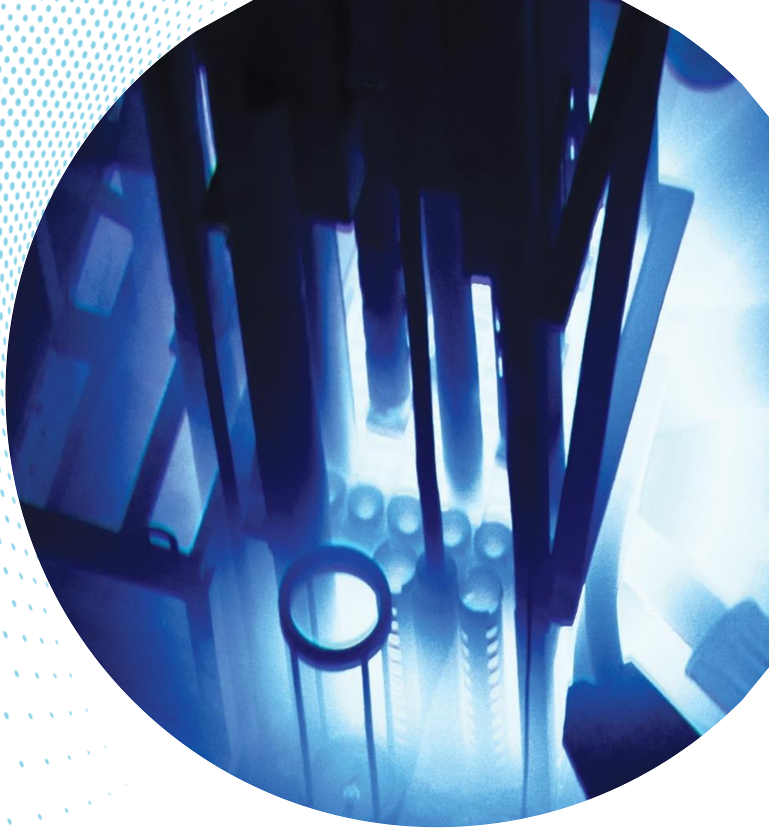
# Radioisotopes in Medicine

## & the McMaster Nuclear Reactor




Andrea Armstrong

Research Scientist & Adjunct Professor

# Canada's Most Research-Intensive University

## Hamilton, ON, Canada

- Student-centred, research-intensive university
  - Among top 75 universities in the world
  - 70+ research centres and institutes
  - 33,000 students

- Full lifecycle nuclear research programs
  - Nuclear safety
  - Engineering physics
  - Materials science
  - Detector physics
  - Radiation biology & ecology
  - Waste storage & reduction
  - Radiopharmaceuticals



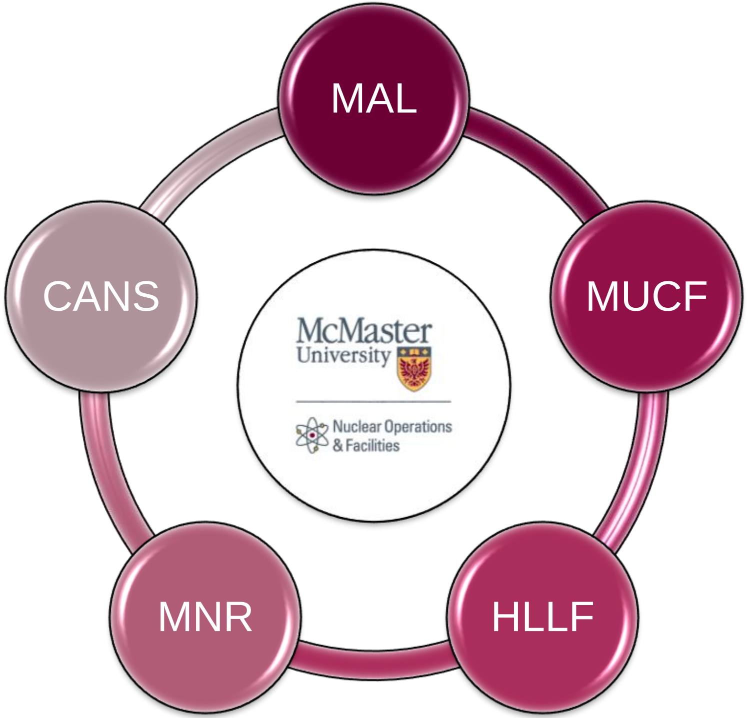


McMaster University

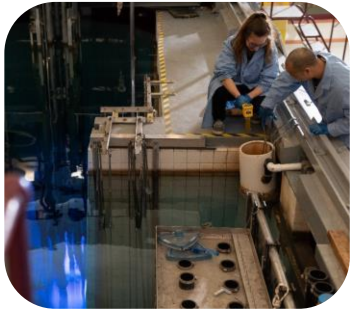
# McMaster: Canada's Nuclear University

Home to a unique suite of world class nuclear research facilities.

