

Cyclotrons for Medicine

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2019-06-03



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

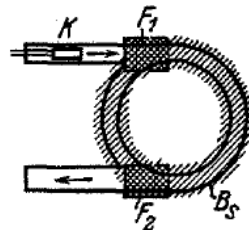
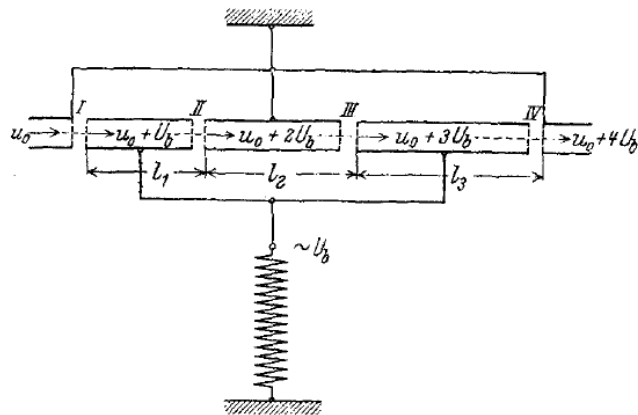


Bild 1. Prinzip der Spannungstransformation mit Potentialfeldern.

200 Widerbe, Ein neues Prinzip zur Herstellung hoher Spannungen. *Archiv für Elektrotechnik*

y) Die Wirkungen der Gasmoleküle auf Elektronenstrahlen im Hochvakuum.

Bei schwachen beschleunigenden Feldern müssen die Elektronen, um hohe Spannungen zu erreichen, weite Strecken durchlaufen (siehe Abschnitt IV). Die Gasmoleküle können deswegen, selbst bei extremem Hochvakuum, noch bedeutende Wirkungen auf die Elektronenstrahlen ausüben.

Die mittlere freie Weglänge der Moleküle ist bei 10^{-4} mm Hg (ein Druck, der sich mit einer Glasapparatur erreichen läßt) für verschiedene Gase:

Gas	H ₂	O ₂	N ₂	CO ₂	H ₂ O
Mittlere freie Weglänge in km = 10^6 cm	14,6	8,1	7,6	0,1	4,3

Druck: 10^{-4} mm Hg = $1,3 \cdot 10^{-4}$ Dyn cm⁻²
Temperatur: $t = 20^\circ \text{C} = 293^\circ \text{K}$

Die mittlere freie Weglänge der Elektronen ist nach Maxwell $4 \cdot \gamma^2$ so groß, die gemessenen Elektronenweglängen scheinen etwas größer zu sein¹, so daß man als ungefähren Wert: 10^6 cm für die freie Weglänge der Elektronen bei 10^{-4} mm Hg ansehen kann. In dem elektrischen Wirbelfeld eines Transformators ist die Feldstärke von der Größenordnung $0,1 \frac{\text{Volt}}{\text{cm}}$. Wir würden also bereits bei der Gewinnung von 10^6 Volt = 1 MVolt in den Bereich der mittleren freien Weglängen kommen. Da aber die Wirkungen der Gasmoleküle auch sehr von der Spannung der Elektronen abhängig sind, hat die freie Weglänge nur einen orientierenden Wert für die Beurteilung dieser Gaswirkungen.

Eine genauere Untersuchung über die Wirkungen der Gasmoleküle auf beschleunigte Elektronen (wesentlich auf Grund der Arbeiten Lenards auf diesem Gebiete) haben nun folgende Ergebnisse gezeigt:

Die Gasmoleküle bewirken Absorption, Spannungsverlust und Abkanken der Elektronen aus der Bahnkurve. Bei den in Frage kommenden Werten von Feldstärke (etwa $0,1 \frac{\text{Volt}}{\text{cm}}$) und maximal zu erreichender Spannung (etwa 10 MV) spielt man die Absorption und der Spannungsverlust bei Drücken unterhalb 10^{-4} mm Hg keine Rolle. Die Diffusion der Elektronen ist dagegen nicht zu vernachlässigen. Sie bedingt eine untere Grenze für die Anfangsspannung U_0 . Diese Grenze würde in unserem Falle etwa zwischen 0,5 und 10 kV liegen.

