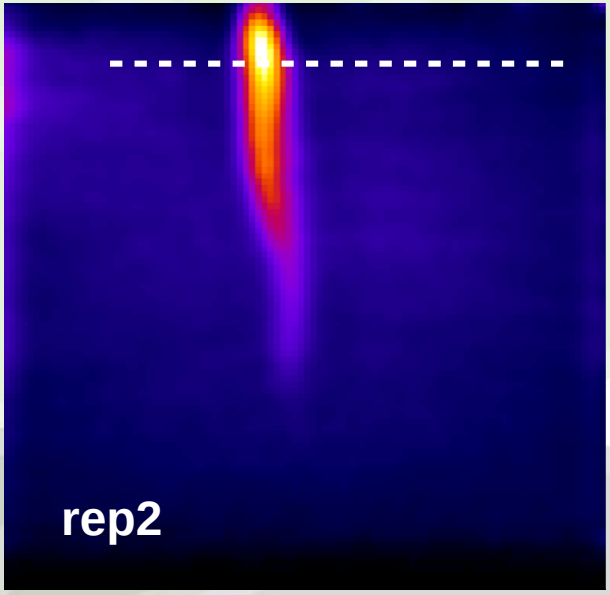


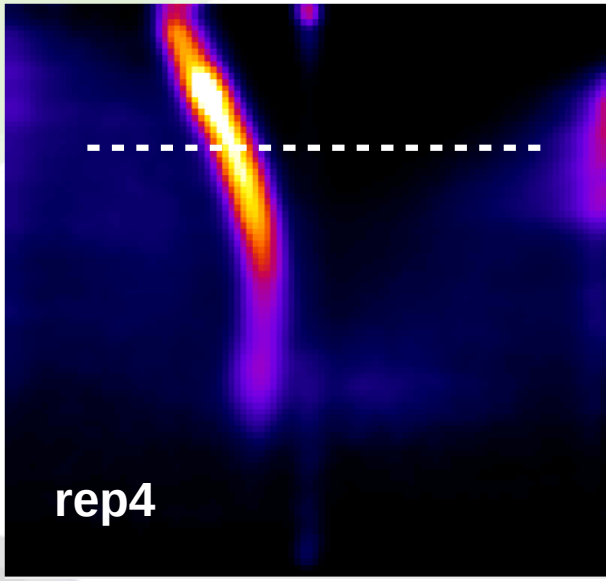
Preliminary – Glucose (FDG) allocation in Canola roots)



Soil level







EXPANSION CAPACITIES

→ Main facility

→ Rooms still vacant in cGMP clean area

→ Radiopharmacy expansion capacities
→ Room for additional bulk equipment (biosafety cabinets…)

→ Rm 168.1 (between production and research hot labs): vacant

→ Proposal submitted

→ Integrate into cGMP area
→ Outfit it with Grade A processing/dispensing hot cells, mini hot cells, telemanipulator arms, etc.

EXPANSION CAPACITIES

→ Research wing

→ 1 small room being renovated

→ Cell Culture Room
→ Temporarily also used for anesthesia/euthanasia procedures

→ Awaiting funding to renovate remaining 3 large and 2 small rooms

→ 1 large room: Phytosuite equipped with plant growing chamber and all necessary equipment for establishing a strong plant imaging research program (academia + industry)
→ 1 small room: Necropsy suite
→ More pre-clinical imaging equipment (additional microPET scanner…)

Visit from Minister of Science Kirsty Duncan

(January 2017)

- Medical geographer
- Published a book about her 1998 expedition to uncover the cause of the 1918 Spanish flu epidemic
- Also currently an adjunct professor at the University of Toronto

Visit from
Premier Brad Wall
and Minister of Health Jim Reiter
together with the media
(July 2017)

→ To celebrate our recent achievements

- Reliable supply of ^{18}F-FDG to RUH for > 1 year
- Back-up supply of ^{18}F-FDG to Foothills Medical Centre in Calgary

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The end!
Thank you!

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Energy.
Environment.