Centre for Advanced Nuclear Systems




High Level Laboratory Facility



McMaster Nuclear Reactor

McMaster Accelerator Laboratory

# MNR: Supporting High Impact Research

A national research resource

**Health & Medicine**

Radiopharmaceuticals, brachytherapy & implantable devices, disease biochemistry, clinical diagnostics & personalized medicine

**Energy & Environ-ment**

Alternative fuels, ecology, earth science & origins, nuclear energy, nuclear forensics, radiation biology, space exploration

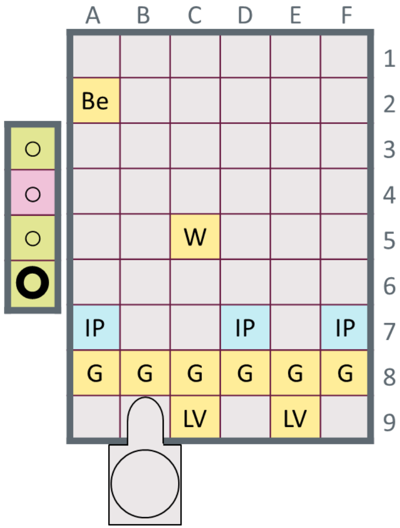
**Materials Science**

Neutron scattering → establishing an national user facility for Canada's neutron beam science community

# The McMaster Nuclear Reactor (MNR)

## Canada's only major neutron source

- 5 MW Materials Test Reactor
  - $\phi_{max} = 1 \times 10^{14}$ n/cm$^2$•s
  - Transition to 24 h operation 2023-24
- Variety of research facilities
  - Neutron diffraction
  - Small Angle Neutron Scattering
  - Neutron radiography
  - Intense positron beam
  - Industrial hot cell
  - 10 kCi Co-60 source (gamma irradiations)
- Range of irradiation facilities
  - Radioanalytical, high flux large volume
  - Differing neutron flux profiles
  - Pb- and Cd-shielded sites available

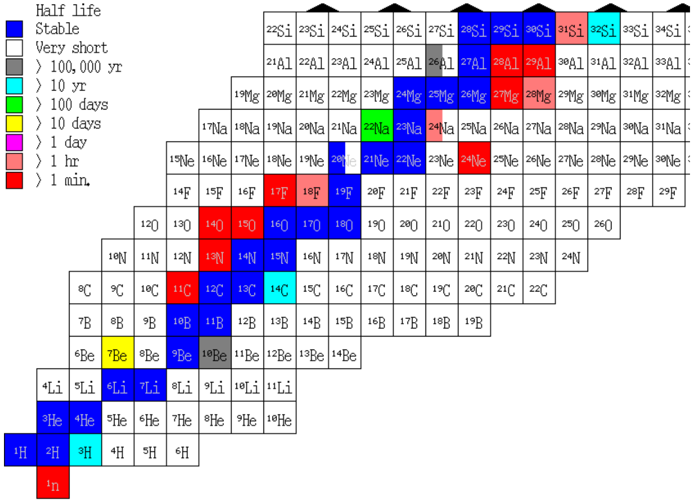




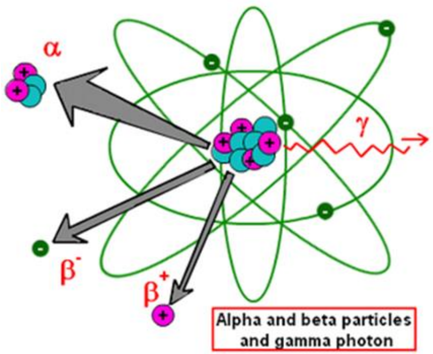

McMaster University

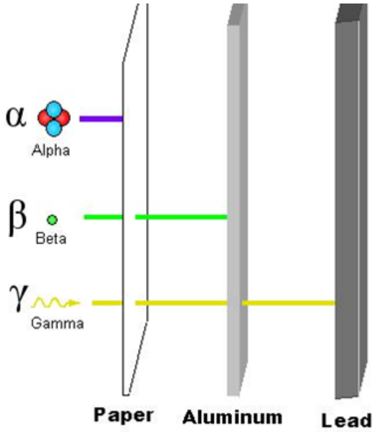
# Radioisotopes: How They’re Made

## Cyclotrons & nuclear reactors are complementary




- Radioisotope: nucleus in excited state




*Decay properties (emissions, half-life) determine utility*

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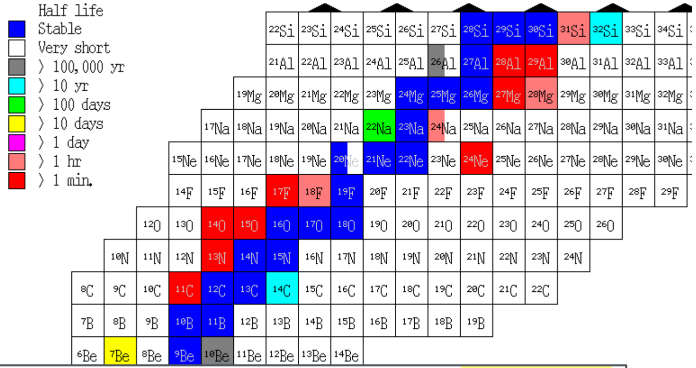
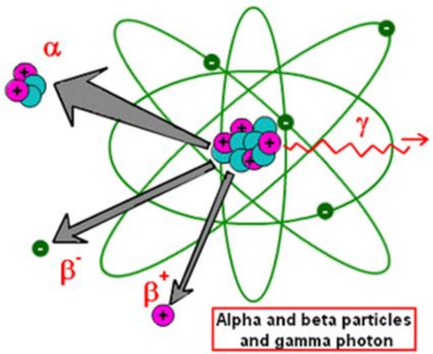
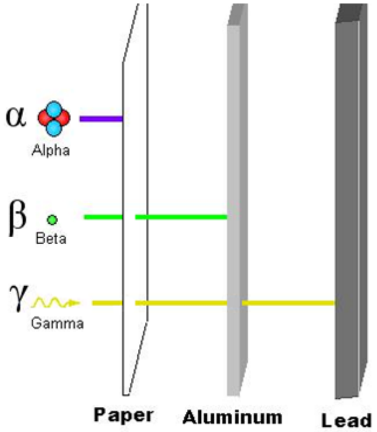
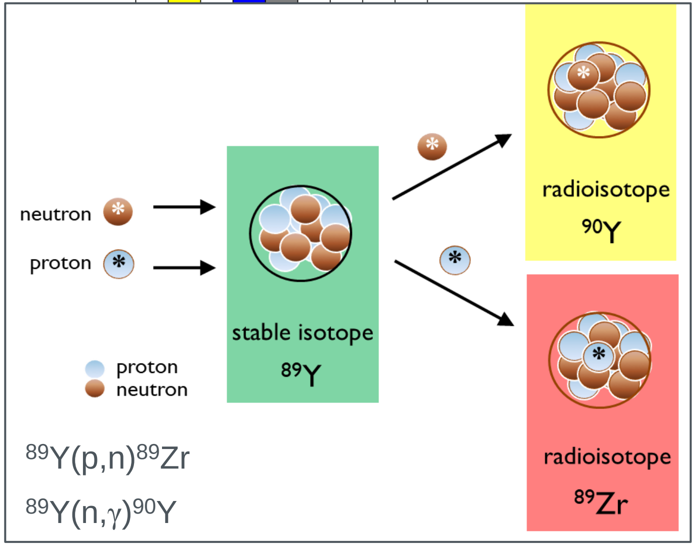