Der Diffusion wegen sollte der Gasdruck nicht höher als 10^{-4} mm Hg sein.

III. Kinetische Spannungstransformation mit Potentialfeldern.

1 Das Prinzip.

Wie bereits erwähnt, läßt sich in elektrischen Potentialfeldern das Prinzip der kinetischen Spannungstransformation verwenden. Die elektrischen Ladungen (in diesem Falle Ionen, s. später) durchlaufen dabei mehrere Potentialfelder und speichern in jedem Feld dessen Spannung als kinetische Energie auf.

Als erster hat G. Löffig eine derartige Anordnung zur Herstellung von Ionenstrahlen hoher Spannung vorgeschlagen². Löffig will die elektrischen Felder mittels Wanderwellen herstellen. Diese Wanderwellen sollen so geführt werden, daß sie die

¹ Paffensch, Ann. d. Phys. 44, 556, 1914.
² G. Löffig, Ark. f. Math. Astron. och Fysik 18, Nr. 20, Heft 4, S. 45, 1923.

200 Widerbe, Ein neues Prinzip zur Herstellung hoher Spannungen. *Archiv für Elektrotechnik*

Beschleunigungselektroden zur selben Zeit wie die Ionen erreichen. Die Ausführung dieses Gedankens dürfte große Schwierigkeiten bereiten (z. B. die Vermeidung von Reflexionen und unerwünschte Koppelungen der Wanderwellen); irgendwelche Ergebnisse sind bis jetzt nicht veröffentlicht worden.

In Bild 1 ist eine günstigere Anordnung der Transformation gezeigt.

Die elektrischen Felder werden mittels der Wechselspannung U_1 über vier Beschleunigungstrecken I-IV erzeugt (die Zahl der Strecken ist im Prinzip natürlich nicht beschränkt). Die Ionenstrahlen erreichen die erste Beschleunigungstrecke auf der Anfangsspannung u_0 . Während einer halben Periode werden die Ionen in I

Bild 1. Prinzip der Spannungstransformation mit Potentialfeldern.

und III beschleunigt, in II und IV werden sie gebremst. Wird nun der Abstand l zweier Beschleunigungstrecken so gewählt, daß die Ionen diesen Weg in einer halben Periode zurücklegen, so werden sie in allen Strecken mit der Spannung U_1 beschleunigt werden.

Zwischen zwei Beschleunigungstrecken sind die Ionen (im Innern eines Zylinders) vor jeder elektrostatischen Beeinflussung geschützt. Während dieser Zeit werden die Ionen und der Zylinder dem Potential $-U_1$ auf dem Potential $+U_1$ gegeben; die anwachsende kinetische Energie der Ionen wird also der Wechselstromquelle als erhöhter Aufladestrom entzogen.

Man sieht jetzt auch, warum für derartige Anordnungen Ionen gewählt worden sind. Je langsamer die elektrischen Ladungen sich bei der betreffenden Spannung bewegen (s. groß), um so kleiner werden die Abstände l und die Frequenzen der Wechselspannung U_1 . Die Transformation mittels Elektrodenstrahlen würde Frequenzen von etwa 10^6 sec⁻¹ und große Abmessungen der Beschleunigungsgrößen (~ 1 m) erfordern. Die Ionen haben bei derselben Spannung eine 100-1000mal kleinere Geschwindigkeit und bieten deswegen keine derartigen technischen Schwierigkeiten.

2. Theorie der resultierenden kinetischen Spannungen.

a) Die Grundgleichung.

Wir werden in folgendem, um einen Überblick über die auftretenden Erscheinungen zu erhalten, die einfache Anordnung mit 2 Beschleunigungstrecken untersuchen. Das Hinzufügen weiterer Beschleunigungstrecken bietet nichts prinzipiell Neues, die Untersuchungsmethoden bleiben die gleichen.

