TRIUMF

Cyclotrons for Medicine

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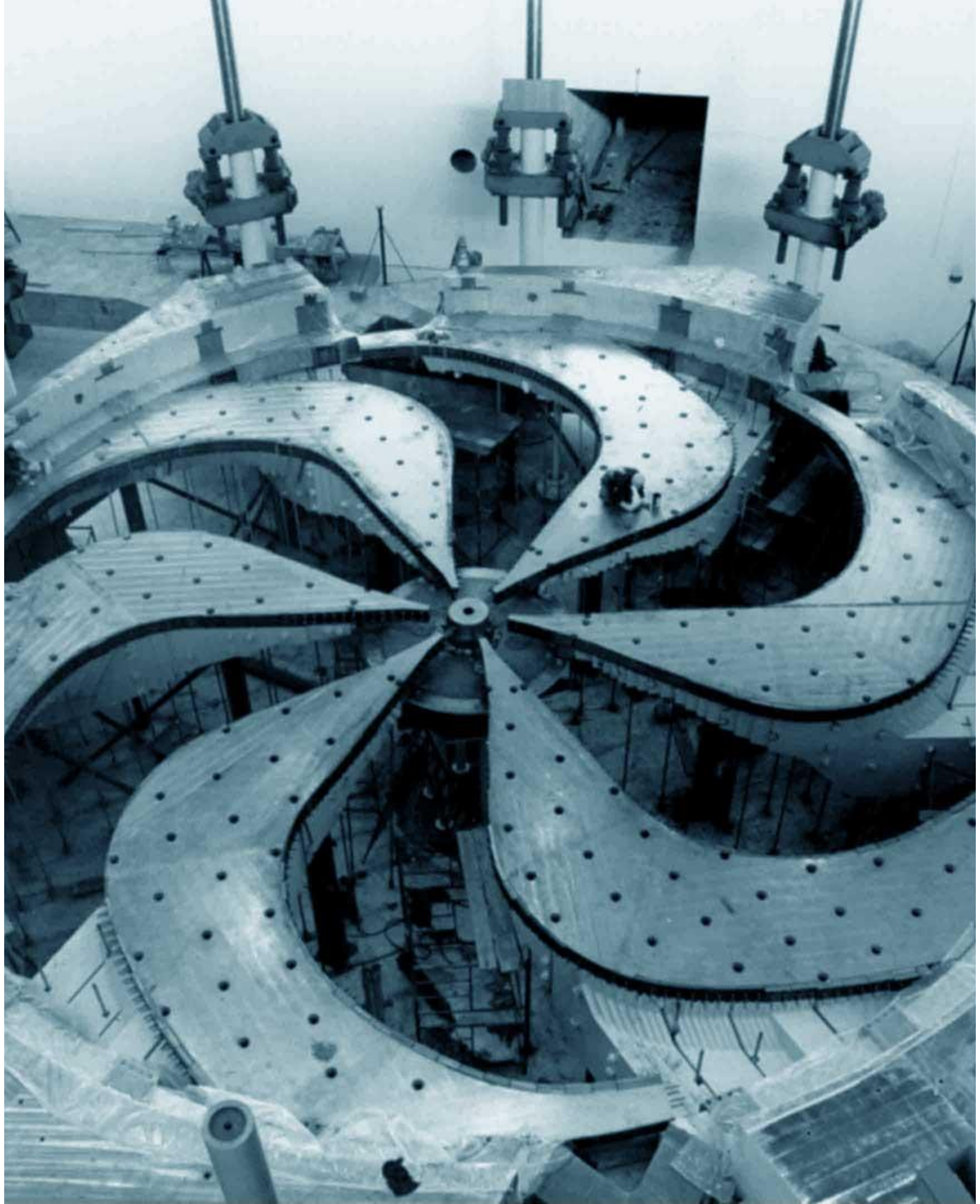
2019-06-03



Discovery,
accelerated

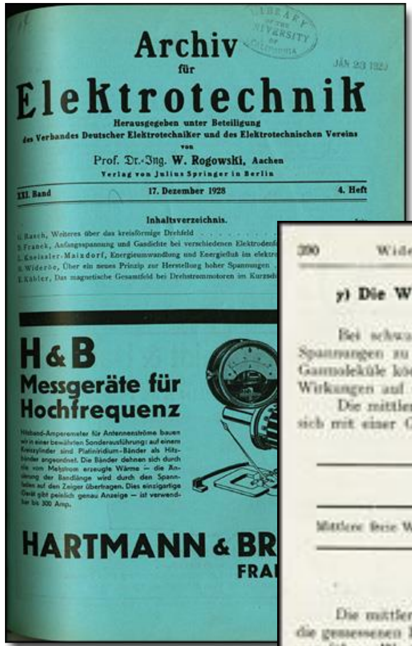
Outline

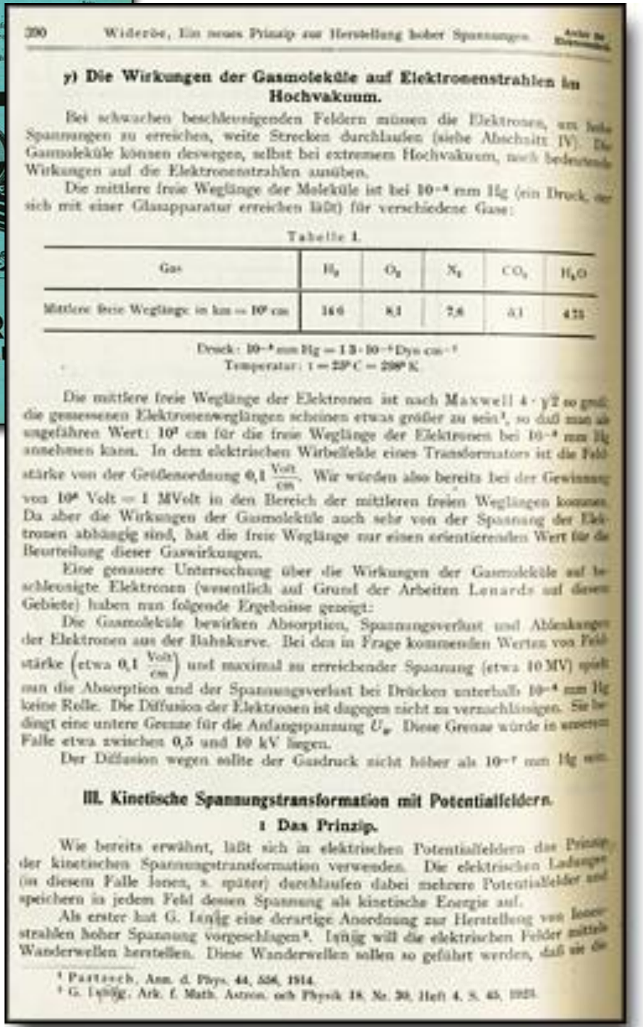
- Cyclotrons – history and basics on how they work
- Nuclear medicine and radioisotopes
- Radiotherapy – external with cyclotrons

  – internal with radioisotopes

Cyclotron - history

- Invented by Ernest Lawrence at Berkeley 1929/30,
- Built by grad student Livingston,
- Patent 1932,
- Nobel prize 1939




Widerøe, Ein neues Prinzip zur Herstellung hoher Spannungen.

γ) Die Wirkungen der Gasmoleküle auf Elektronenstrahlen im Hochvakuum.

Tabelle 1.

Gas	H_2	O_2	N_2	CO_2	H_2O
Mittlere freie Weglänge in km = 10^5 cm	16,6	8,1	7,6	5,1	4,75

III. Kinetische Spannungstransformation mit Potentialfeldern.

1. Das Prinzip.

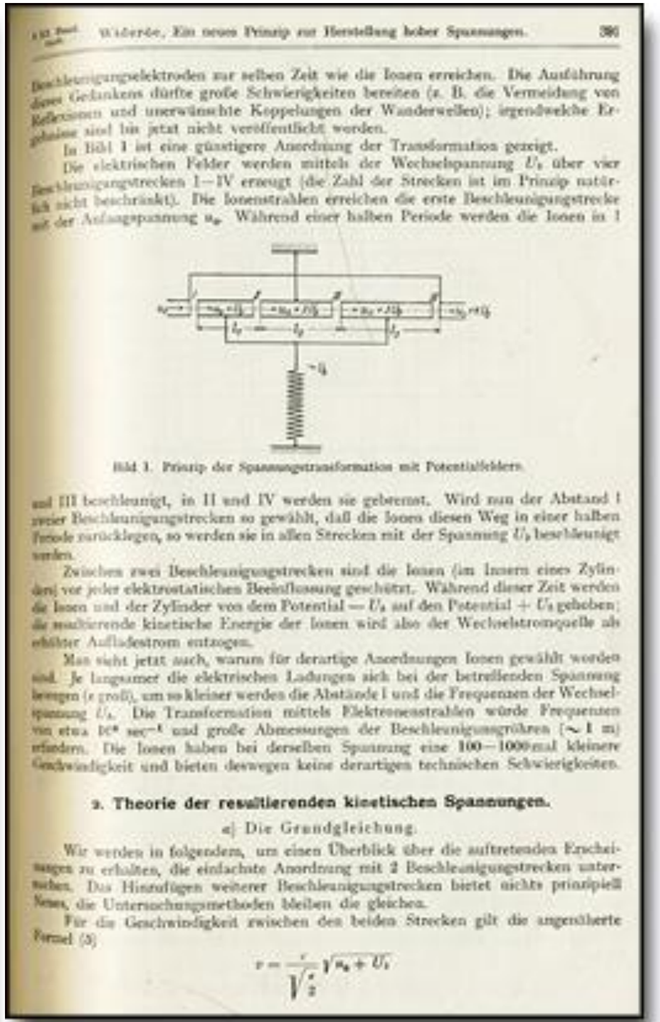

Widerøe, Ein neues Prinzip zur Herstellung hoher Spannungen.

Bild 1. Prinzip der Spannungstransformation mit Potentialfeldern.

2. Theorie der resultierenden kinetischen Spannungen.

a) Die Grundgleichung.

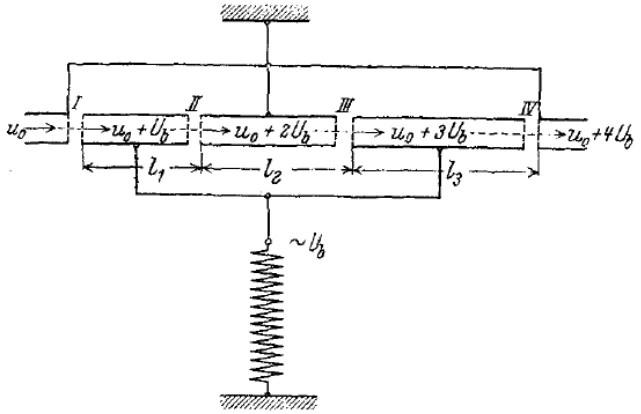
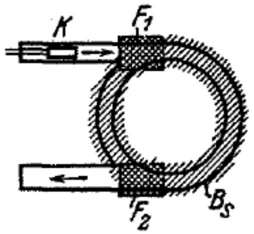


Bild 1. Prinzip der Spannungstransformation mit Potentialfeldern.



Cyclotron – how it works

$$\mathbf{F} = q\ \mathbf{v} \times \mathbf{B}$$

$$q\,\cancel{r\omega}B = m\,\cancel{r}\omega^{\cancel{2}} = m\,\omega.$$

orbits are isochronous

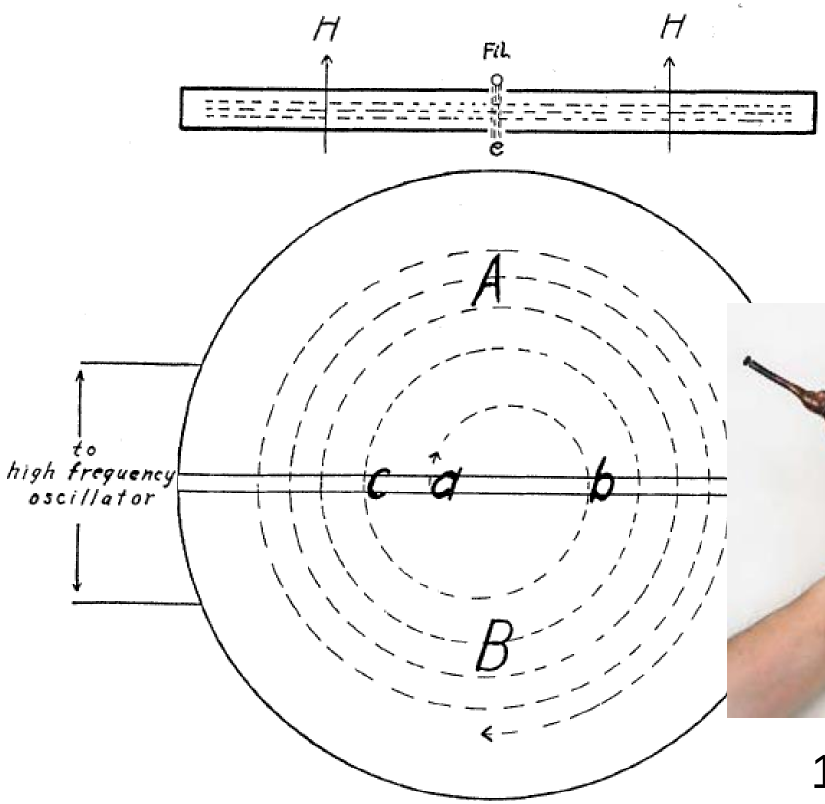
$$\omega = \frac{qB}{m} \qquad r = mv/qB.$$

APRIL 1, 1932 PHYSICAL REVIEW VOLUME 40

THE PRODUCTION OF HIGH SPEED LIGHT IONS WITHOUT THE USE OF HIGH VOLTAGES

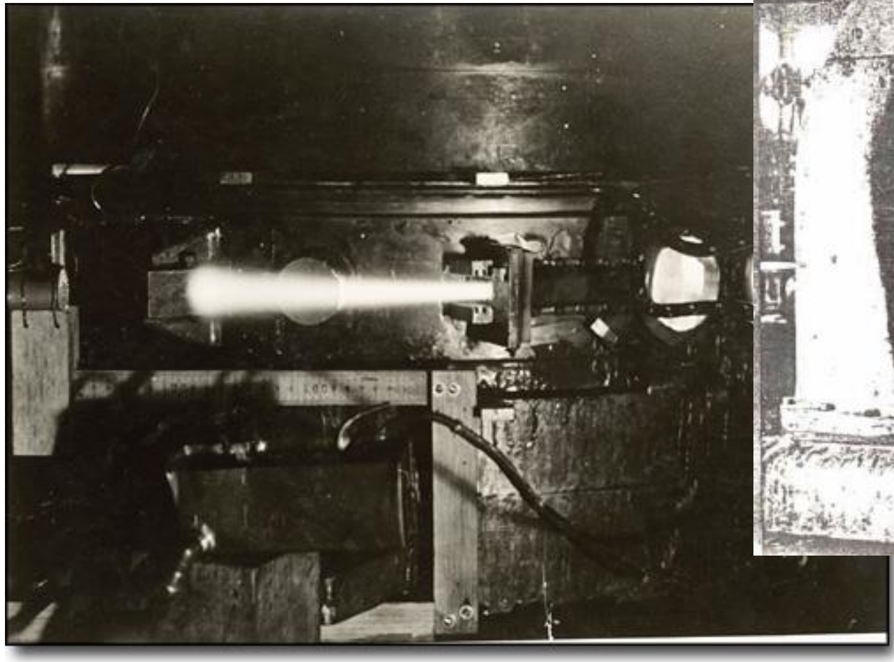
By Ernest O. Lawrence and M. Stanley Livingston
University of California

(Received February 20, 1932)

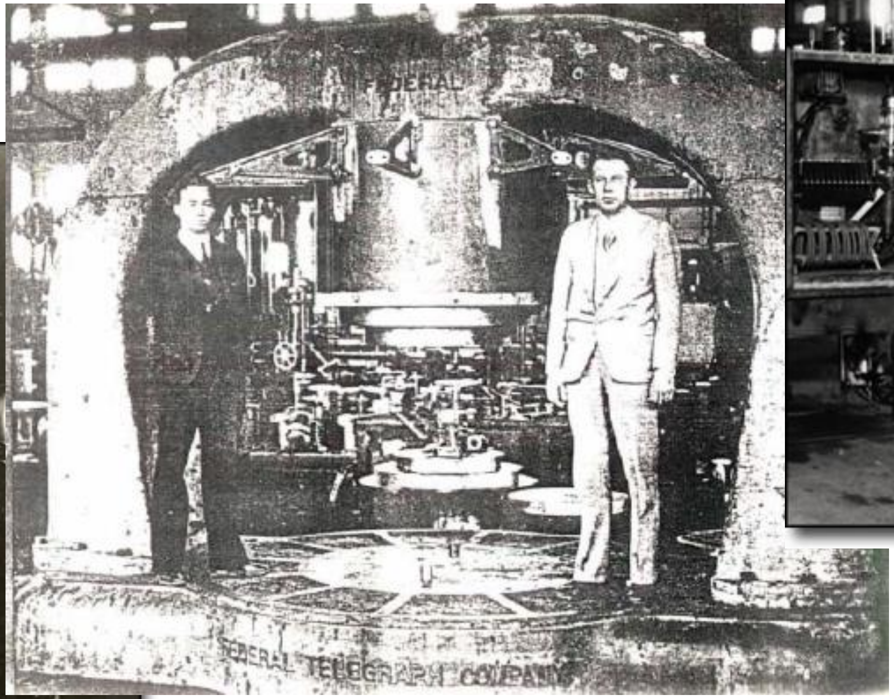


13 keV protons

Cyclotron - history



Glow from 11" (1.22 MeV protons) Cyclotron Beam

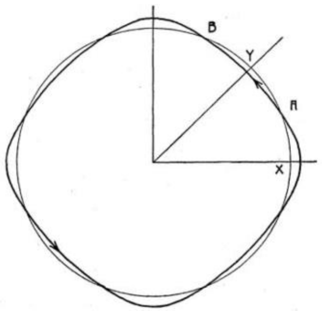


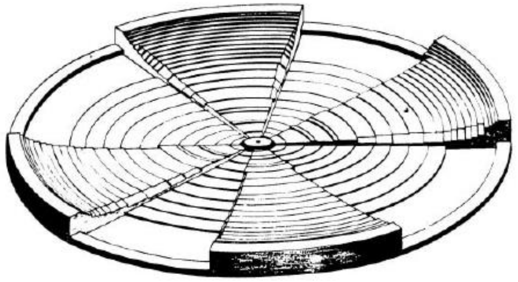
Lingston and Lawrence with the 27" Cyclotron, 6.3 MeV deuterons