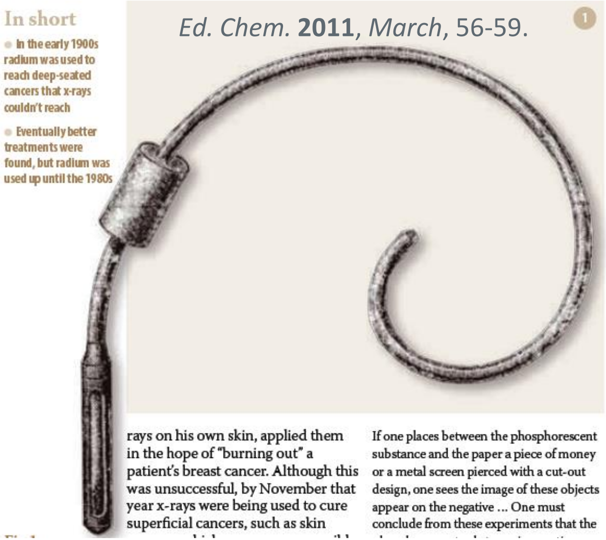

*Decay properties (emissions, half-life) determine utility*

# Radium-226: The Original Medical Isotope  Brachytherapy (1900s)

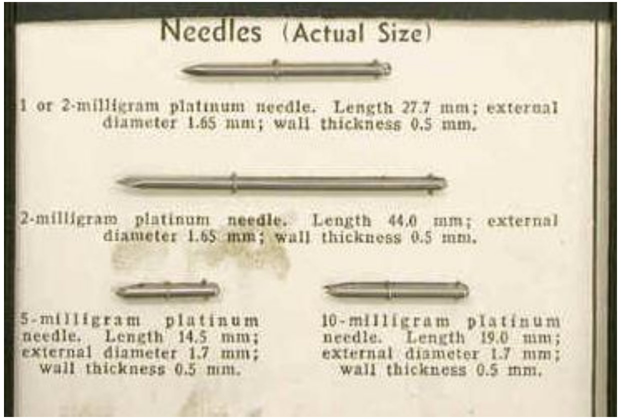
## 1898: Marie Curie discovers radium (Ra-226)

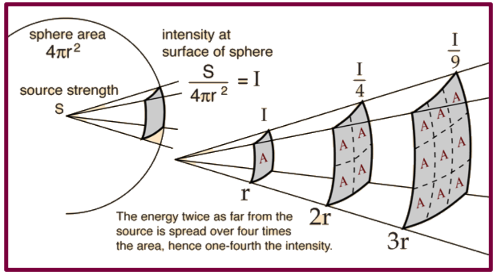
*“Furthermore, radium owns astonishing physiologic properties. An exposure of the arm to two 20 minute sessions  has produced **an inflammation of the skin** which has lasted two weeks…”*

*–  Friedrich Walkoff (1900)*




Ed. Chem. **2011**, March, 56-59.



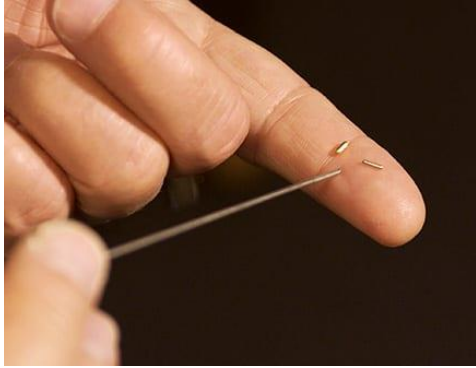




*“…the cervix [had] a large mass of growth with a large crater-like cavity. Twelve exposures of half an hour each with a ‘strong’ tube… [caused] **breaking down and diminishing the malignant tissue**.”*