Für die Geschwindigkeit zwischen den beiden Strecken gilt die angenäherte Formel (5)

$$v = \frac{v_0}{\sqrt{2}} \sqrt{u_0 + U_1}$$

Cyclotron – how it works

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)

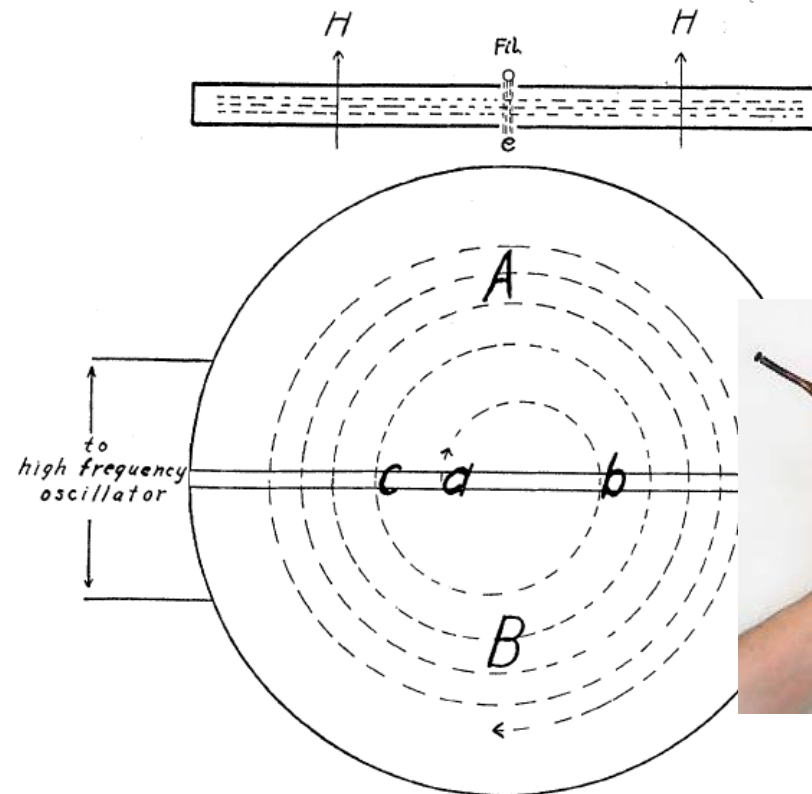
$$\mathbf{F} = q \mathbf{v} \times \mathbf{B}$$