Lawrence at Work on the 37" Cyclotron, 1937, 8.5 MeV deuterons

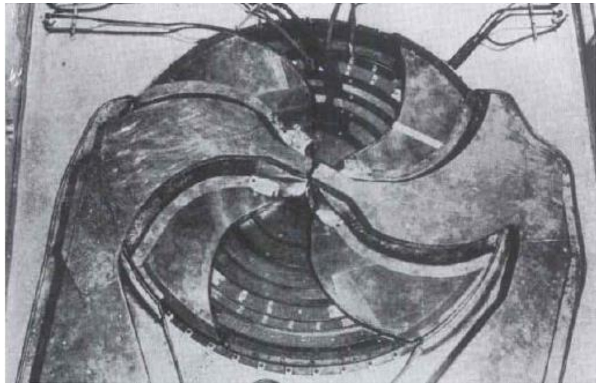
Higher energy cyclotrons

$$B_z(\theta) = \langle B_z(\theta) \rangle \,(1 + f \cos N\theta)$$

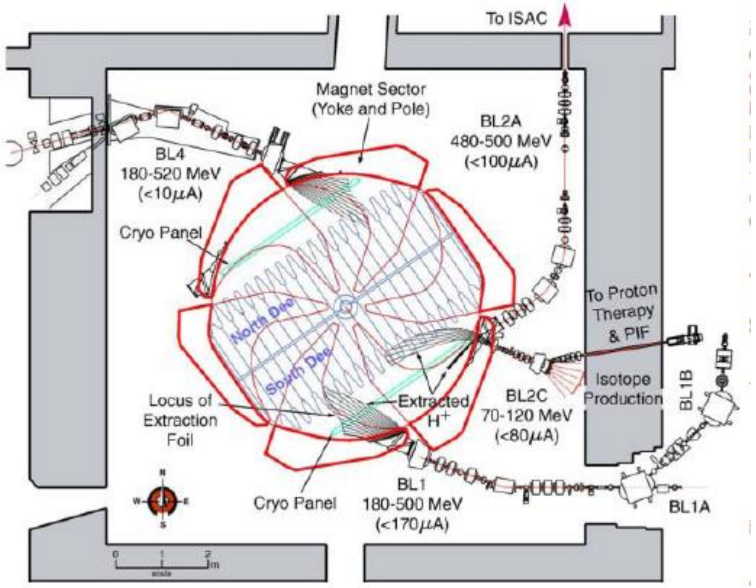




12.7 MeV Delft cyclotron



UCLA 50 MeV cyclotron



TRIUMF 500 MeV cyclotron

Nuclear Medicine - history

- 1898 discovery of radioactivity by Marie and Pierre Curie – radium therapy

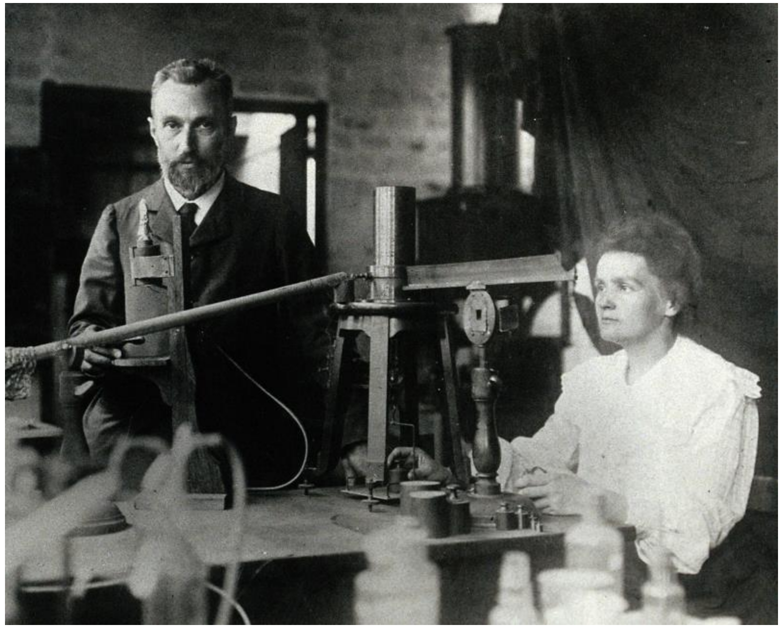
- First tracer study in 1924: blood circulation with Bi-212

- Irene Joliot-Curie & Frederic Joliot: Nature 1934 – producing radioactivity artificially

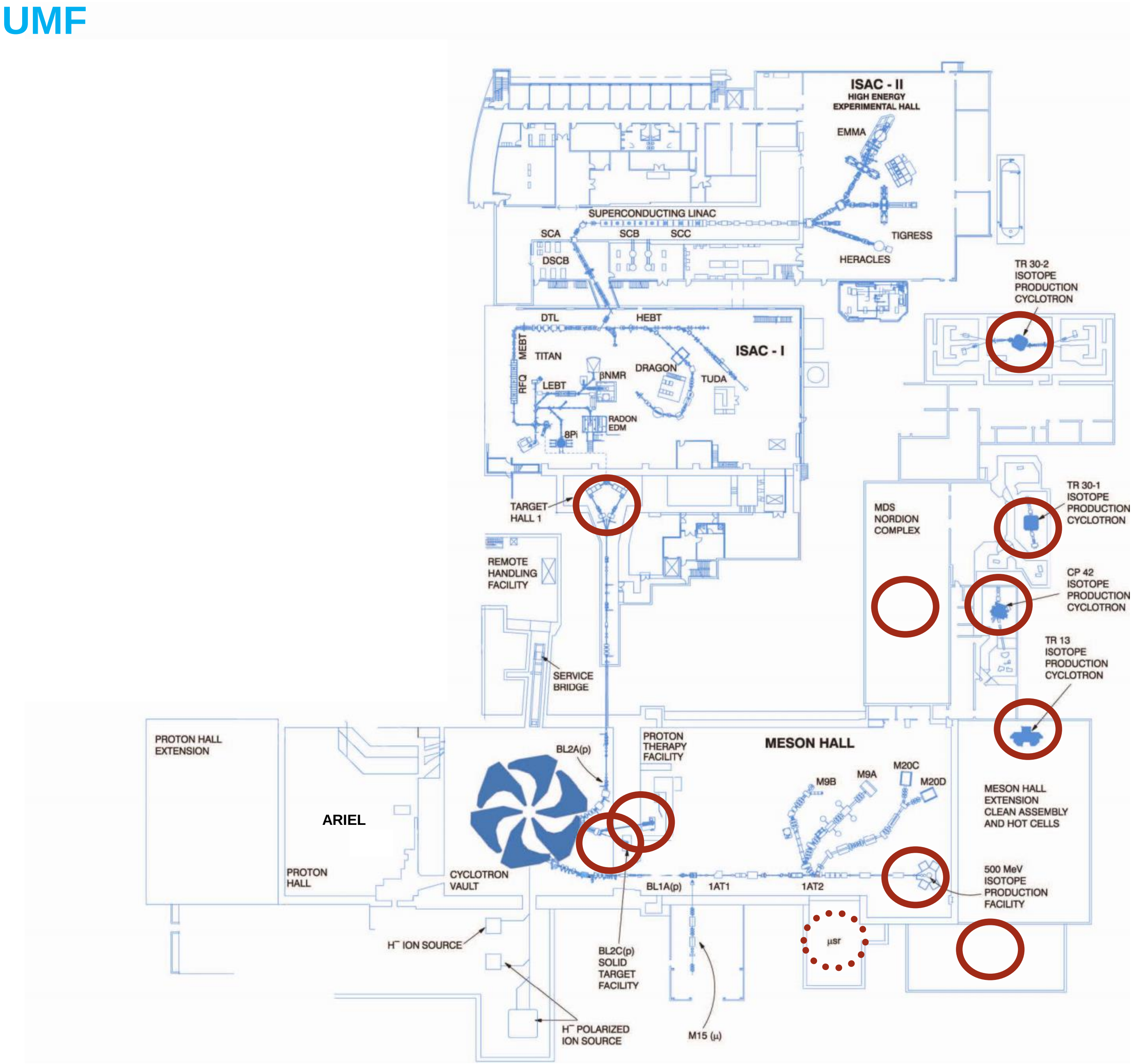
- Read by E. Lawrence ….. Cyclotron and Geiger counter were on the same circuit!

- SPECT – most common Tc-99m

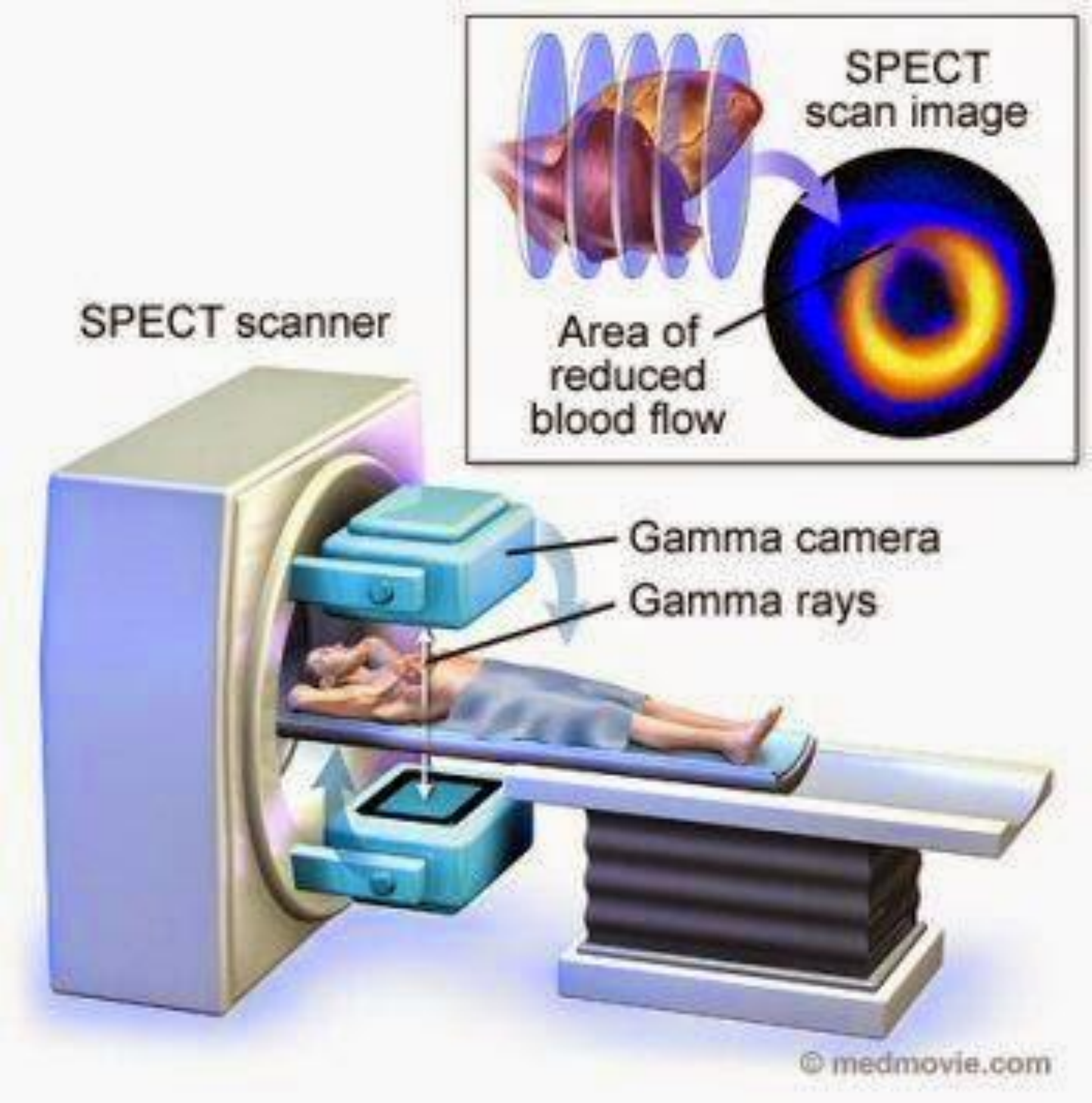
- PET – most common [F-18]FDG



Medical Application @ TRIUMF



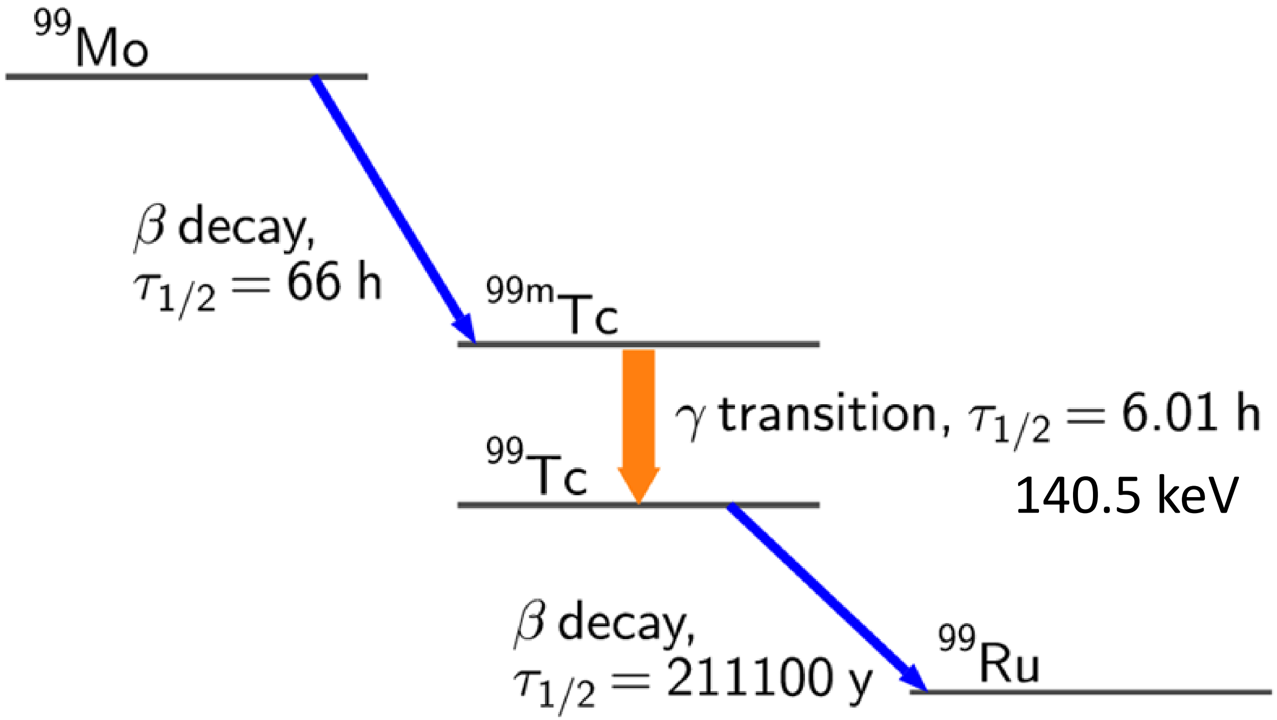
SPECT



Single-Photon Emission Computed Tomography

Most common SPECT isotope **Tc-99m**
40 Million doses every year
>1 scan/second (brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, tumors)