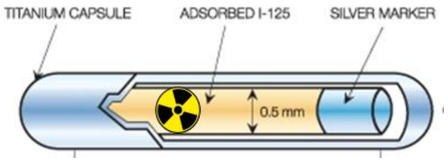
*– John MacLeod (1904)*

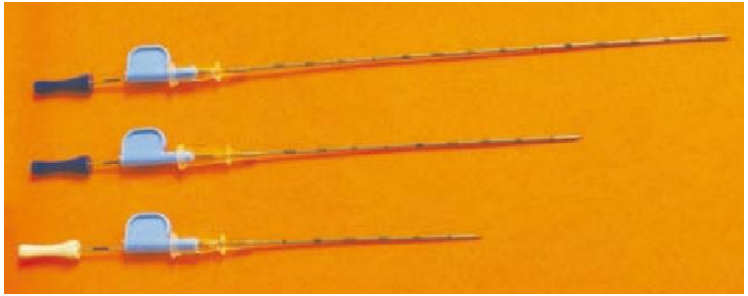
# Low Dose Rate (LDR) Brachytherapy Today

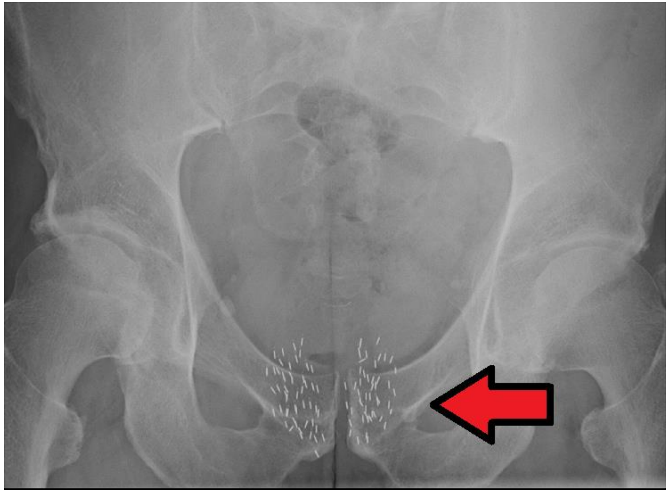
Iodine-125: $t_{½}$ = 60 d; $E_{\gamma}$ = 28-31 keV.
Palladium-103: $t_{½}$ = 17 d; $E_{\gamma}$ = 21 keV.



- Localized, non-aggressive (prostate) cancer
  - 52% decline in mortality 1993-2015



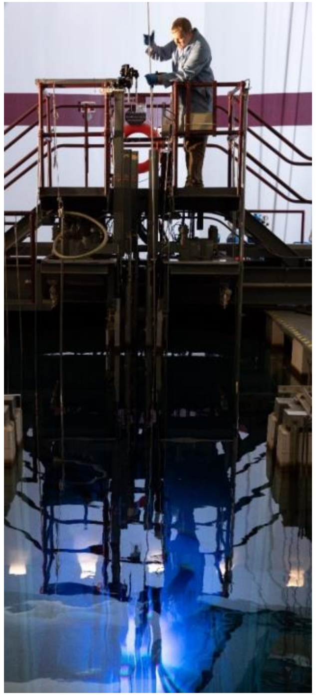


*X-ray image of implanted I-125 seeds*

# Iodine-125 Production Overview

## McMaster: 60% of global supply – 70,000 patients every year

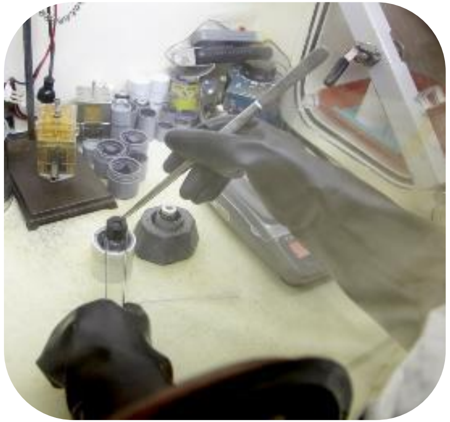
*Xe-124 loaded into cylinder*



*Neutron irradiation*

*Chamber containing I-125 removed*

*I-125 recovery*



*Making a stock solution*

# Iodine-125 Production Overview

## More than 200 patients treated every day

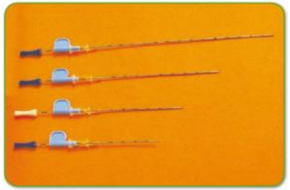
*“Dispensing” stock solution*

*Customer vial*

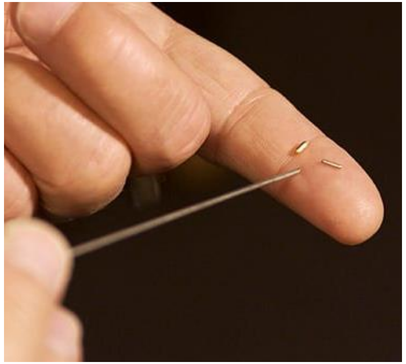
*Shipping to seed manufacturers*

# Modern Brachytherapy

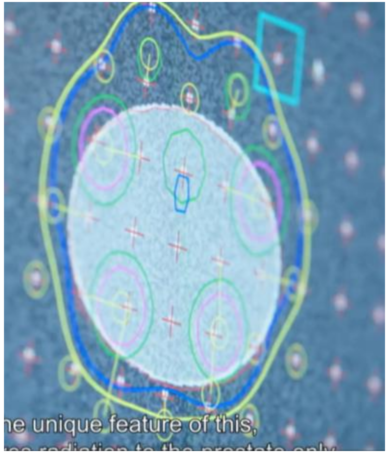
## Permanent (Low Dose Rate), iodine-125 or palladium-103