$$q r \omega B = m r \omega^2 = m \omega.$$

orbits are isochronous

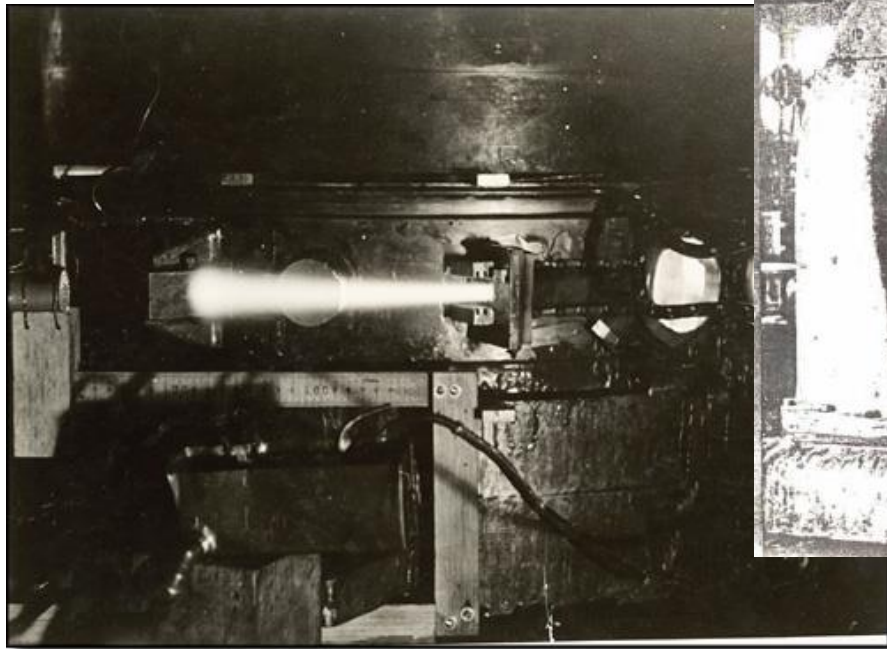
$$\omega = \frac{qB}{m}$$

$$r = mv/qB.$$

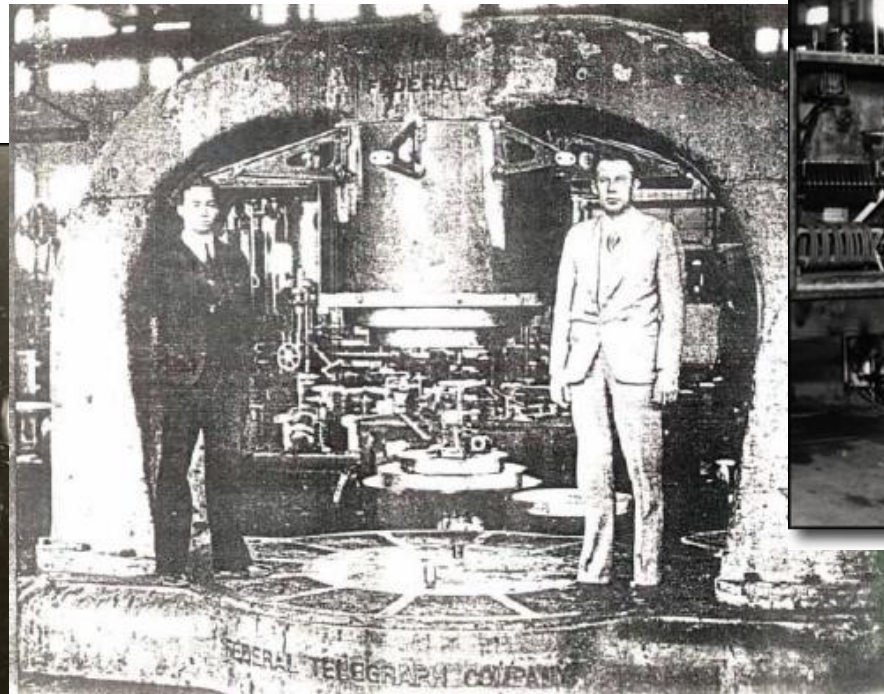


13 keV protons

Cyclotron - history



Glow from 11" (1.22 MeV protons)
Cyclotron Beam



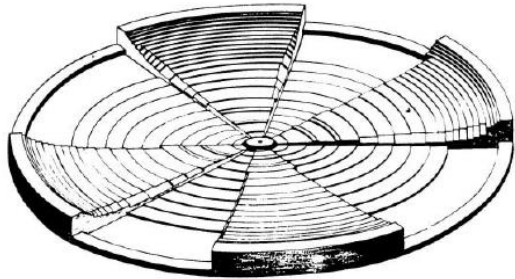
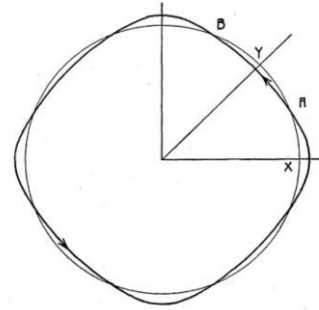
Lingston and Lawrence with
the 27" Cyclotron, 6.3 MeV
deuterons



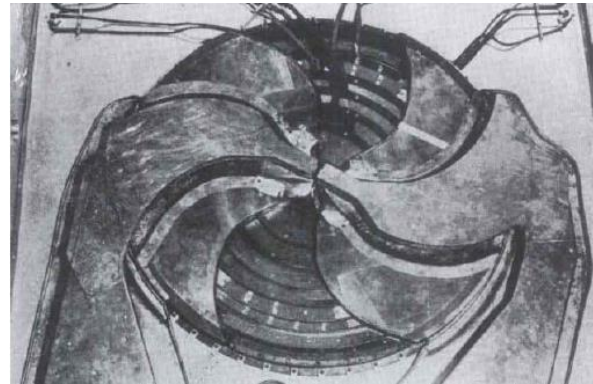
Lawrence at Work on the 37"
Cyclotron, 1937, 8.5 MeV
deuterons