SPECT: Tc-99m



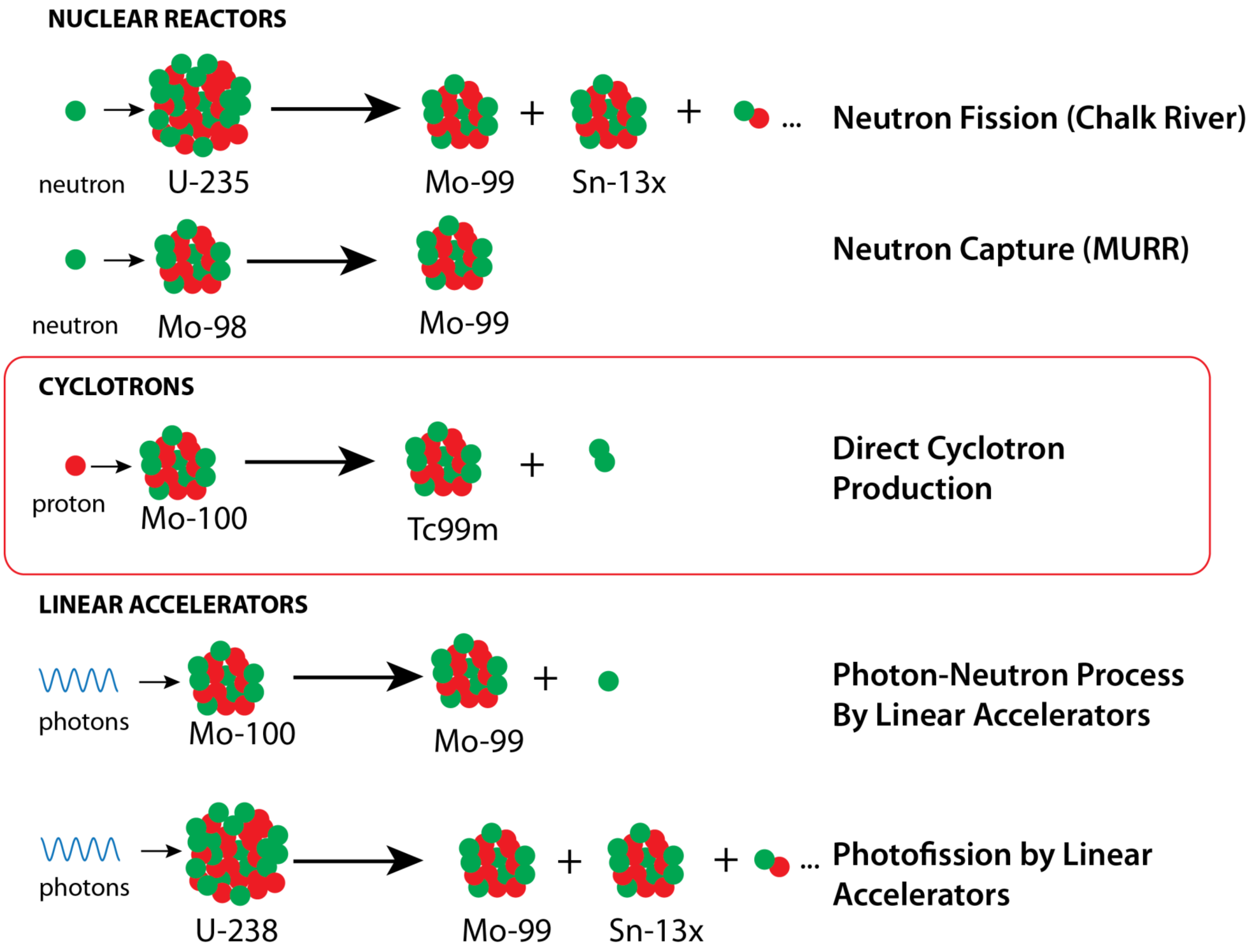
- Simple distribution & use

Making Isotopes

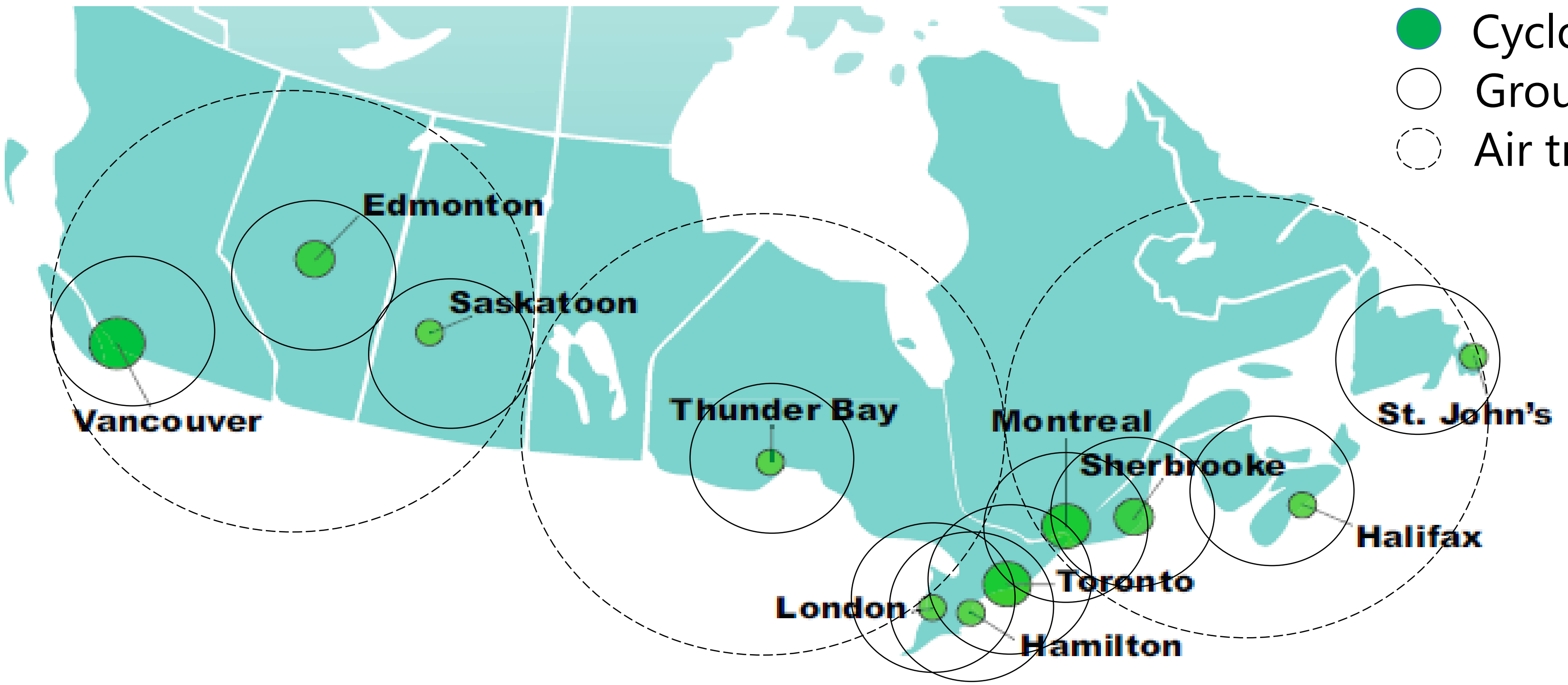
Reactor

Cyclotrons
(Accelerators)

The Technology



Alternative ^{99m}Tc Production



- Decentralized Production
  - ^{99m}Tc locally produced, locally used, competitively priced
  - Redundant supply to avoid widespread shortages
  - Complementary to:
    - other medical isotopes produced by cyclotrons (^{18}F)
    - other sources of ^{99m}Tc

J. Beaver, H. Hupf, J Nucl Med 1971;12:739-741

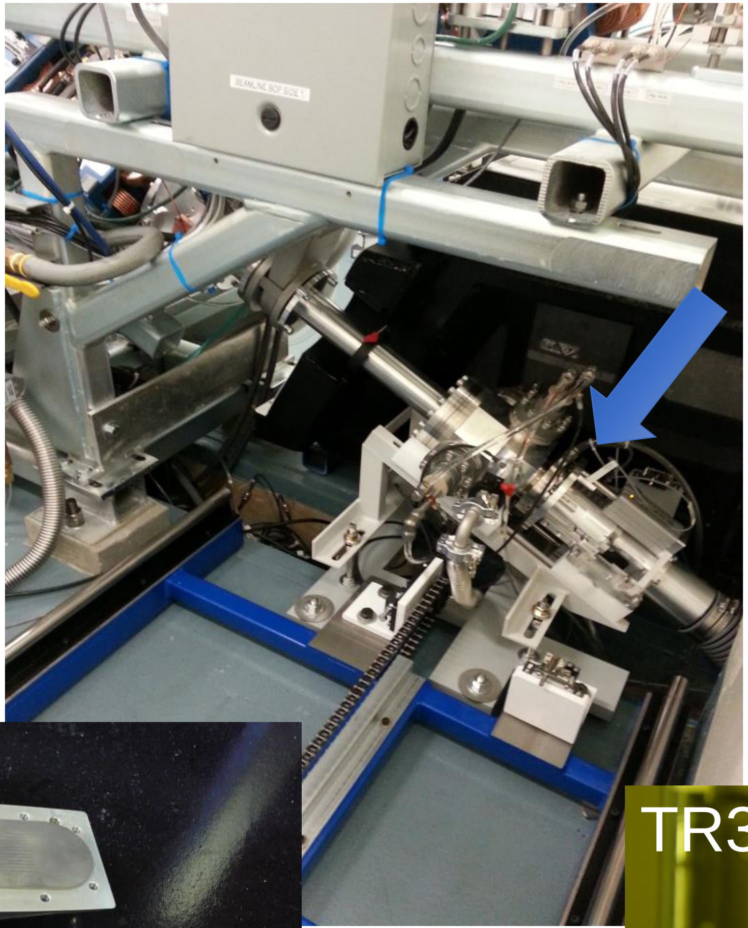
CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

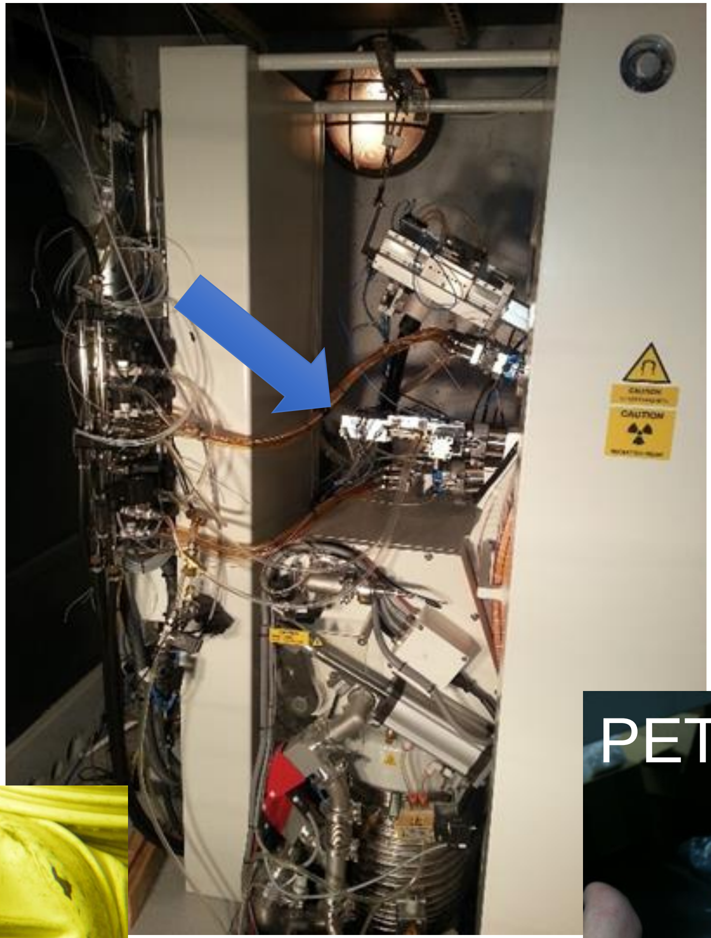
NSERC CRSNG

Natural Resources Canada | Ressources naturelles Canada

Canada

Cyclotron Production of ^{99m}Tc



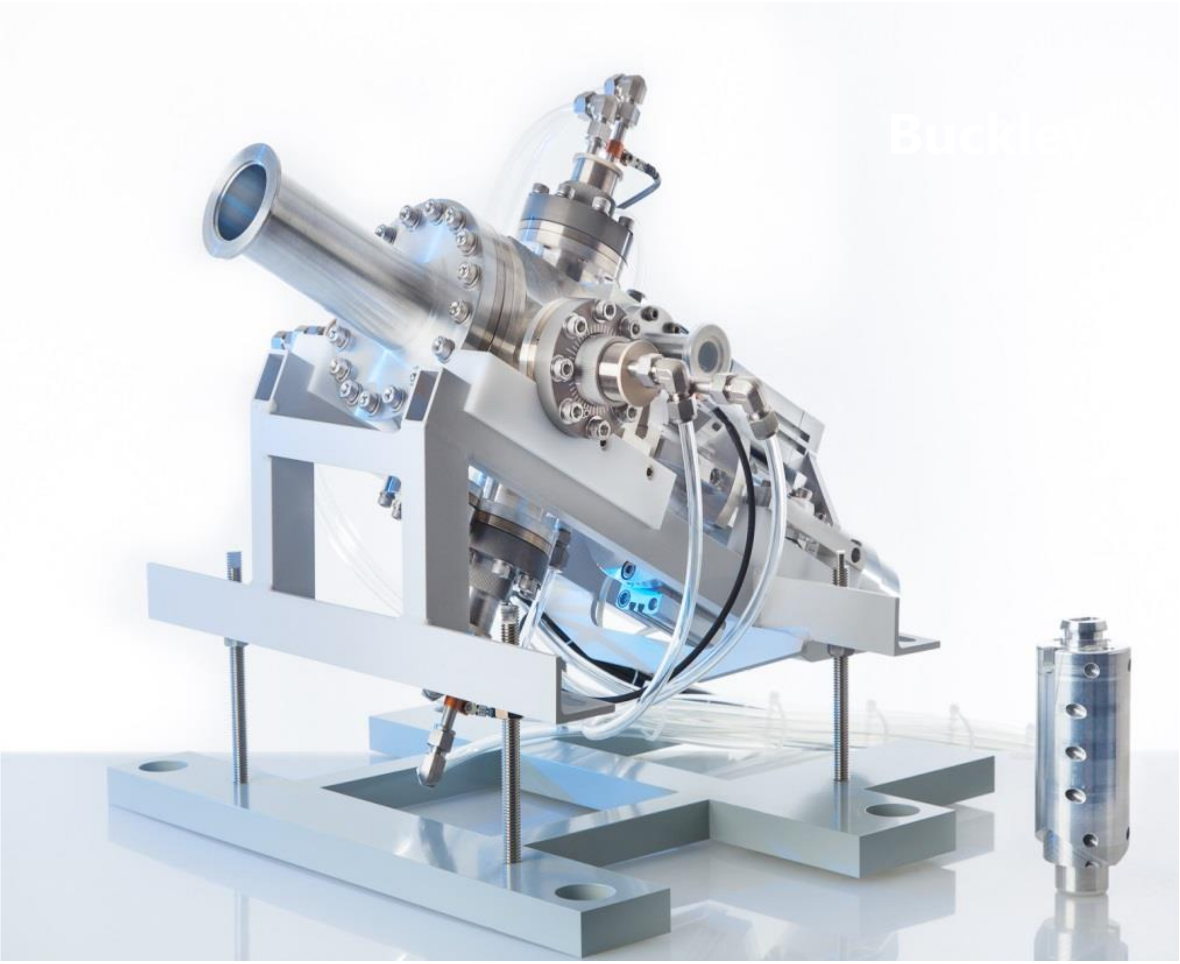


^{99m}Tc Path Forward: Clinic and Commercialization

- 2015 Brockhouse Canada Prize for Interdisciplinary Research in Science and Engineering by NSERC

- Project Status
  - 4.7 Ci (GE), 15 Ci (TR19), 32 Ci (TR30)
  - Clinical Trials Finished
    - Bone/thyroid (60/60 patients scanned)

- Commercialization
  - Sole license issued to ARTMS Products Inc.
  - Several systems sold and installed – more ordered



ARTMS ^{99m}Tc Production System

PET Scan

<u>P</u>ositron <u>E</u>mission <u>T</u>omography

Radioactive tracer injected into body,
Uptake into different organs

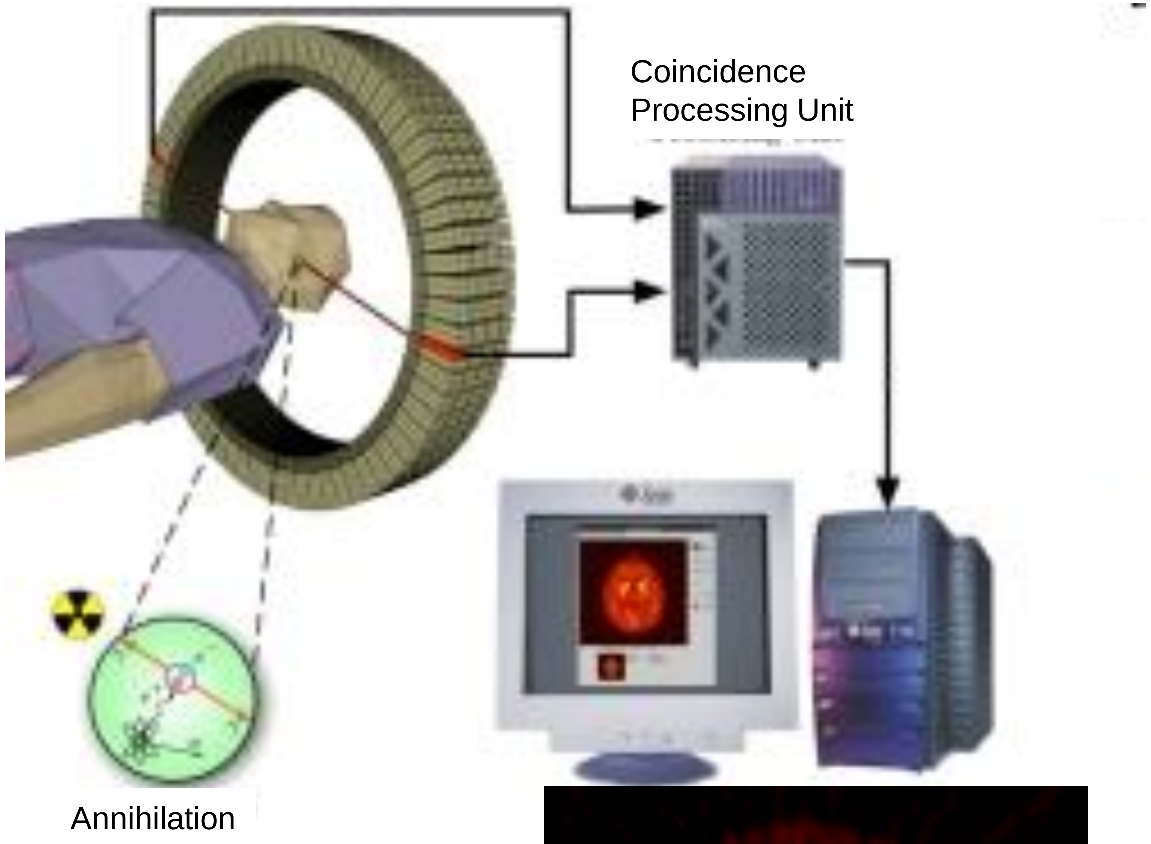
Positron decay

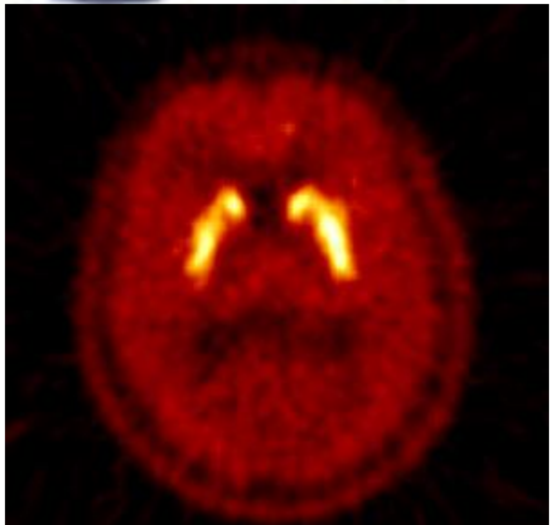
↓

Two 511keV gammas

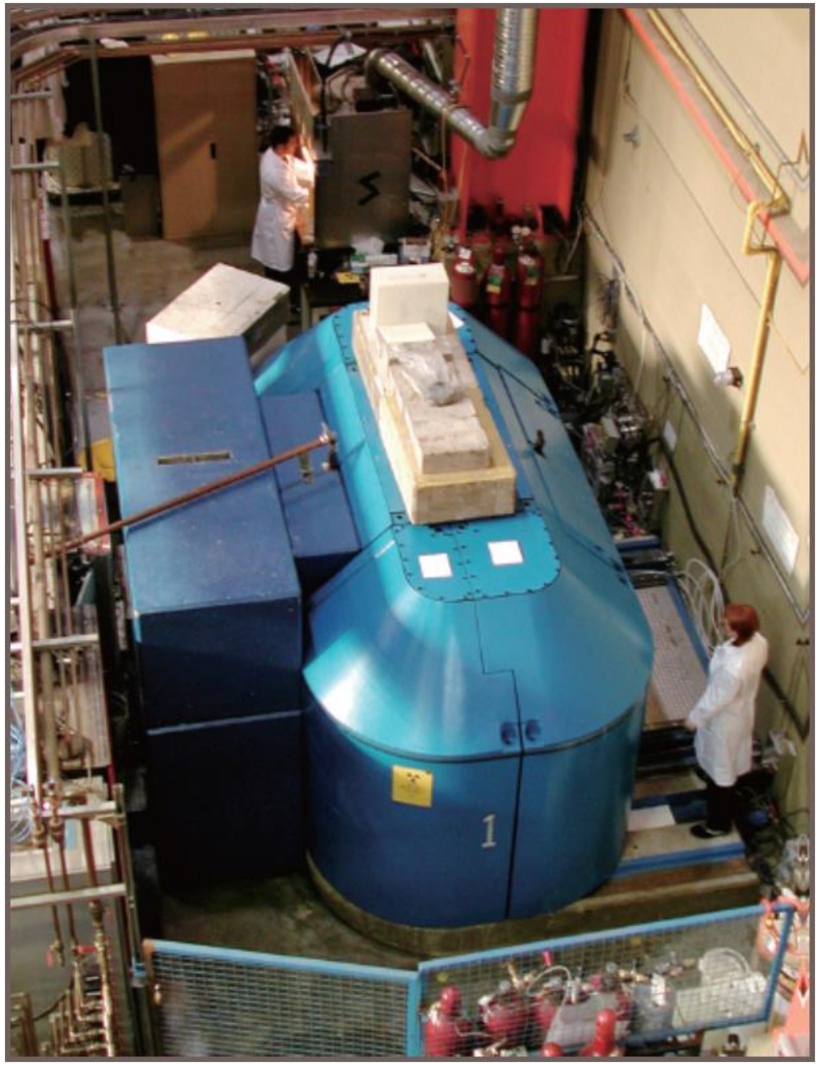
Measured in coincidence

Function rather than structure





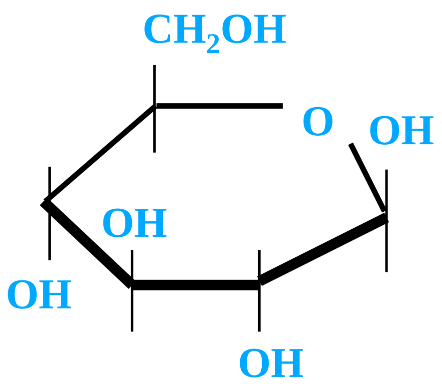
TR13 Cyclotron



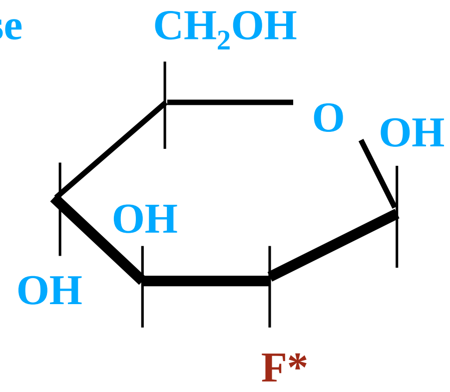
- 13 MeV (19 MeV)
- Negative hydrogen ions
- Dual beam extraction
- Eight targets