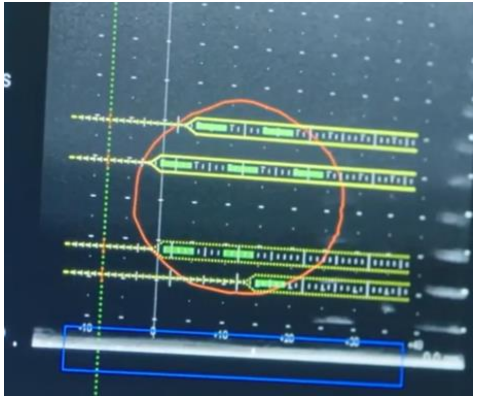


- Image-guided implantation, complete in 60-120 minutes

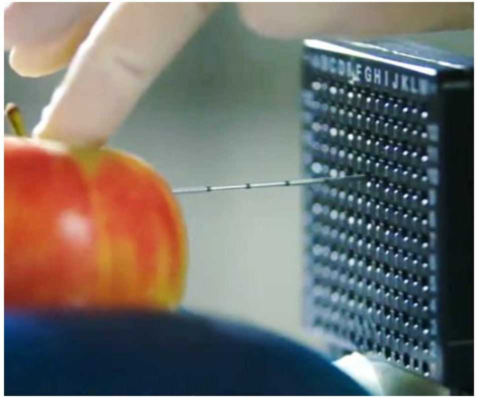


*Seed manufacturing*



*Treatment planning: seed selection & implantation modelling*



*Seed implantation*

- Alternative to External Beam Radiation Therapy?
    - $2,719 US per patient

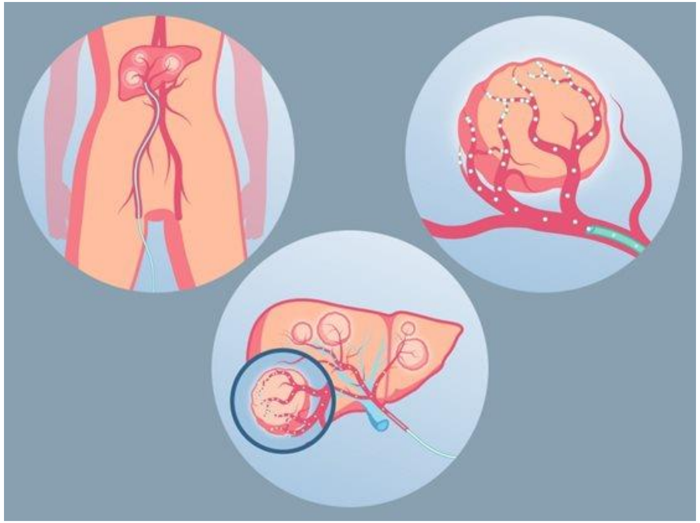


Cost: Brookland & Mallin, *Bull. Am. Coll. Surgeons* 2019 (April)

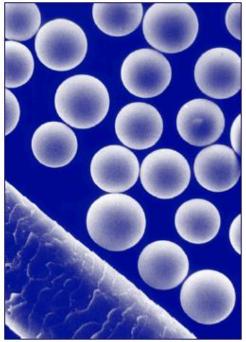
# Building on Brachytherapy: Radioembolic Therapy

## Liver cancer therapy (1990s)

- Dual action therapy
  1. Block blood supply to tumour
  2. Blast with beta particles



- TheraSphere (Y-90 in glass matrix)
  - 70,000+ patients, FDA approval 2021
  - Similar to SIRSpheres (resin)



*TheraSphere & human hair*

*PET imaging before (left) and after (right) treatment*

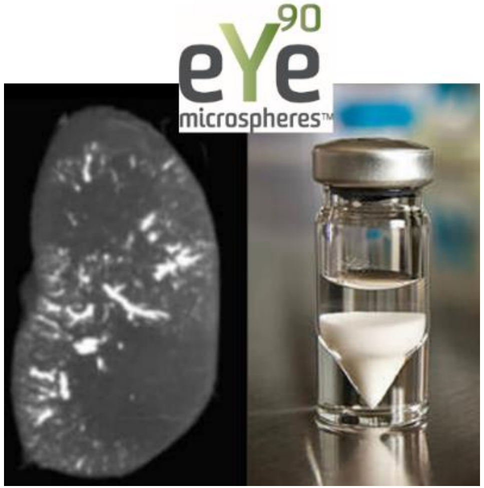
*J. Vasc. Interv. Radiol.* **2005**, *16*, 1641–1651