Higher energy cyclotrons

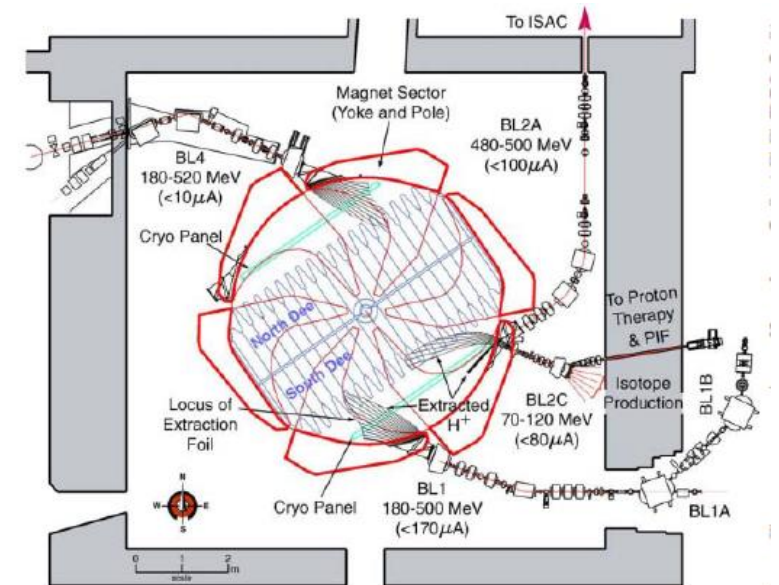
$$B_z(\theta) = \langle B_z(\theta) \rangle (1 + f \cos N\theta)$$