FDG

Glucose

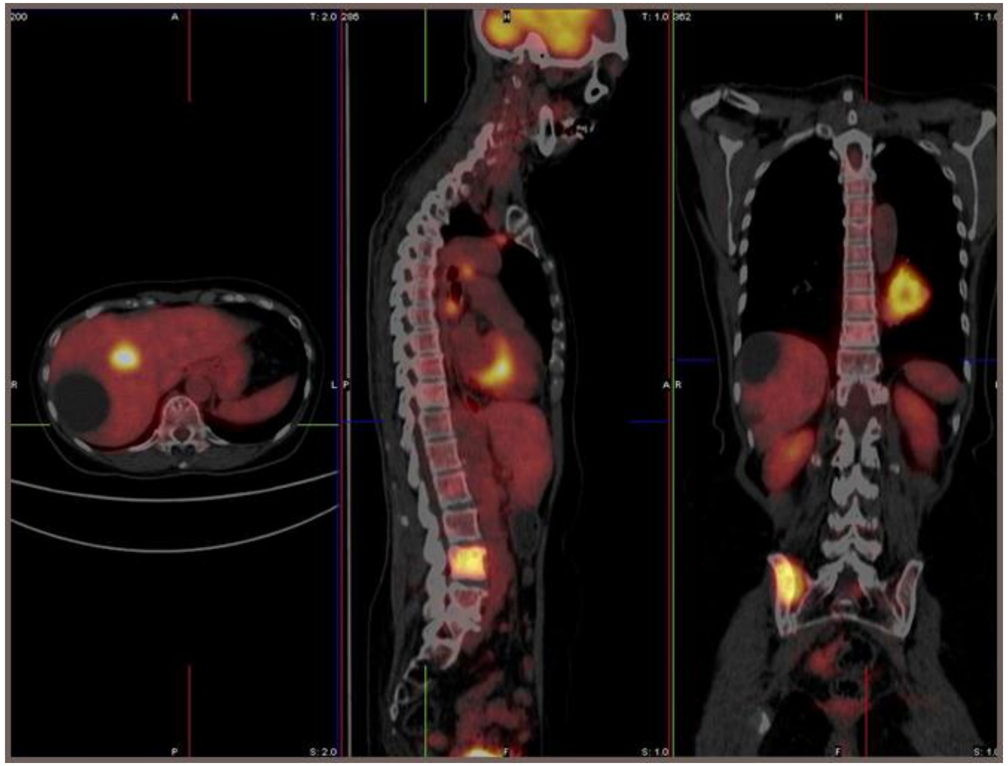


Fluorodeoxyglucose (FDG)



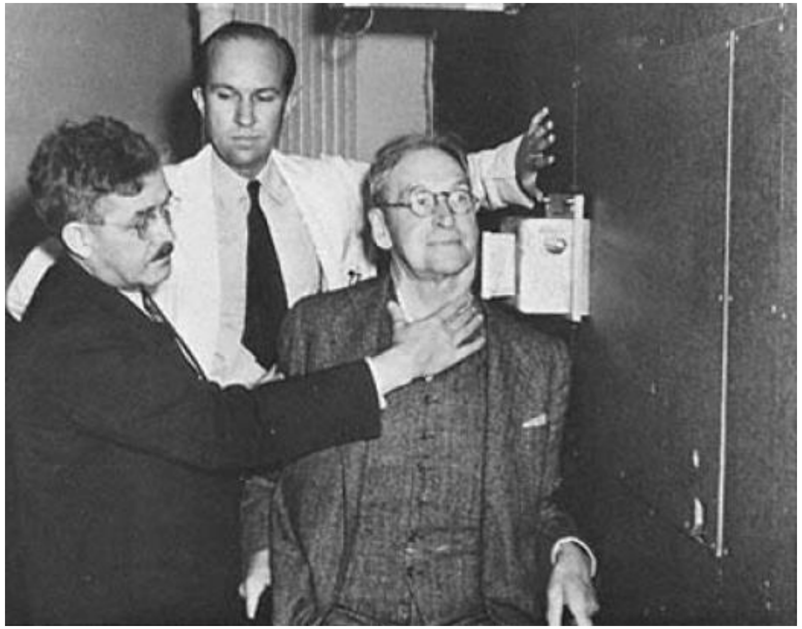
Combined PET/CT scanner (BC Cancer)

PET/CT scan of a cancer patient: Yellow indicates a high uptake of FDG in the brain, heart, bladder and tumour.



Radiotherapy

- External and internal
- External: most common photons
  - Electrons
  - Neutrons
  - Protons and heavy ions
- Internal with gamma emitters, beta emitters, alpha emitters



Lead by John Lawrence, neutron therapy starting in 1938 by bombarding beryllium targets with deuterons.

Nuclear medicine - history

Radioactivity by Bombardment

A high frequency oscillator is used in a new bombardment technique whereby ordinary elements are converted into radioactive ones, thus producing inexpensive radium substitutes suitable for medical and laboratory use. The theory and practice of the process

By JOHN J. LIVINGOOD, Ph.D.
Radiation Laboratory
Department of Physics
University of California

THE first successful transmutation of the chemical elements was performed by Rutherford[1] in 1919, not by chemical means, but by the physical process of driving one type

or porcelain tubes by high speed electrons.

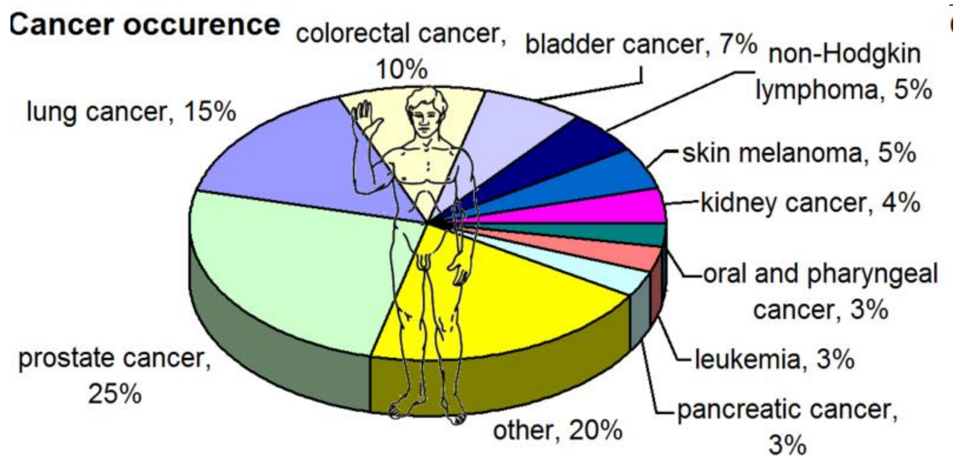
It was in an endeavor to avoid these inherent disadvantages of high voltage equipment that

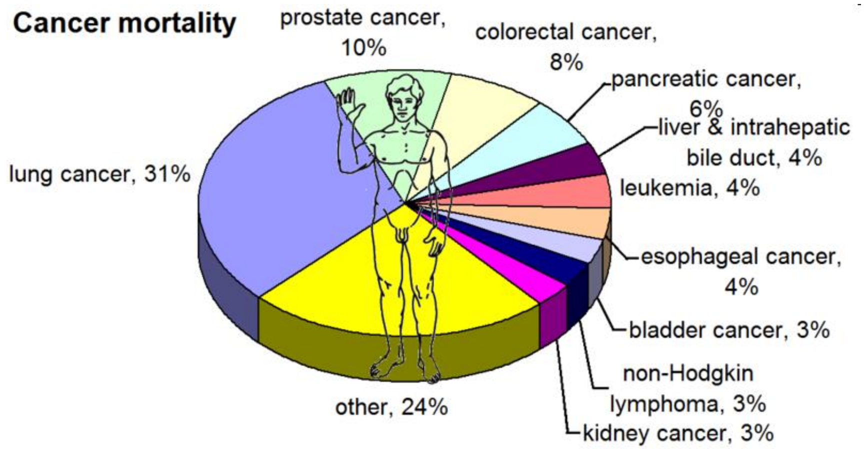
Uses in Biology

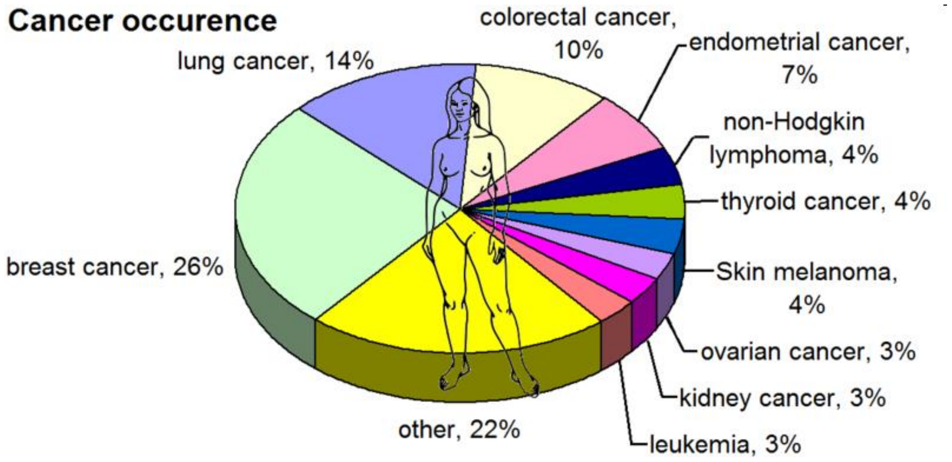
On the biological side, a cheap and effective substitute for radium appears to be at hand, which may be of great value in the treatment of cancer. Instead of inserting into the tissue a small capsule of radium, or of its derivative radon, it may prove possible to inject directly into the tumor a salt solution containing, for example, radiosodium, made by bombarding ordinary salt with deuterons[12]. This emits gamma rays of approximately three million electron-volts energy, as well as electrons with energies ranging up to two million electron-volts. Best of all,

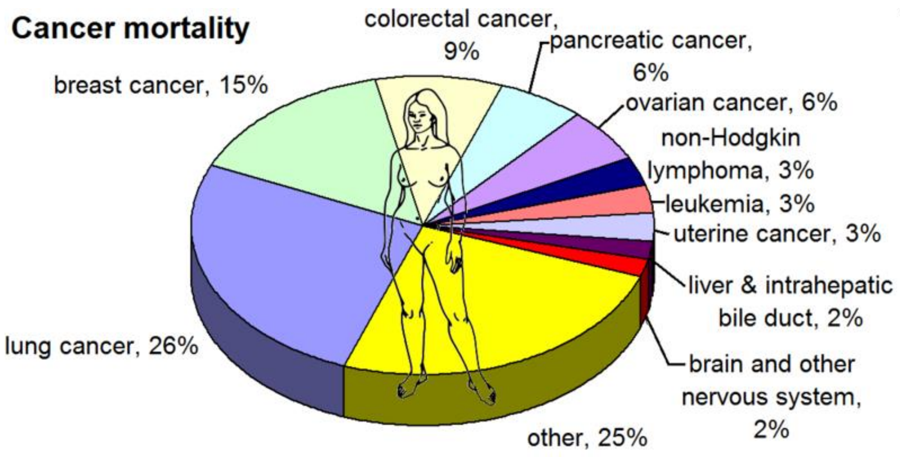
ment, either stable or radioactive. A new science is being born, which, because of the fusion of subject matter, may equally well be called either nuclear chemistry or nuclear physics.

Cancer


Cancer occurence
colorectal cancer, 10%
bladder cancer, 7%
non-Hodgkin lymphoma, 5%
lung cancer, 15%
skin melanoma, 5%
kidney cancer, 4%
oral and pharyngeal cancer, 3%
leukemia, 3%
prostate cancer, 25%
pancreatic cancer, 3%
other, 20%


Cancer mortality
prostate cancer, 10%
colorectal cancer, 8%
pancreatic cancer, 6%
liver & intrahepatic bile duct, 4%
lung cancer, 31%
leukemia, 4%
esophageal cancer, 4%
bladder cancer, 3%
non-Hodgkin lymphoma, 3%
other, 24%
kidney cancer, 3%

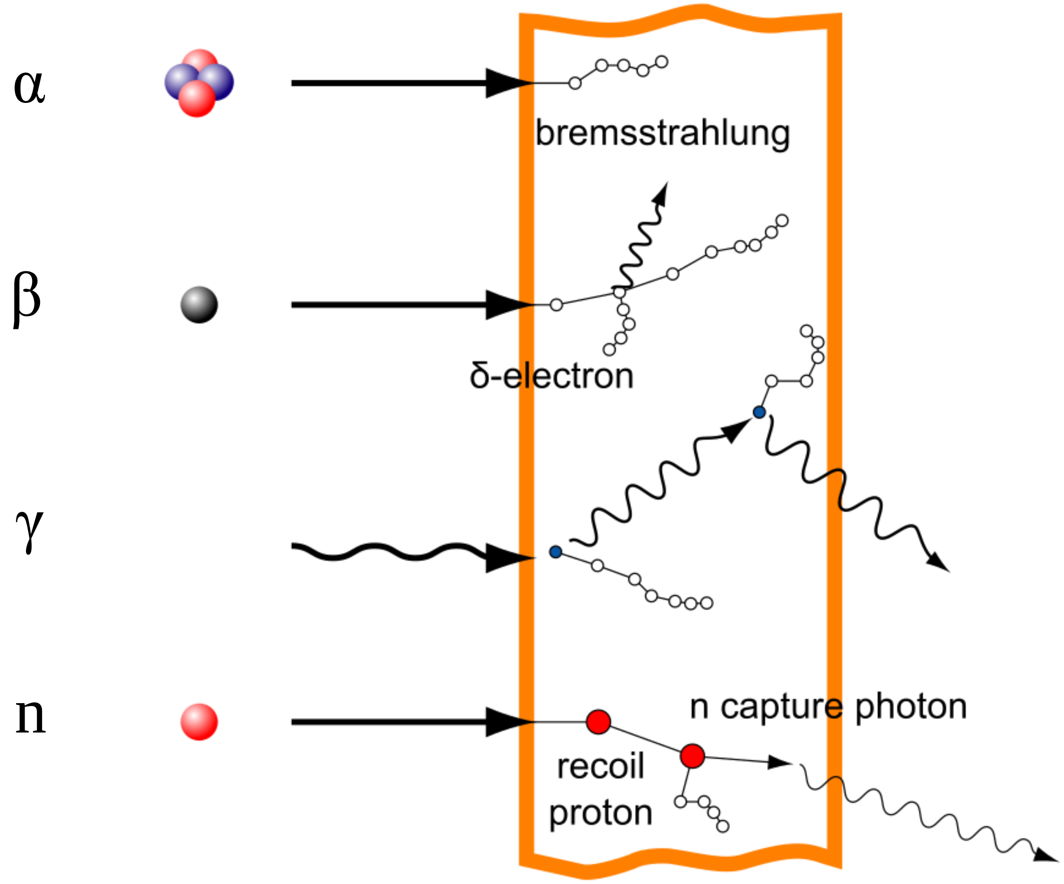

Cancer occurence
colorectal cancer, 10%
endometrial cancer, 7%
lung cancer, 14%
non-Hodgkin lymphoma, 4%
thyroid cancer, 4%
breast cancer, 26%
Skin melanoma, 4%
ovarian cancer, 3%
kidney cancer, 3%
other, 22%
leukemia, 3%


Cancer mortality
colorectal cancer, 9%
pancreatic cancer, 6%
breast cancer, 15%
ovarian cancer, 6%
non-Hodgkin lymphoma, 3%
leukemia, 3%
uterine cancer, 3%
liver & intrahepatic bile duct, 2%
lung cancer, 26%
brain and other nervous system, 2%
other, 25%

If you were to develop cancer:
Surgery – to remove the tumor
Chemotherapy – to kill the tumor with drugs (fast-dividing cells)
Radiotherapy – to kill the tumor with radiation
* External beam therapy – photons, neutrons, protons, ions
* Internal therapy – brachytherapy (radioactive isotopes)

Success: Tumor control vs. complications
Destroy/remove tumor without damaging healthy or normal tissue nearby

Ionizing Radiation

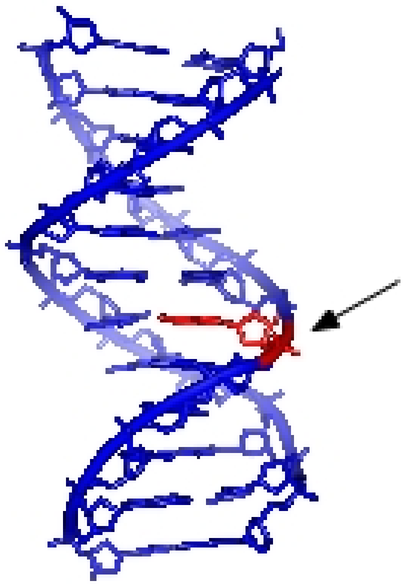


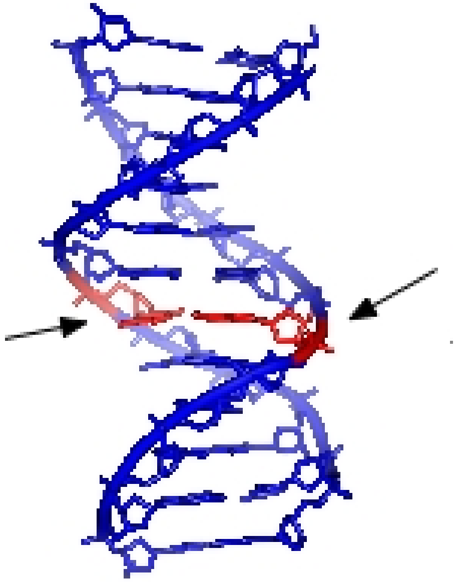
Radiation Therapy

- DNA (Deoxyribonucleic acid): genetic instructions for development and functioning
- Cell needs information from DNA for survival