# The Next Generation: Imageable Radioembolics

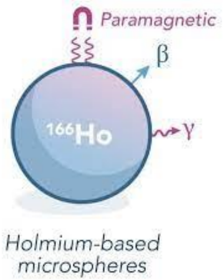
## R&D at the McMaster Nuclear Reactor

DALHOUSIE UNIVERSITY

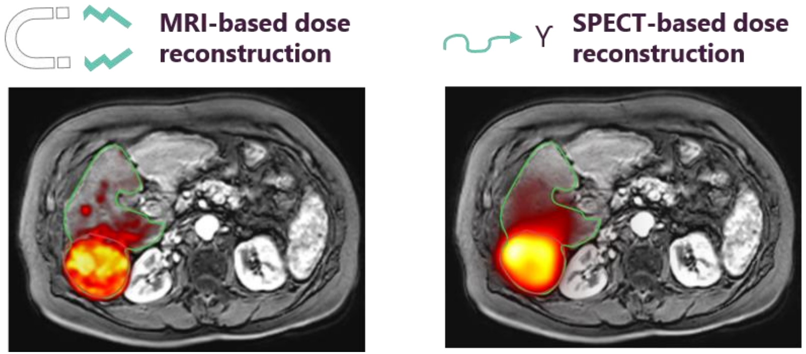
ABK BIOMEDICAL




*"Radiopaque" glass microspheres (Y-90)*




Quirem

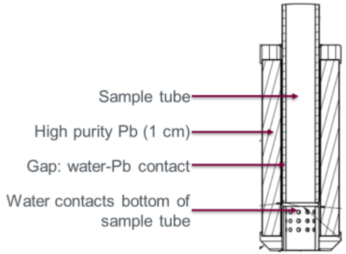



*Polylactic acid containing holmium (→ Ho-166)*

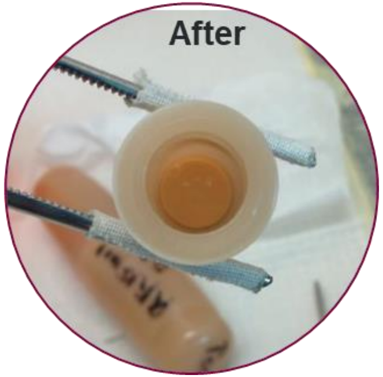
McMaster University

# QuiremSpheres: Low Gamma Irradiations Required

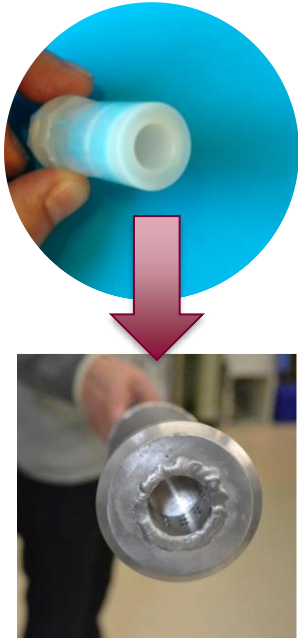
## Vial & site redesign




- Initial experiments: standard conditions


- Pb sample chamber



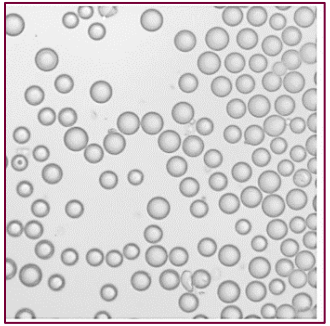
- First patient treatment from McMaster June 2019
  - 20-90% of global supply (Europe)
  - Production capacity +200% since 2019

# Current QuiremSpheres Work

## North American clinical trial launching 2023

Centre for Probe Development and Commercialization

- cGMP Dispensing Lab: joint initiative with CPDC
    - Clinical trial site in Vancouver – possible first in North America

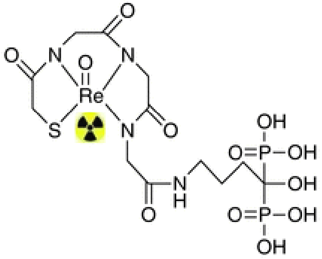


- Basic science: enhancing survival of QS post-suspension
    - Roles of beta, gamma, temperature, etc

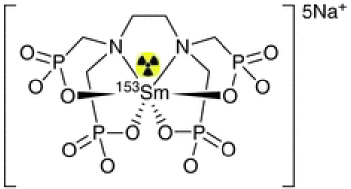
# Therapeutic Radiopharmaceuticals (Targeted Internal Radionuclide Therapy)

Treating systemic (not localized) cancers

- 1937: John Lawrence uses P-32 to treat blood cancers
  - Questionable effectiveness
- 1942: use of I-131 to treat metastatic thyroid cancer
  - Standard of care for decades
- 1980s: bone pain palliation
  - Sr-89, Sm-153, Lu-177, Re-186, Re-188, etc.
- 1990s: antibody based drugs
  - Bexxar (I-131), Zevalin (Y-90)
  - Non-Hodgkins Lymphoma