12.7 MeV Delft cyclotron



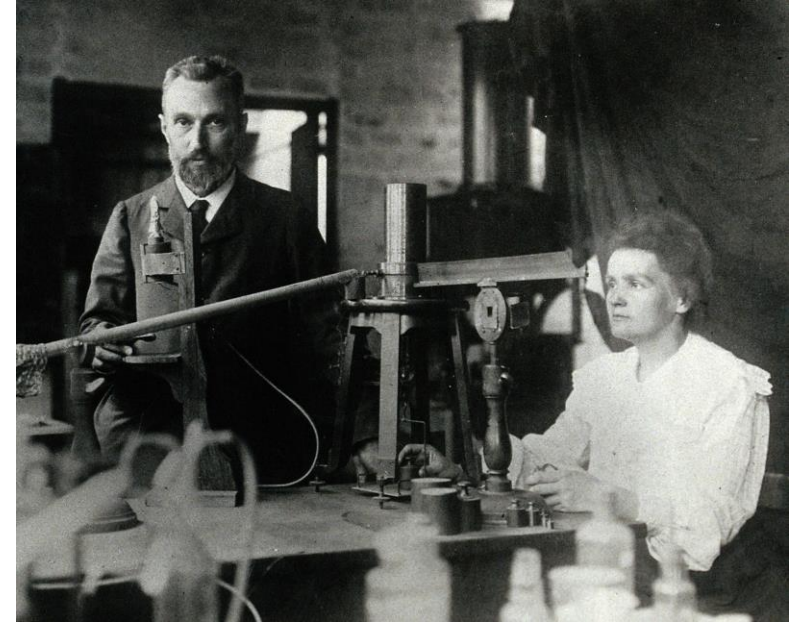
UCLA 50 MeV cyclotron



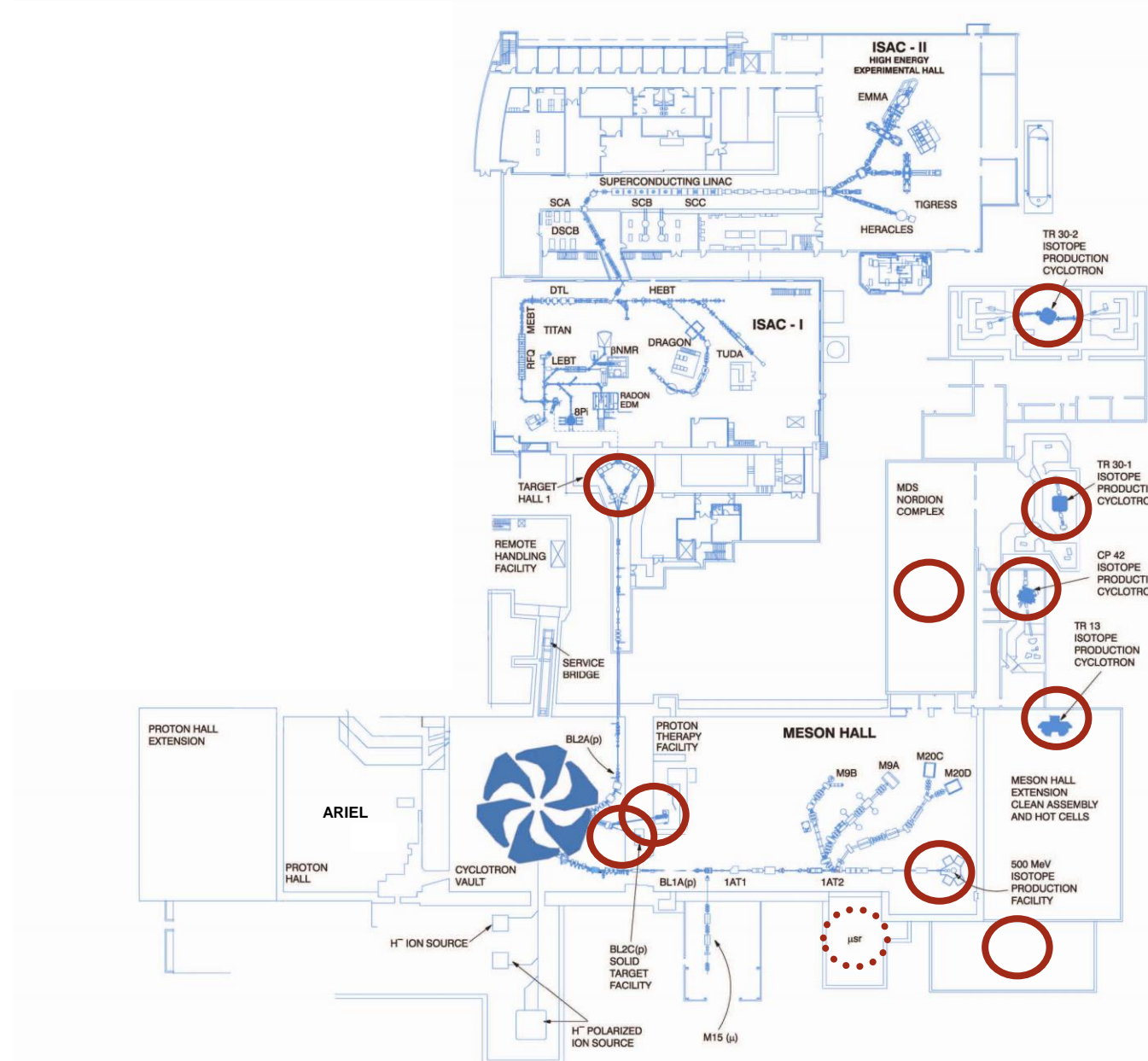
TRIUMF 500 MeV cyclotron

Nuclear Medicine - history

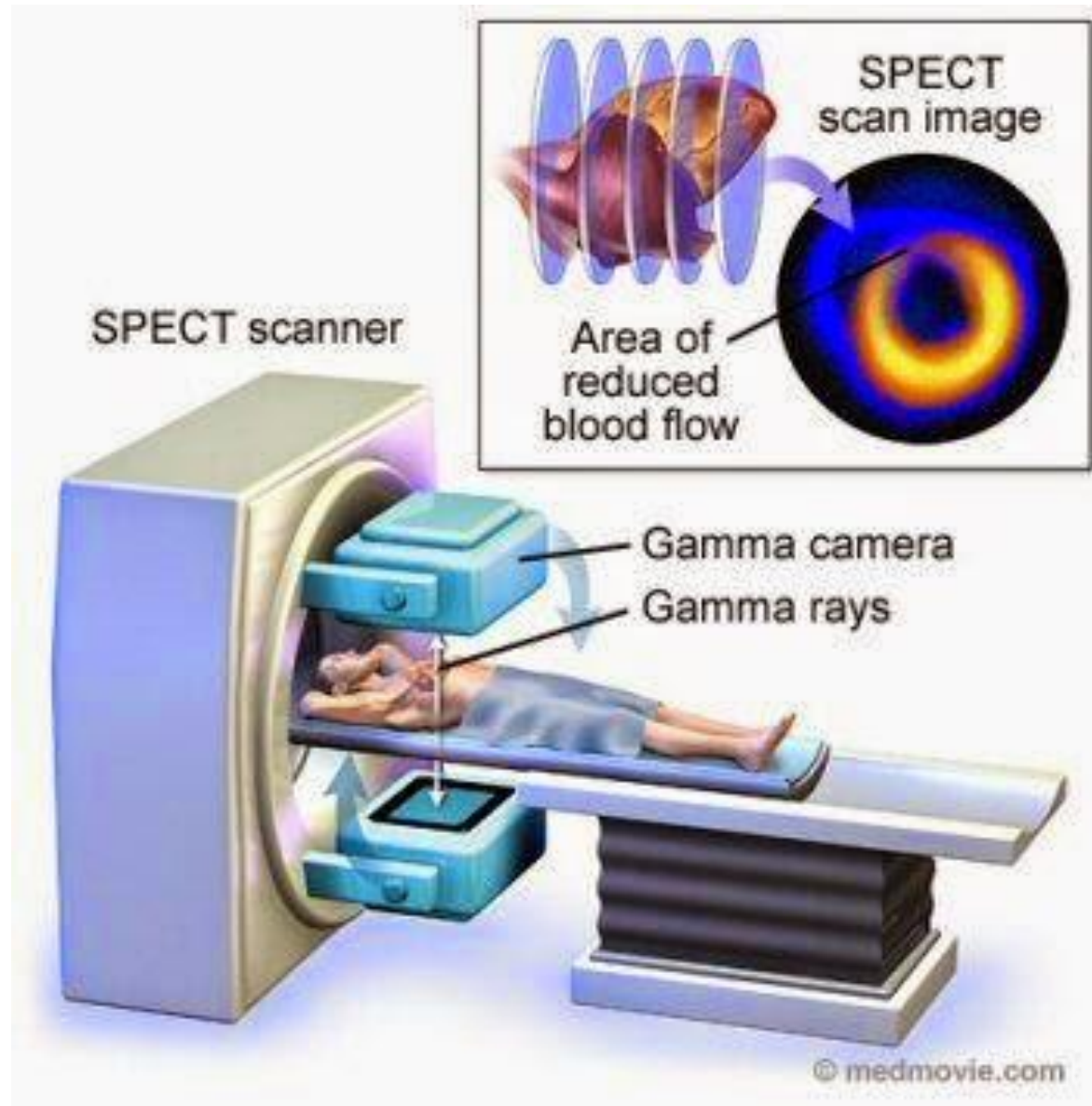
- 1898 discovery of radioactivity by Marie and Pierre Curie – radium therapy
- First tracer study in 1924: blood circulation with Bi-212
- Irene Joliot-Curie & Frederic Joliot: Nature 1934 – producing radioactivity artificially
- Read by E. Lawrence Cyclotron and Geiger counter were on the same circuit!
- 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**