- Single helix break easy to repair
- Double helix break more difficult to repair
- Cell can not survive

Radiotherapy: as many double helix breaks in cancer cells as possible with as few double breaks as possible in healthy cells





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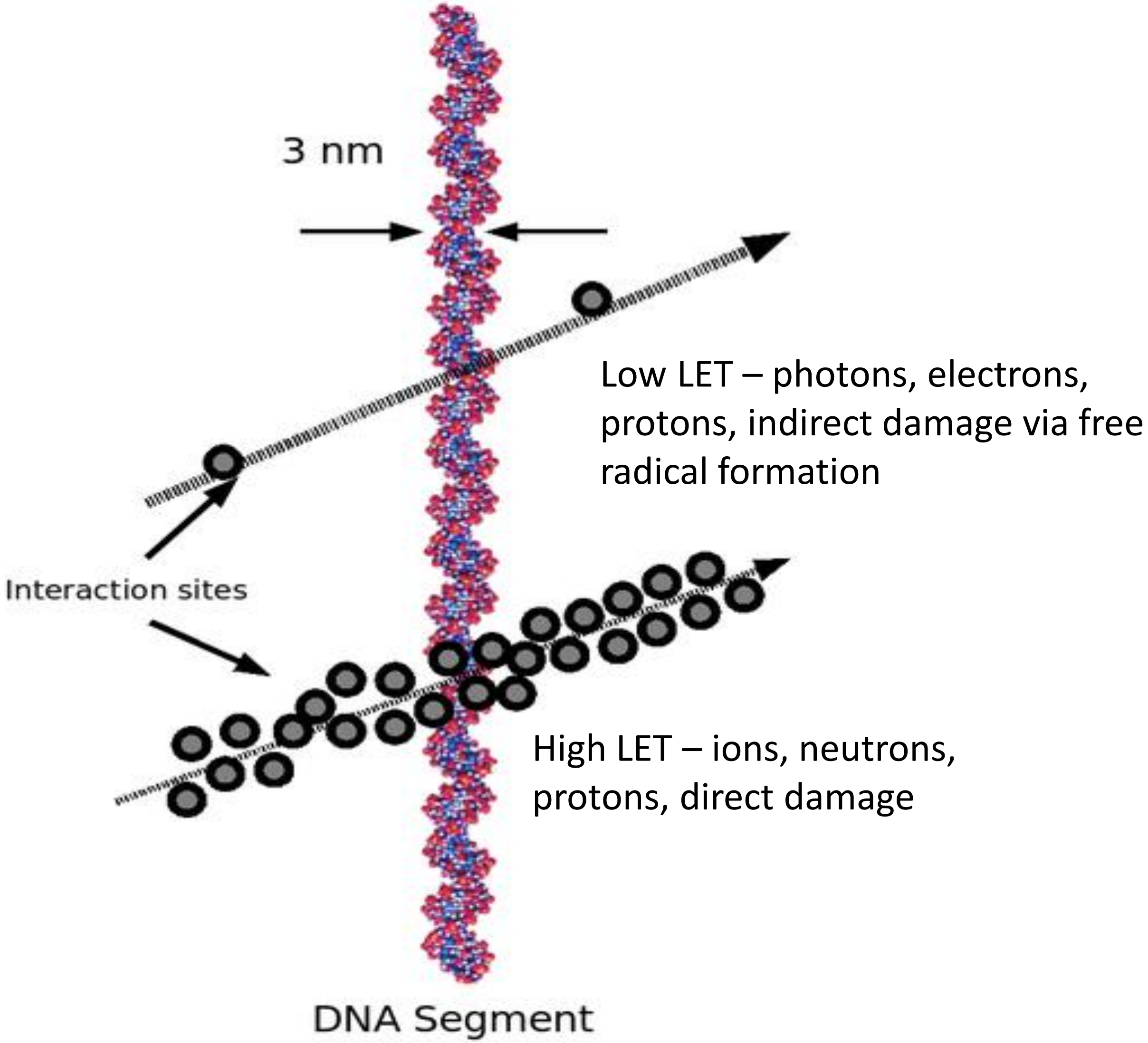
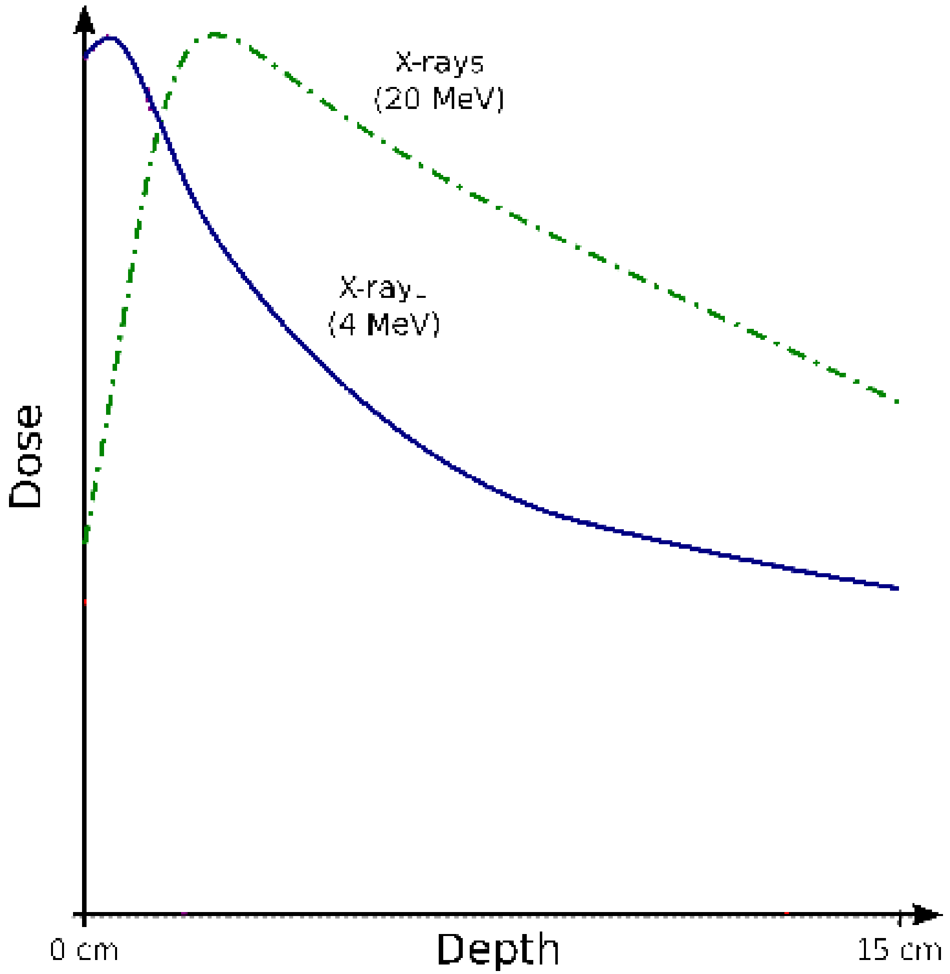


Linear Energy Transfer (LET):
Energy transferred (ionization, secondary electrons) per unit distance

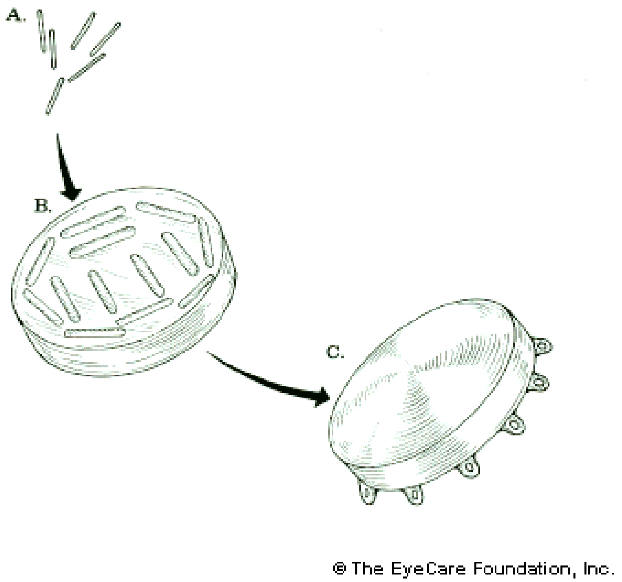
External: X rays



- Cost-efficient, easy set-up, very common
- Many techniques to minimize dose to healthy tissue (multiple beams, wedges, intensity modulation…)
- Dose does not stop after tumor
- Low LET

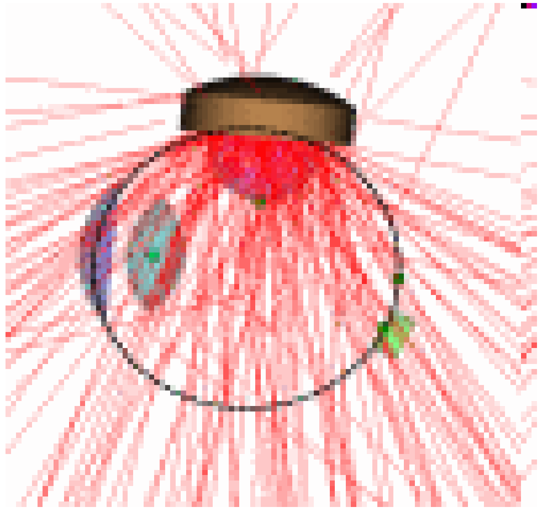
Internal: Brachytherapy

From the Greek word *brachys*, meaning "short-distance“, most isotopes used are gamma emitters



Advantages

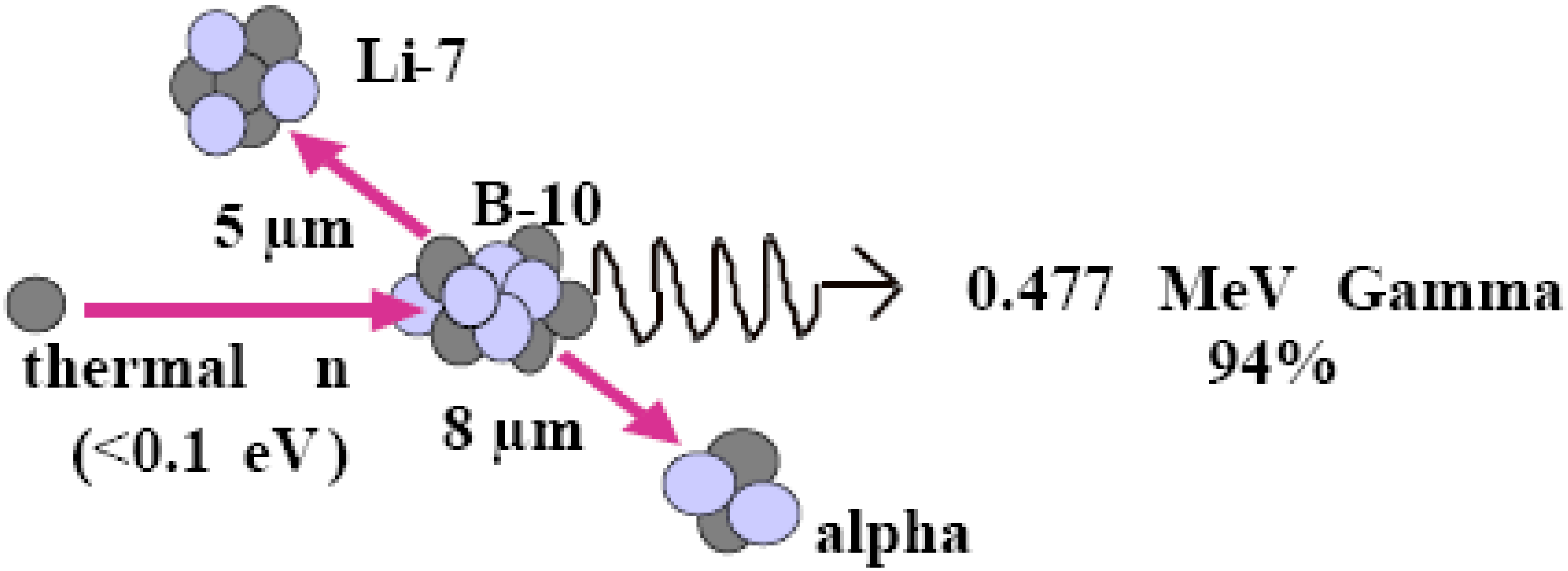
- Very localized
- Can have shorter treatment times
- Moves with tumor
- Can be permanent or temporary



Disadvantage

- High dose to medical personnel
- Dose not homogeneous (in some cases 40% of dose can be deposited in 15% of tumor)
- Tumor-size dependent

External/Internal: Boron Neutron Capture Therapy (BCNT)



- BNCT (thermal <0.1eV)
- Only experimental (treatment for hours)
- Tracer development still in beginning

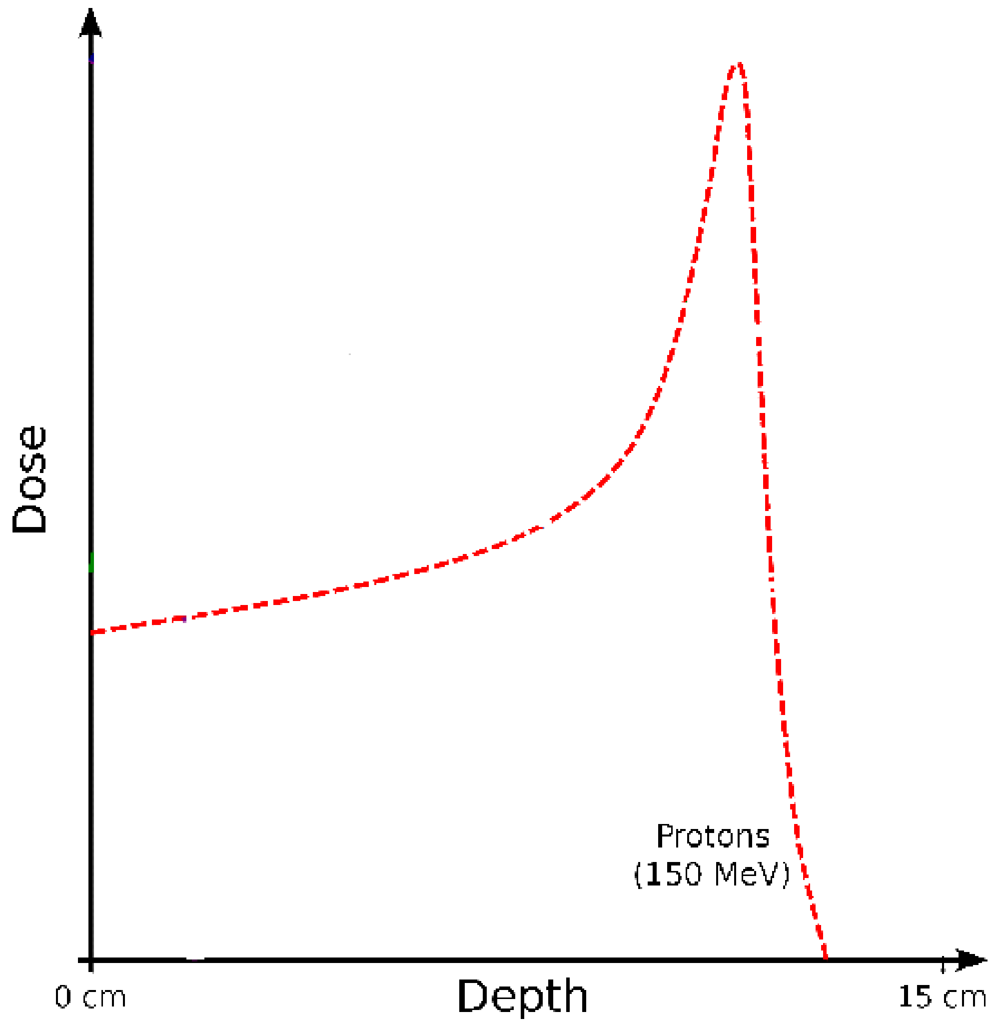
External: Ion Beam Therapy

Advantage

- Less dose to surrounding tissue (Bragg peak)
- Very homogeneous tumor dose
- High control over position of Bragg peak (low to high LET)

Disadvantage

- Need higher-energy accelerator
- 250MeV for 30cm in human tissue
- Expensive



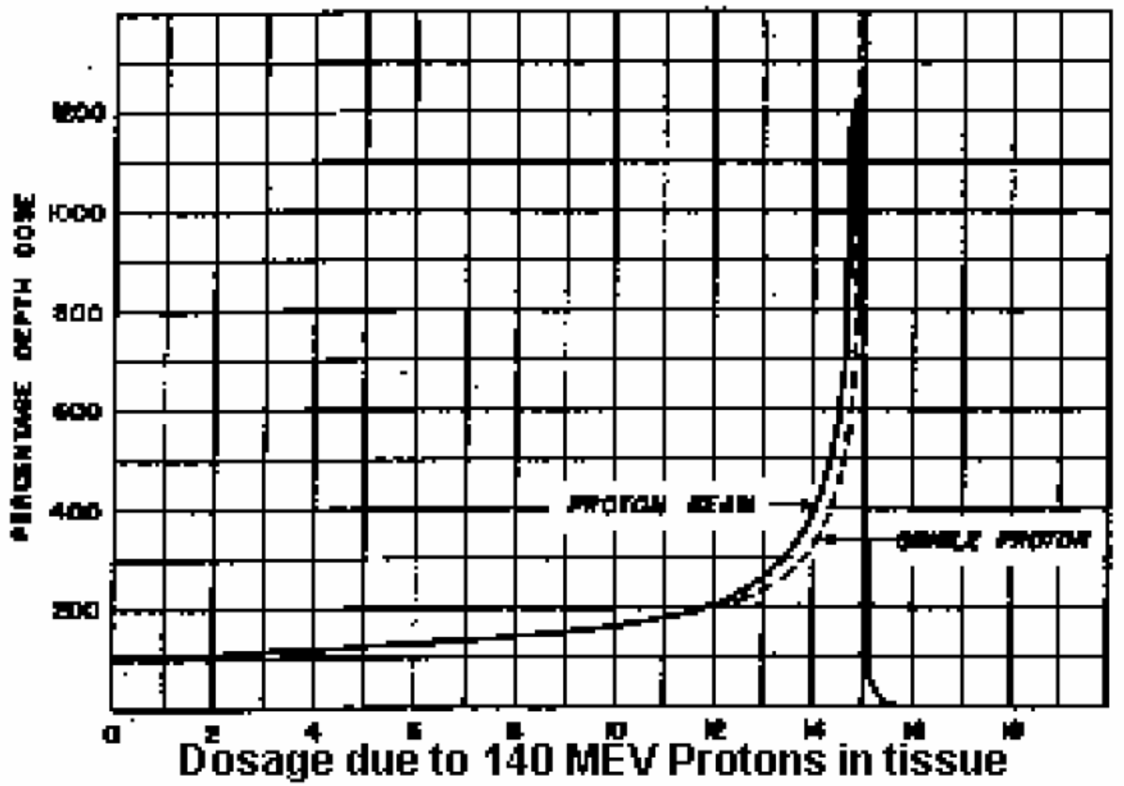
Bethe-(Bloch) Equation

Hans Bethe,
1930 and 1932

$$-\frac{dT}{dx} = \frac{4\pi e^4 z^2}{m v^2} Z \ln \frac{2 m v^2}{E},$$

Zur Theorie des Durchgangs schneller Korpuskularstrahlen durch Materie, Annalen der Physik. vol. 397, pp. 325-400, 1930