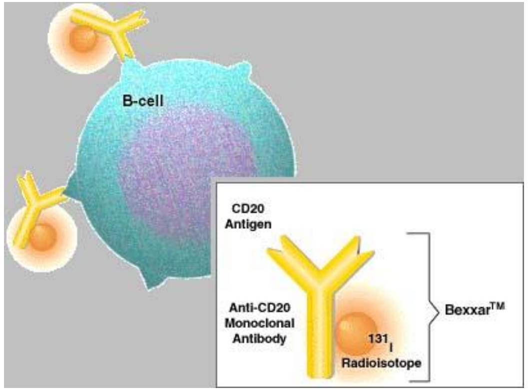


$^{186}Re/^{188}Re$-HEDP



$^{153}Sm$-EDTMP

*"Disguising" radiometals as phosphate*

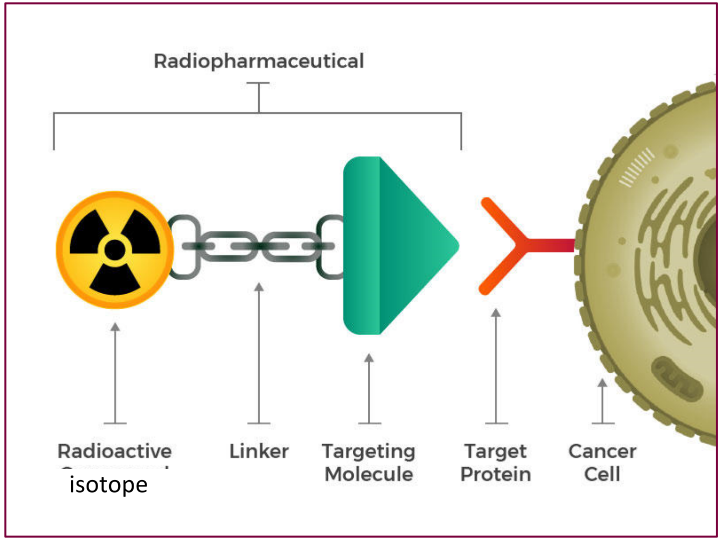



*Monoclonal antibody directs I-131 to cancer*

# Receptor/Antibody-Targeted Radiopharmaceuticals

## Advances in molecular biology enable new drugs

- 2000s: biochemical differences in healthy & diseased tissues
  - Attach biological “vector” to hit “target” cells
- $^{177}$Lu-DOTA-TATE (neuroendocrine tumours)
  - EU since 1990s, Health Canada approval 2019
- $^{177}$Lu-PSMA-617 (prostate cancer)
  - US FDA approval 2022
- Biological targets: HER2, PSMA, UPAR, ER, HGF…




*Schematic representation of a targeted radiopharmaceutical*

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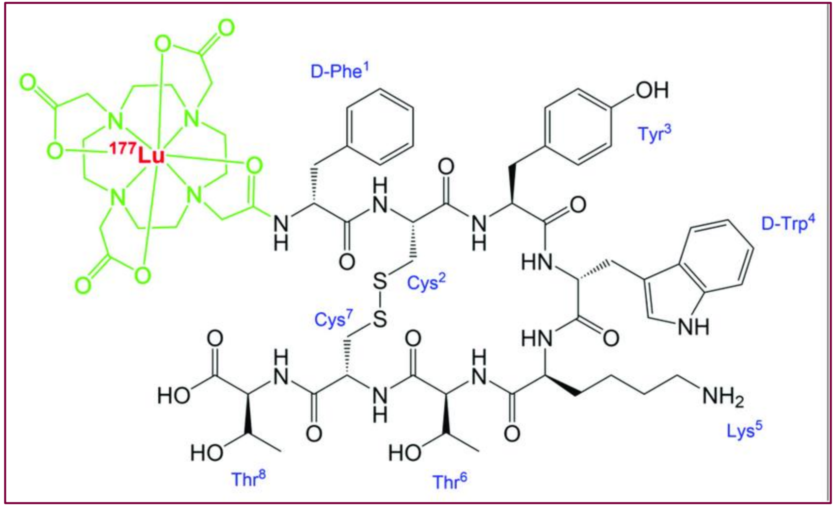
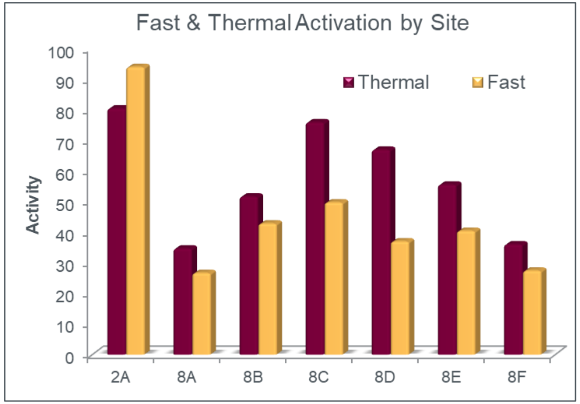



*Peptide seeks out NETs; Lu-177 destroys them*

# Direct Production of Lu-177: $^{176}Lu(n,\gamma)^{177}Lu$ ($\sigma$ = ~~2100~~ 2915 b)

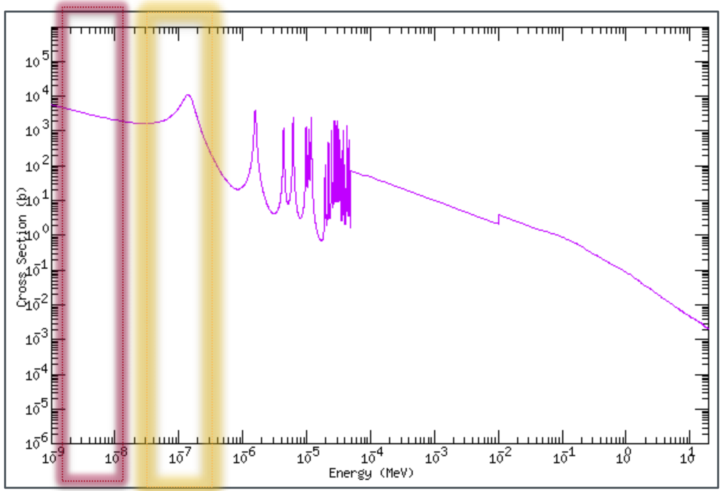
Supporting Canadian researchers since 2012.