Robert Wilson – Father of Proton Therapy



Radiological Use of Fast Protons,
Radiology vol. 47, pp. 487-91, 1946

External: ion-beam therapy

Advantage

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- Very homogeneous tumor dose
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Disadvantage

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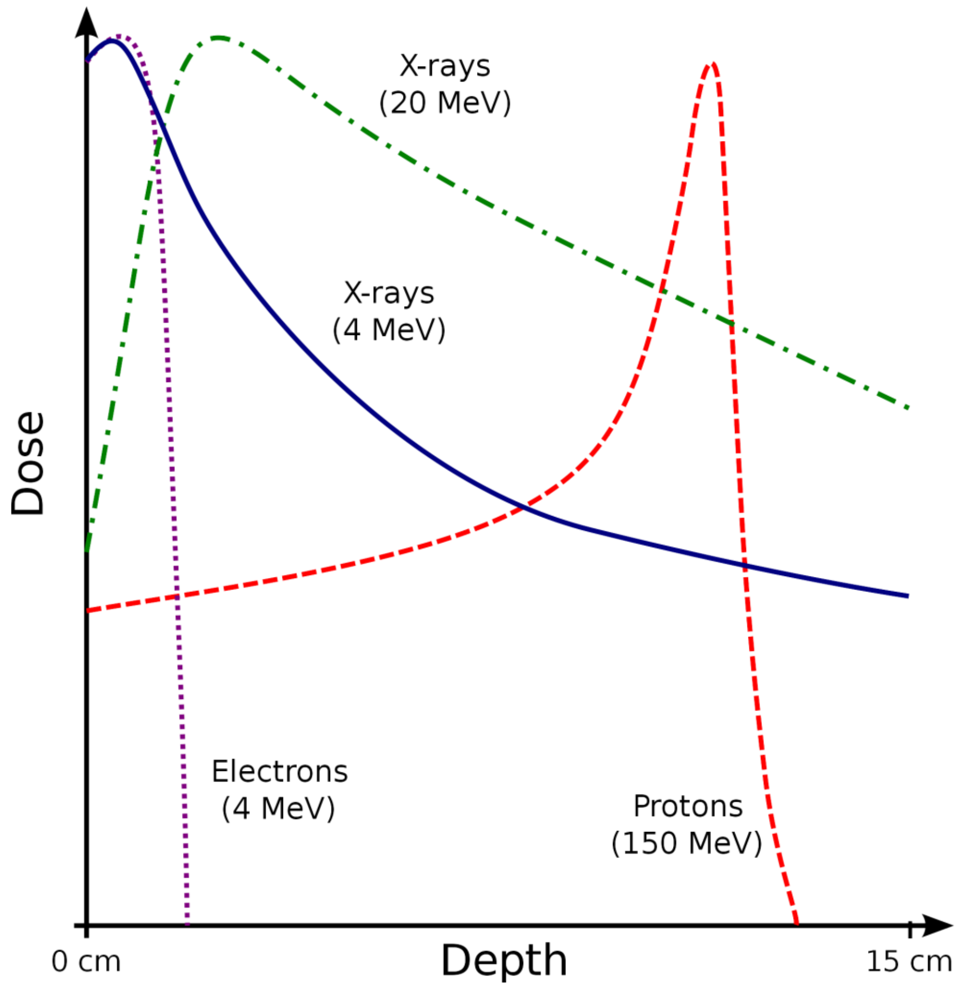
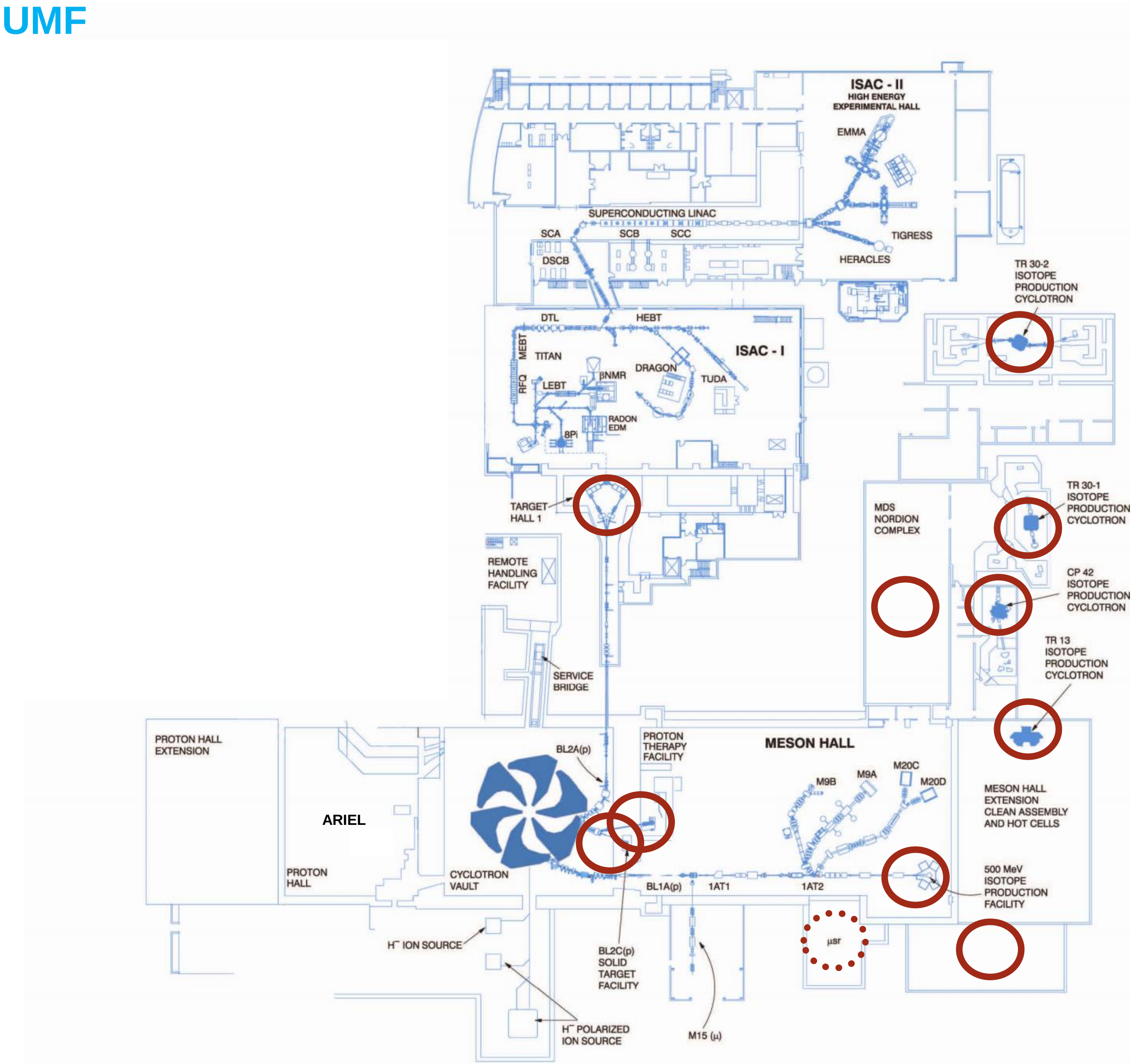
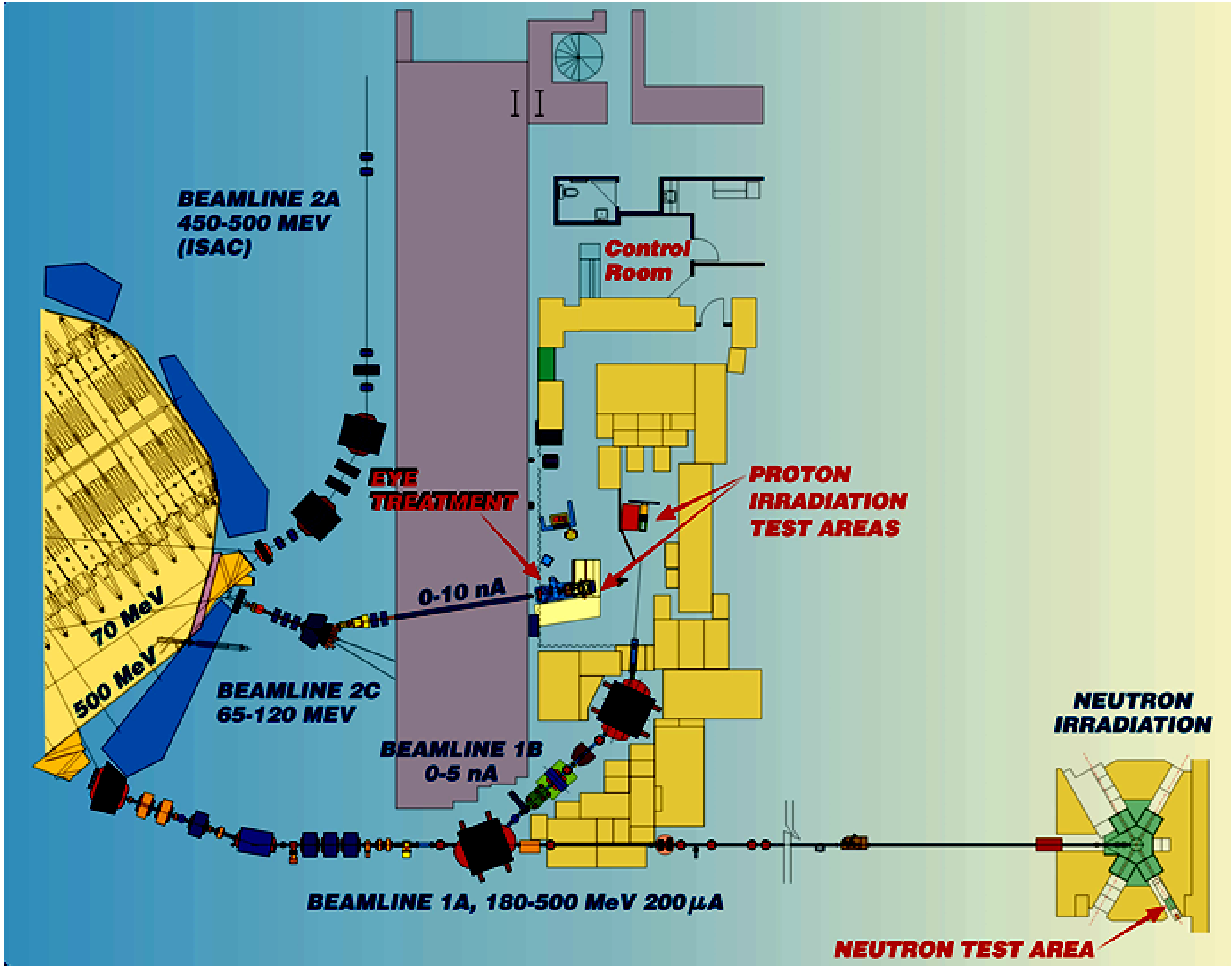


Medical Application @ TRIUMF



Proton Therapy at TRIUMF

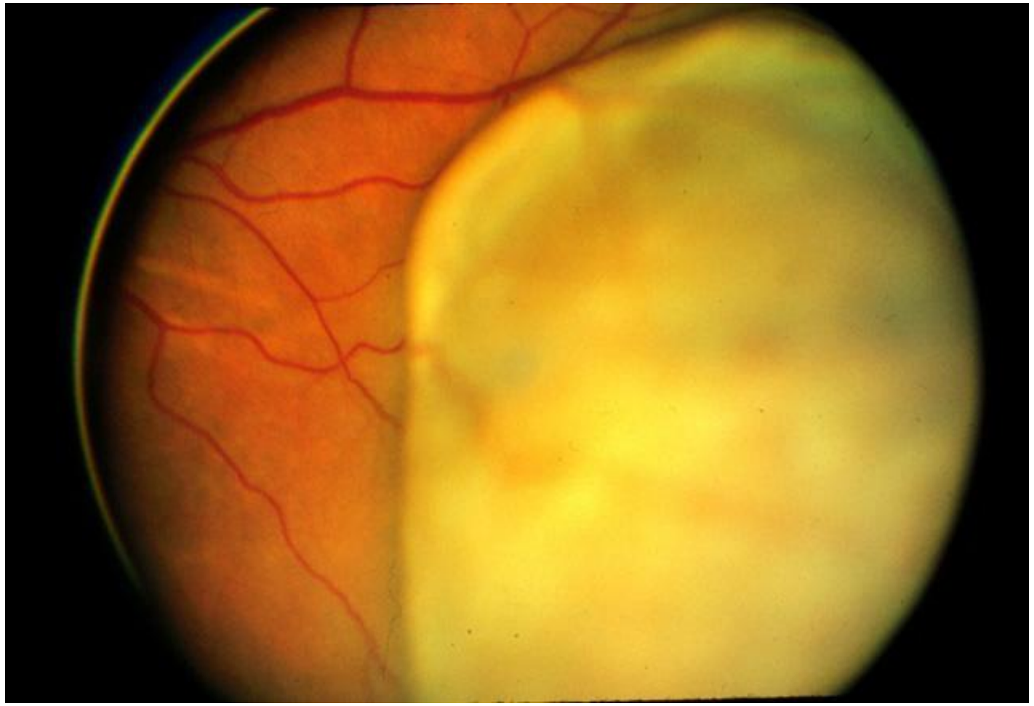


- Since 1995
- Ended Feb 2019

Ocular Melanoma

Frequency: 5 -6 cases/year per million population

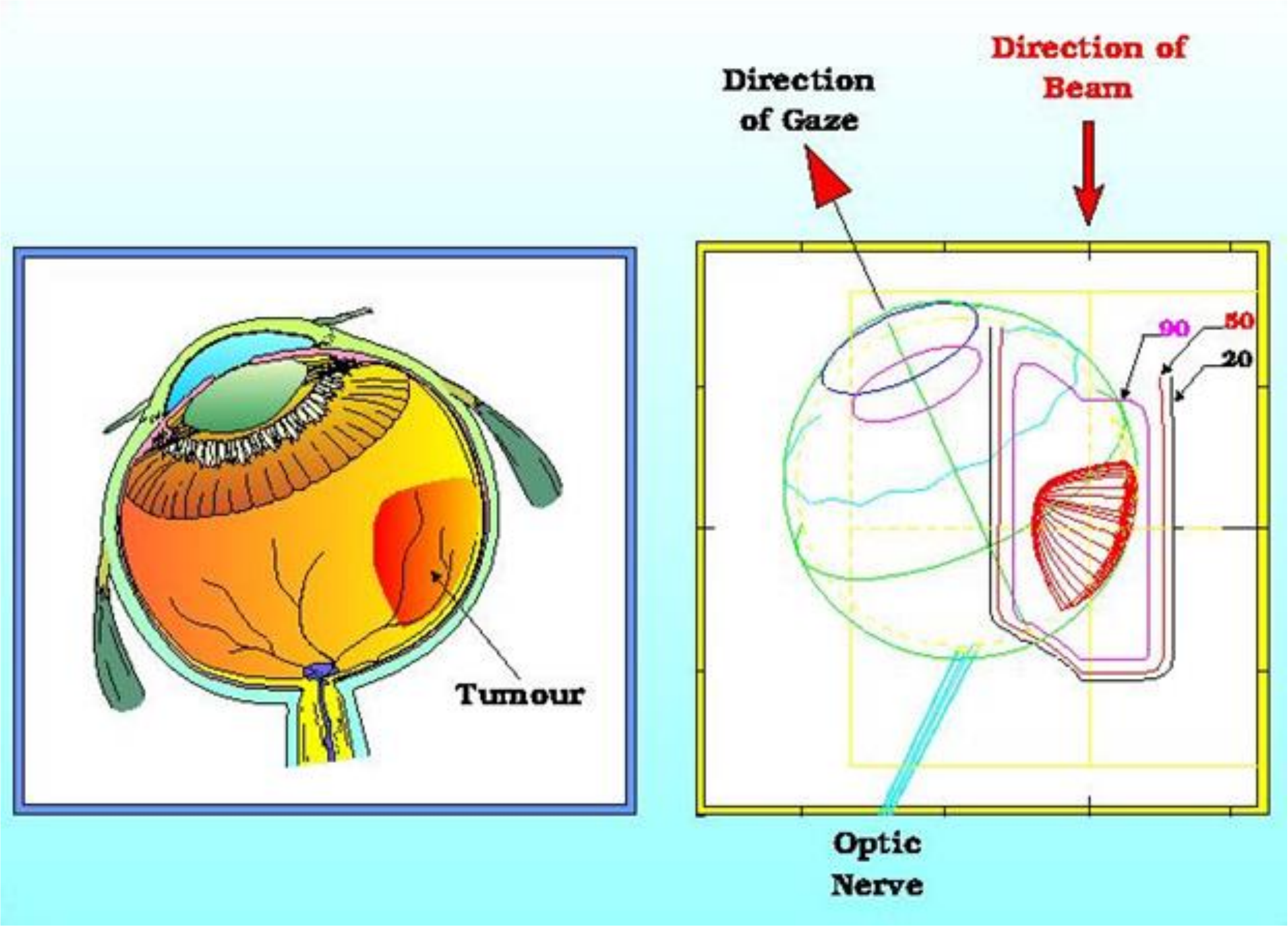
Treatment protocols: Radioactive plaque therapy
Charged-particle radiotherapy
Enucleation



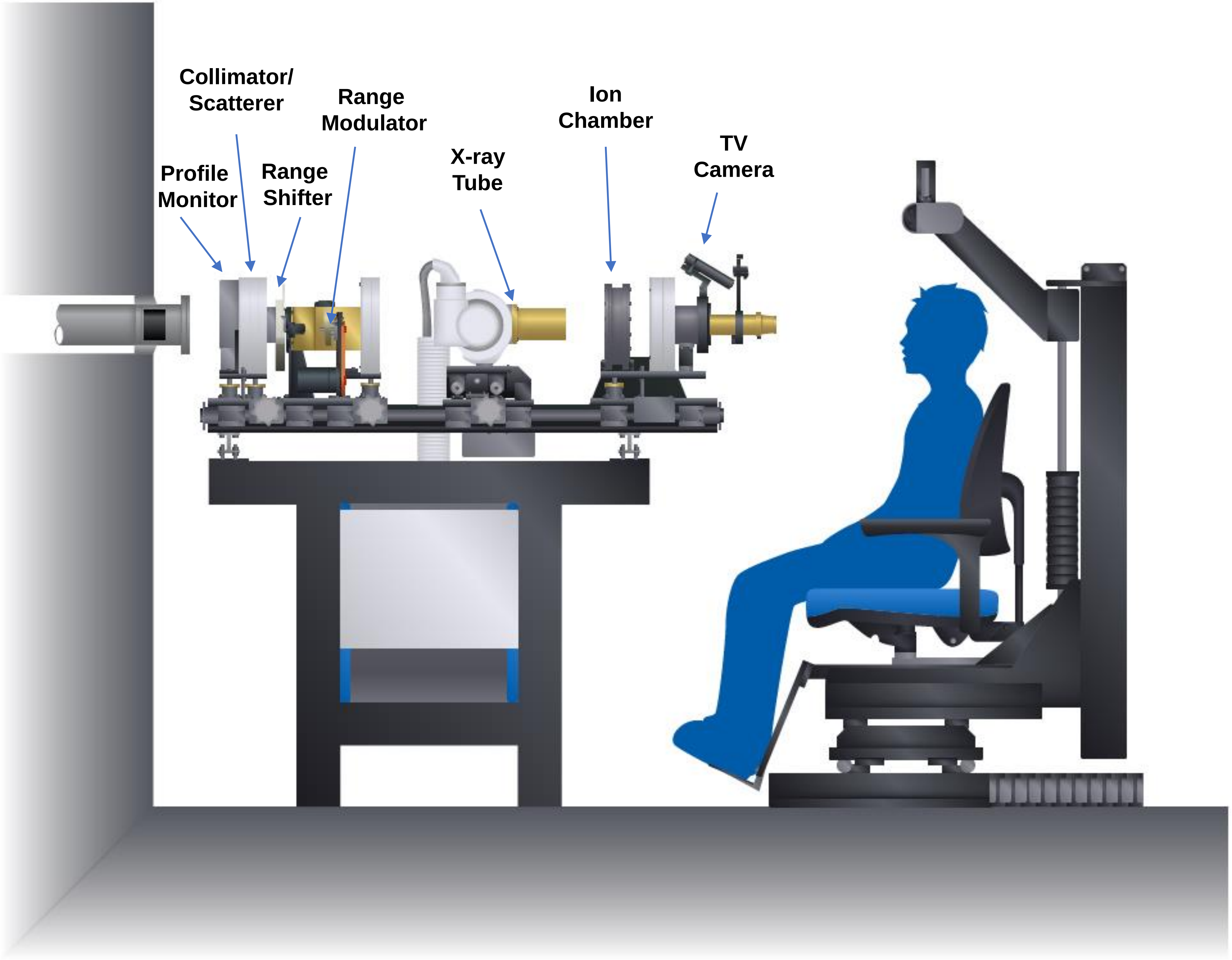
Uveal Melanoma before proton beam treatment

Uveal Melanoma after proton beam treatment

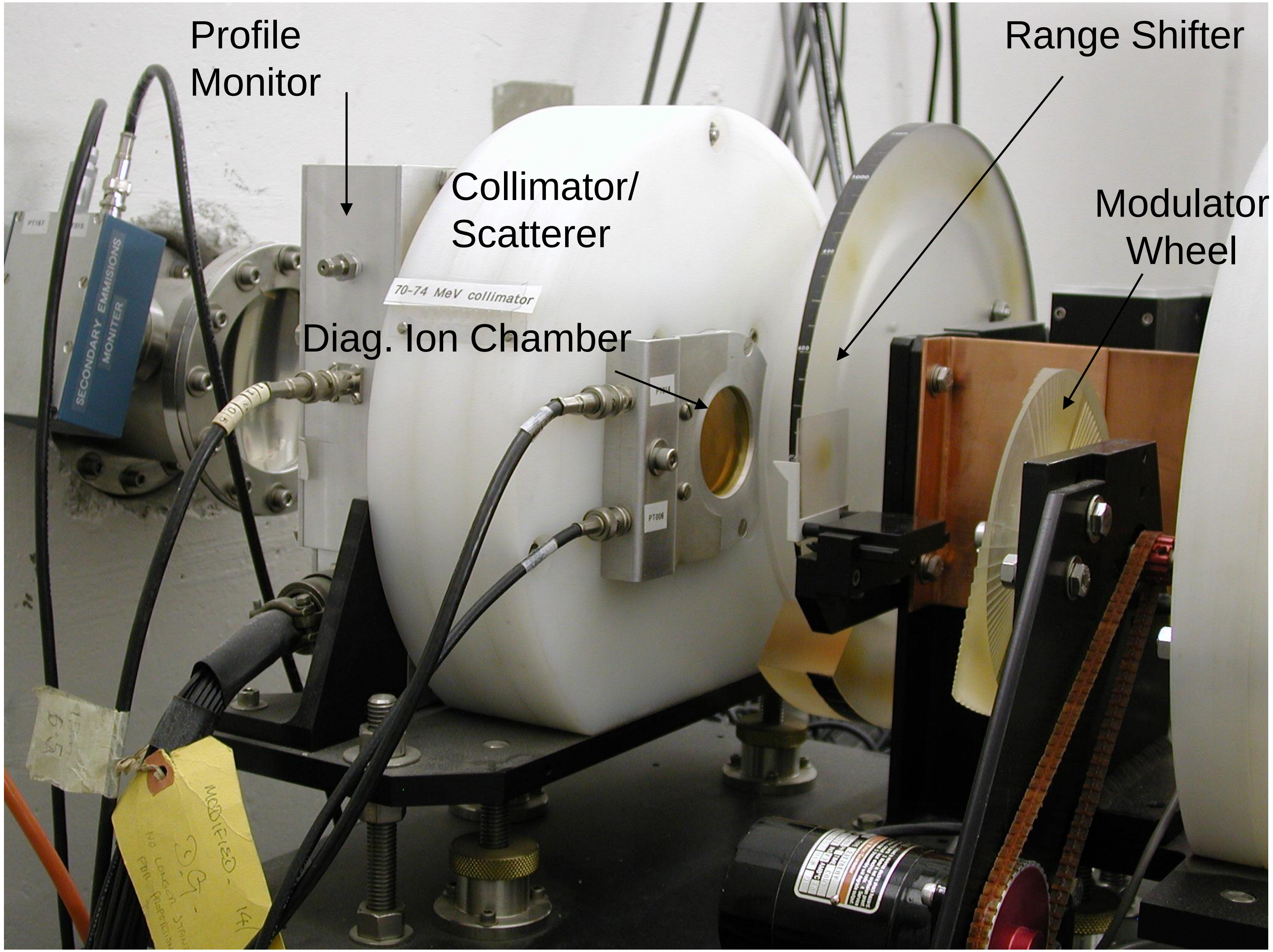
Treatment Planning



Beamline


Collimator/
Scatterer
Range
Modulator
Ion
Chamber
TV
Camera
X-ray
Tube
Profile
Monitor
Range
Shifter

Beamline

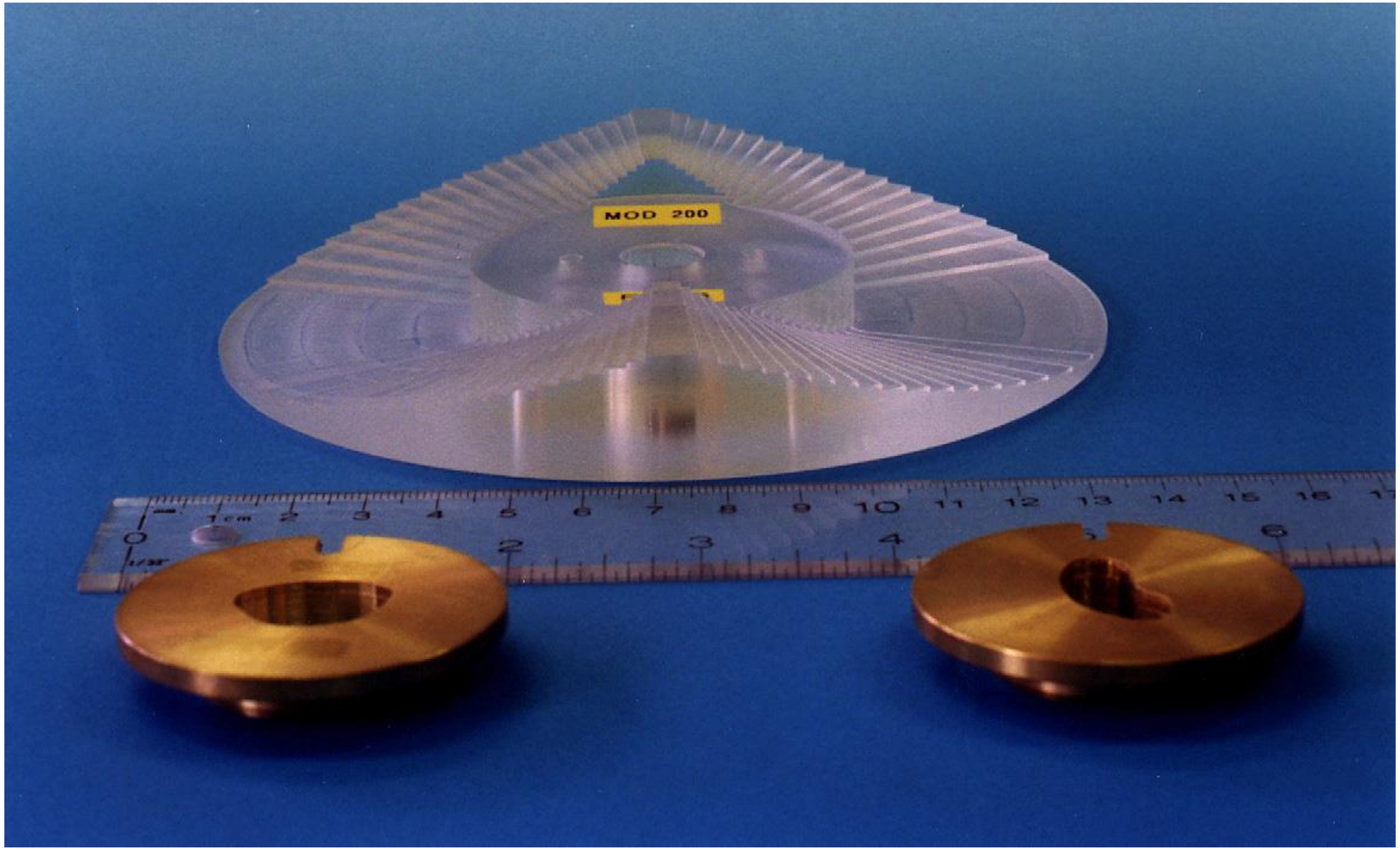


Profile Monitor
Range Shifter
Collimator/ Scatterer
Modulator Wheel
Diag. Ion Chamber
70-74 MeV collimator
SECONDARY EMMISIONS MONITER

Modulator and Collimator

- Modulators: 5 mm to 27 mm in 1 mm increments (depth control)

- Brass collimators (lateral control)

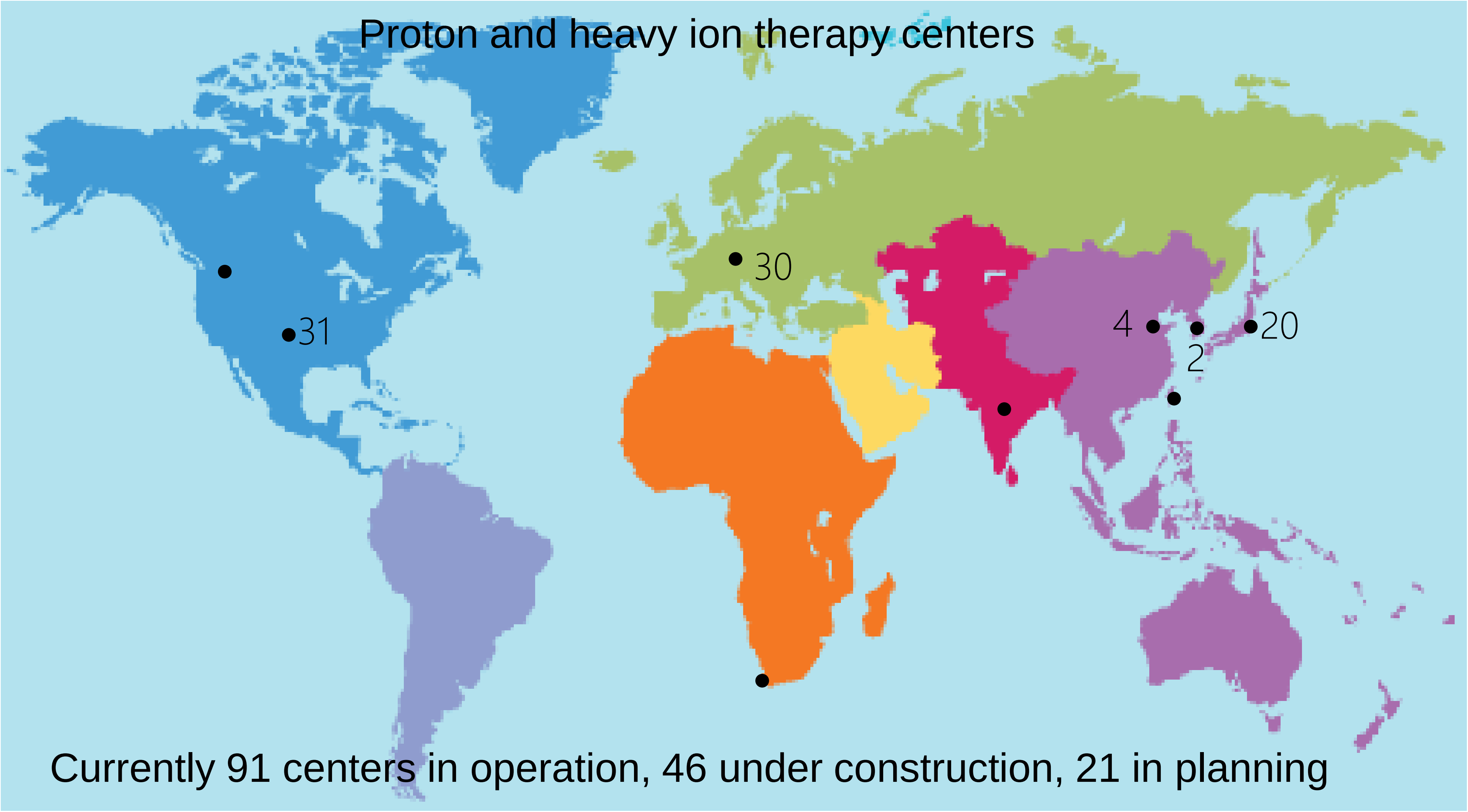


PT Treatment Results

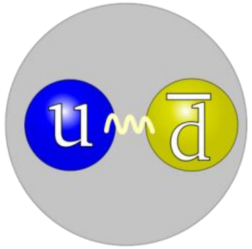
Summary paper with 59 patients
(E. Tran et al., Int. J. Radiat. Oncol. Biol. Phys. 83 (2012) 1425)

- 20 patients T1, 28 patients T2, 11 patients T3
- Median tumor size: diameter 11.4 mm, 3.5 mm thick
- Median follow-up time 63 month
- 19 patients treated with 54 CGE and 40 patients treated with 60 CGE
- **5-year local control rate 91%**
(T1 100%, T2 93%, T3 59%) **and 97%** with 60 CGE, 83% 54 CGE
- **Metastasis-free survival rate 82%** (T1 94%, T2 84%, T3 47%)
- 5-year neovascular glaucoma 31% (T1-2 23%, T3 68%)
- Enucleation T1 0%, T2 14%, T3 72%

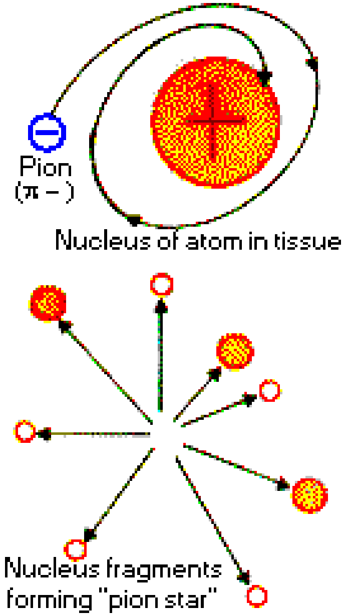
Hadrontherapy around the World

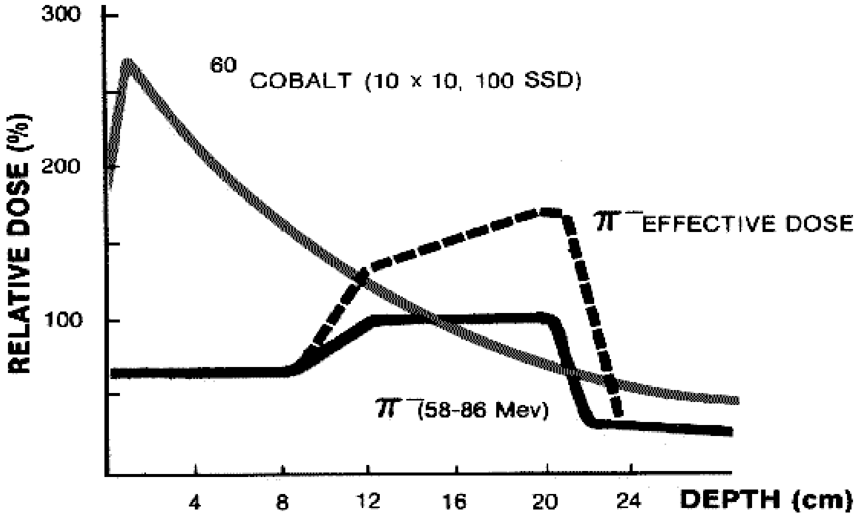


External: Pion-beam treatment

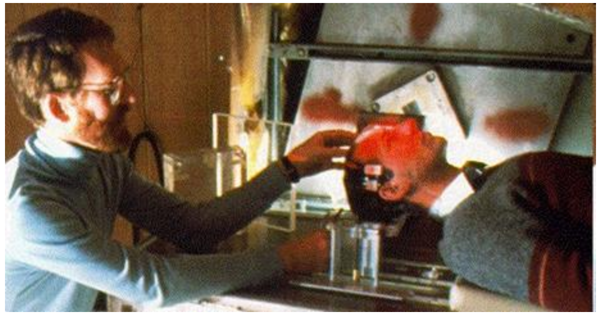


- Pion - subatomic particle, meson
- In nuclei, glue to hold protons and neutrons
- Some are charged
- Have Bragg peak, little damage to surrounding tissue, high LET in Bragg peak
- Lots of damage at Bragg peak ('pion star')





Pion-beam treatment at TRIUMF



• Study from 1980 – 1994 (over 300 patients), one of only three in the world
• Brain tumors (glioblastoma) and prostate cancer

• Result of study: no advantage over conventional photon therapy

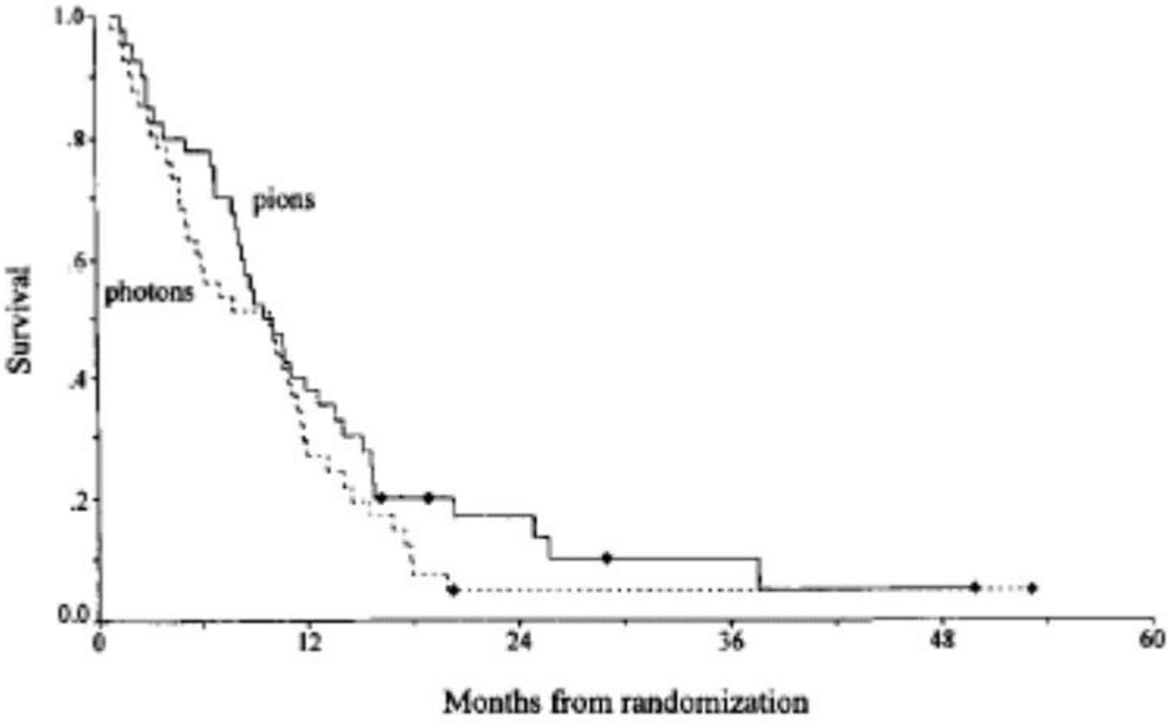


Fig. 2. Overall survival for both treatment groups. Median survivals are: photons, 10 months; pions, 10 months. Log rank: $p = 0.22$.