- Capitalizing on fast neutron resonance (site 2A)
  - S.A. >1.6 Ci/mg @ 80% enrichment (20 Ci/mg 24/5 @ 5 MW)
  - Lu-177m content 0.0097%
  - Production capacity essentially unlimited




Thermal neutron flux from $^{50}Cr(n,\gamma)^{51}Cr$

Epithermal/fast flux from $^{27}Al(n,\alpha)^{24}Na$

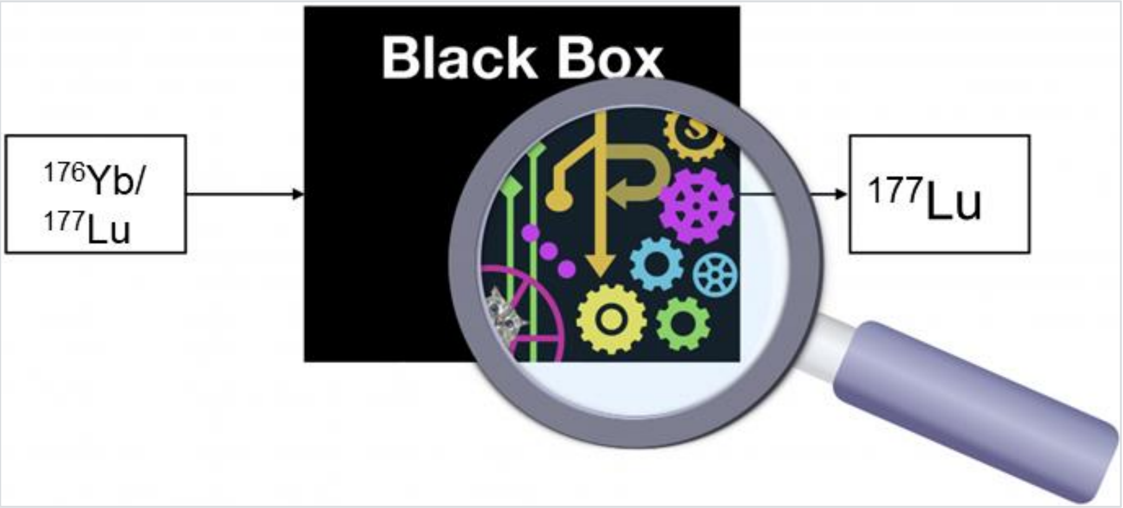



$^{176}Lu(n,\gamma)^{177}Lu$ energy-dependent cross-section

# Whiteboarding No Carrier Added Lu-177 at McMaster

## Reflecting on chromatography-based process (March 2020)

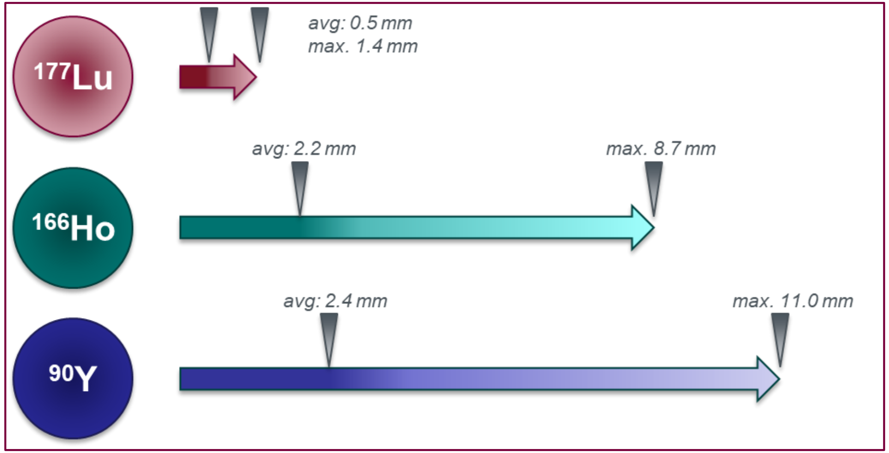
- Ideal process characteristics
  - 1 gram target (with potential for scale-up)
  - Minimal waste
  - Easy-to-recycle target
  - All components readily available
  - Potential for automation/standardization (GMP)
  - Deployable at other sites



# Recent Releases & In the Pipeline

## Therapeutics for “personalized medicine”

- n.c.a. Lu-177 distributing since Fall 2021
  - $^{176}Yb(n,\gamma)^{177}Yb \rightarrow {}^{177}Lu$
  - Proprietary method compatible with medium-flux reactors
  - Meets industry-standard specifications
  - Automation in progress (NSERC I2I)
- n.c.a. Ho-166 distributing July 2022
  - $^{164}Dy(n,\gamma)^{165}Dy(n,\gamma)^{166}Dy \rightarrow {}^{166}Ho$
  - Low pressure chromatography
- n.c.a. Y-90 generator design validated ($^{90}Sr/^{90}Y$)
  - Costing assessment for materials, equipment
  - Goal: 1 mCi generator by 2023




*Tripositive therapeutics: beta range in tissue (to scale)*



Range in tissue from *J. Label. Compd. Radiopharm.* **2018**, *61*, 693-714.

# Summary & Conclusions

MNR: Canada's sole source of neutron-rich isotopes, on-demand

- Radioisotopes: treating cancer since 1901!
- New technologies, and new applications of old technology
  - LDR brachytherapy (new populations)
  - Imageable radioembolics (clinical trials beyond liver cancer)
  - Receptor-targeted drugs ("renaissance in radiopharmaceuticals")
    - Paired with diagnostic imaging agents
- Ensuring that researchers have early access to next-generation radioisotopes is essential to building & maintaining a culture of innovation in the radiopharmaceutical space


*Thank-you for your attention.*

Andrea Armstrong

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