Int. J. Radiation Oncology Biol. Phys. **37** 491 (1997)

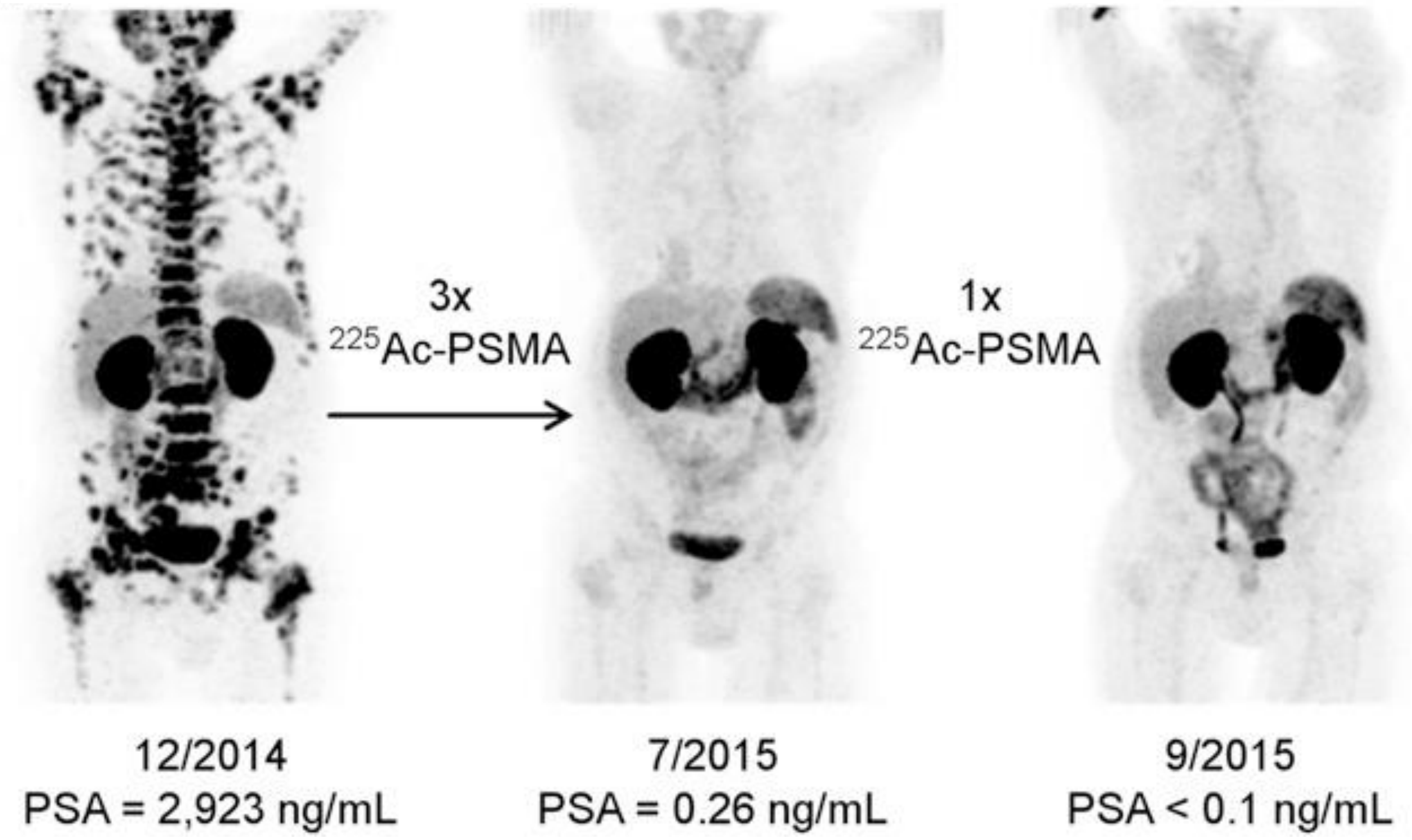
Internal: Alpha Therapy

12/2014
PSA = 2,923 ng/mL

JNM The Journal of NUCLEAR MEDICINE

Kratochwil et al., J. Nuc. Med. July 2016.

Internal: Alpha Therapy



- 11 clinical trials (^{225}Ac and ^{213}Bi)
- > 640 patients (60-80% showed response)
- Want up to 50,000 patient doses a year (120 Ci)

JNM The Journal of NUCLEAR MEDICINE

Kratochwil et al., J. Nuc. Med. July 2016.

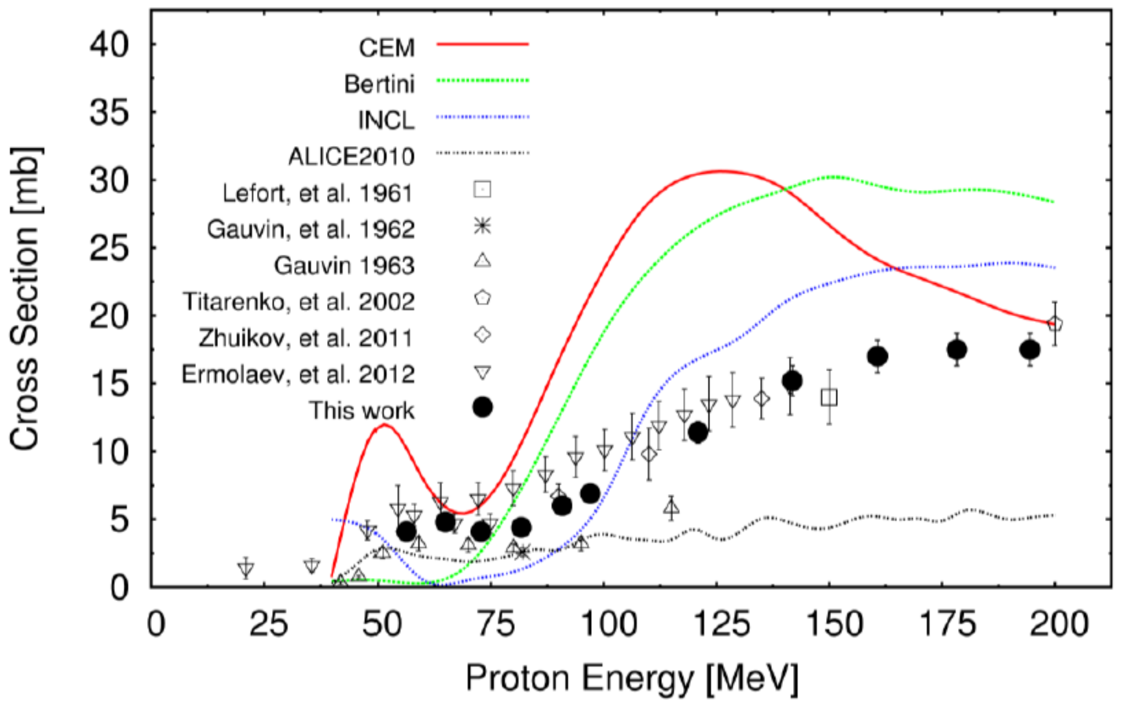
Current ^{225}Ac Production

Primary ^{225}Ac sources:

- ^{229}Th/^{225}Ac generator ($t_{1/2}$ ~ 7880 y) sourced via legacy stockpile, ORNL, ITU
- Alternatives sought
- ^{226}Ra irradiation
- Tri-Lab efforts ^{232}Th(p,x) spallation

Global production is ~1-2 Ci per year

- Promising early clinical trial results
- Supply vs demand is out of balance, but market needs to be nurtured, and supply needs to increase and be reliable



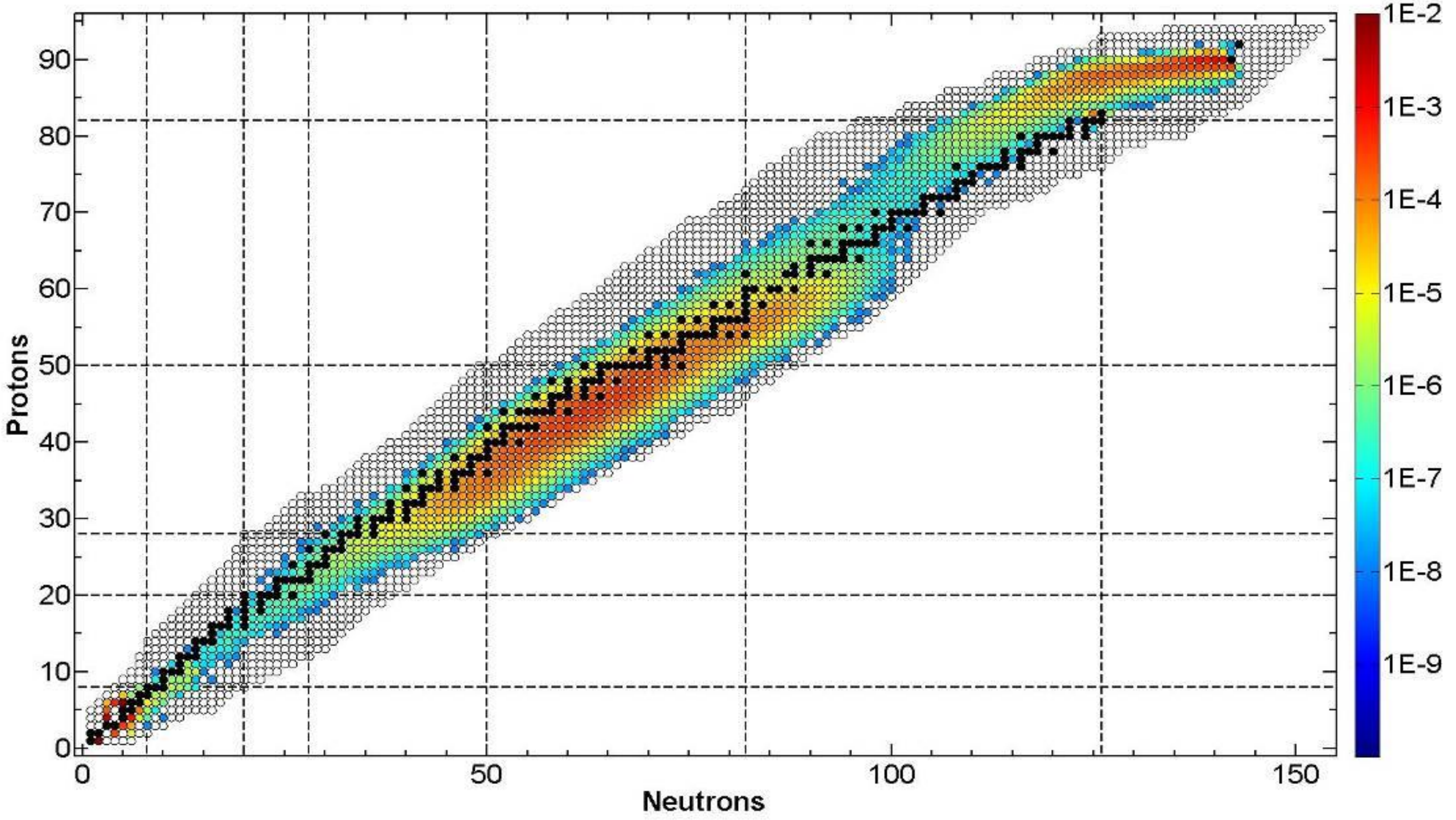
J.W. Weidner et al. Appl. Radiat. Isotop. 2012, 70, 2602

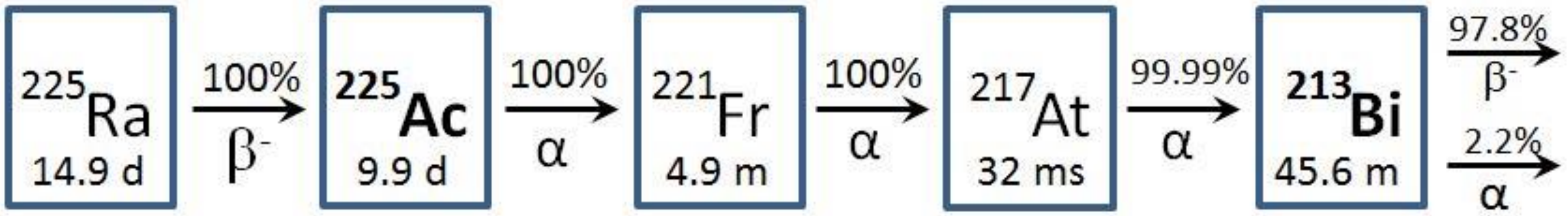
- ^{225}Ac production via Th spallation demonstrated at small scales:

LANL	50 - 200, 800 MeV
INR RAS	40 - 90 MeV

Spallation Reaction on ^{232}Th with 500 MeV Protons

- Hundreds of co-produced isotopes including;
- **^{225}Ra, ^{225}Ac**, ^{224}Ra, ^{223}Ra, ^{213}Bi, ^{212}Pb, ^{212}Bi, **$^{209/211}$At**

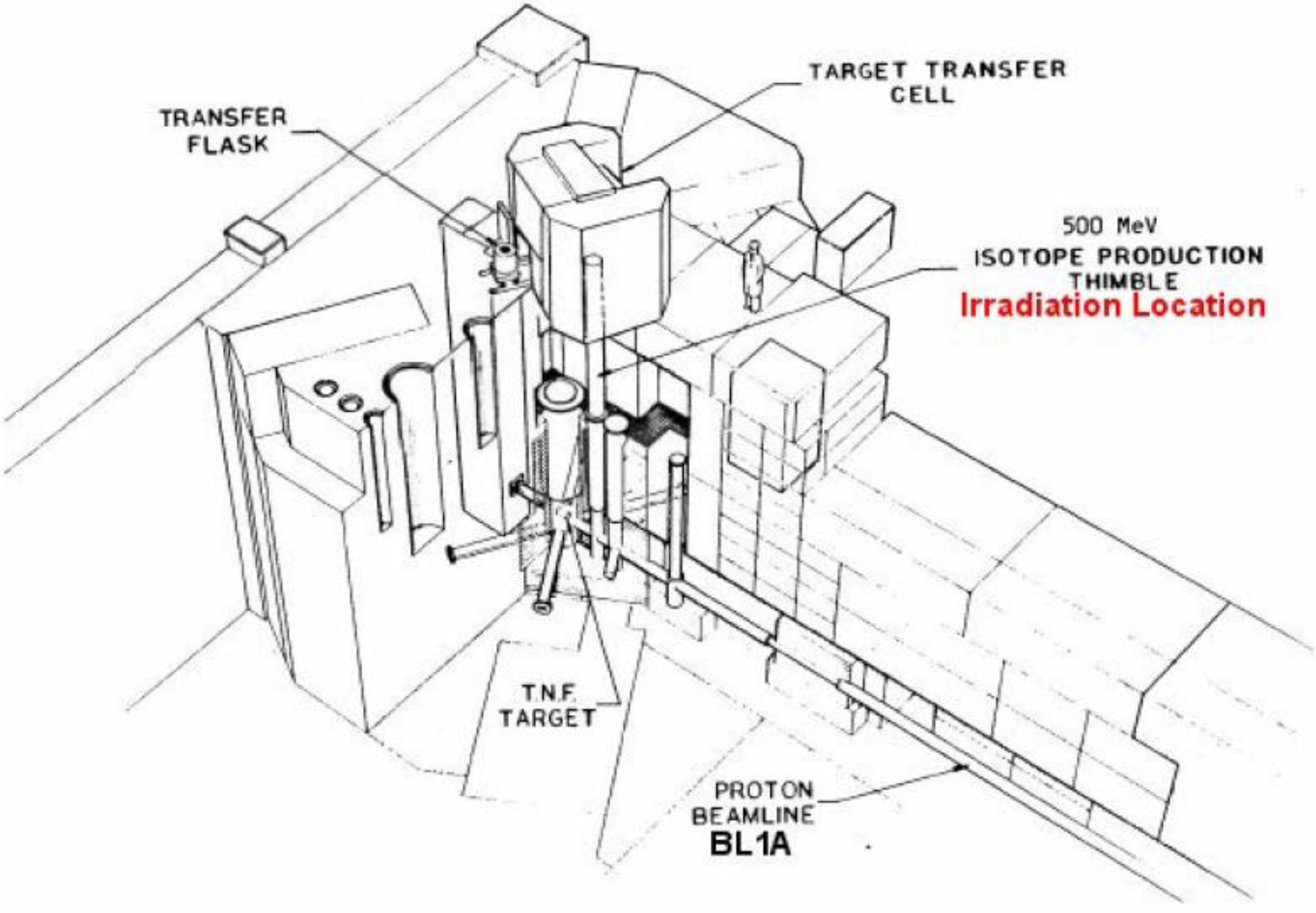




α emitters

500 MeV – IPF (BL1A)
Intermediate activity (MBq), spallation

- Routine, independent production



500 MeV Isotope Production Facility

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a place of mind
UBC

cpdc

NSERC
CRSNG

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Canada

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Thank you
Merci

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