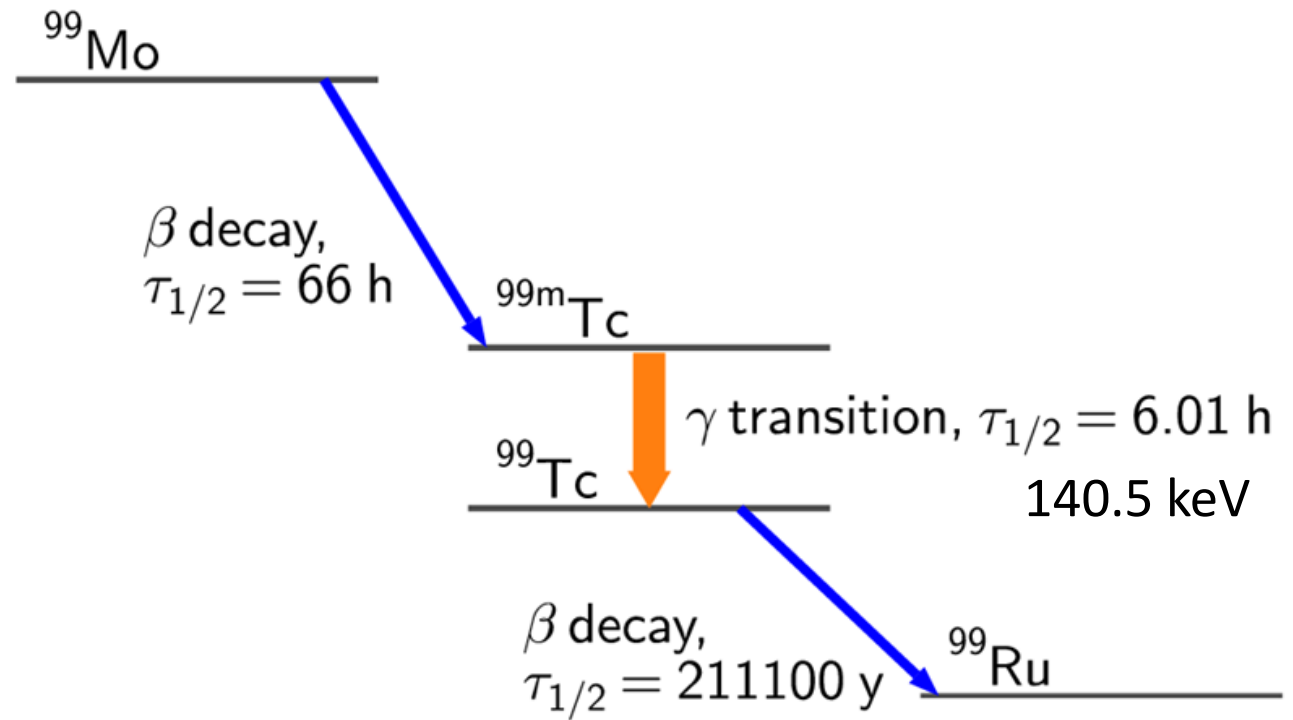
40 Million doses every year

>1 scan/second (brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, tumors)

SPECT: Tc-99m



- Simple distribution & use



Making Isotopes



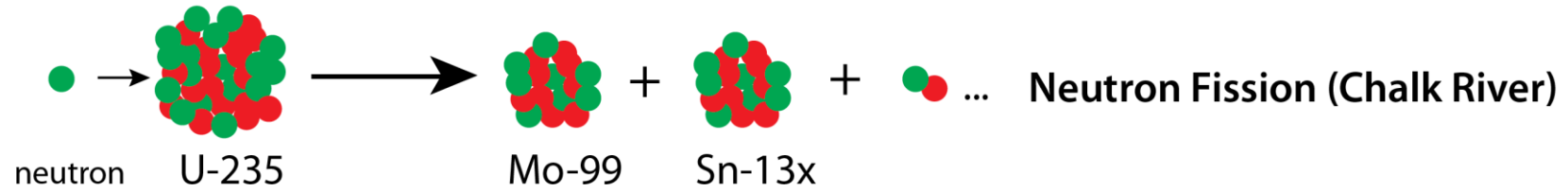
Reactor



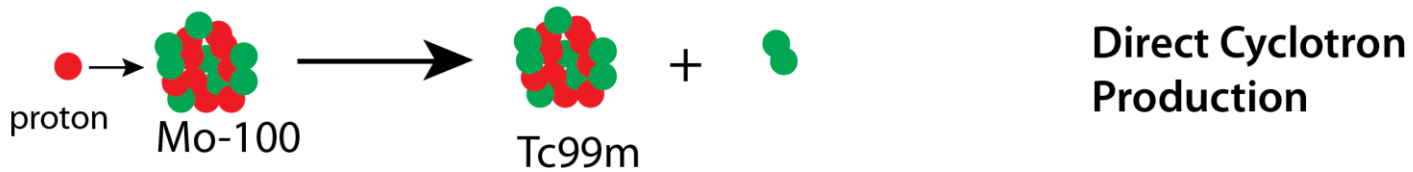
Cyclotrons
(Accelerators)

The Technology

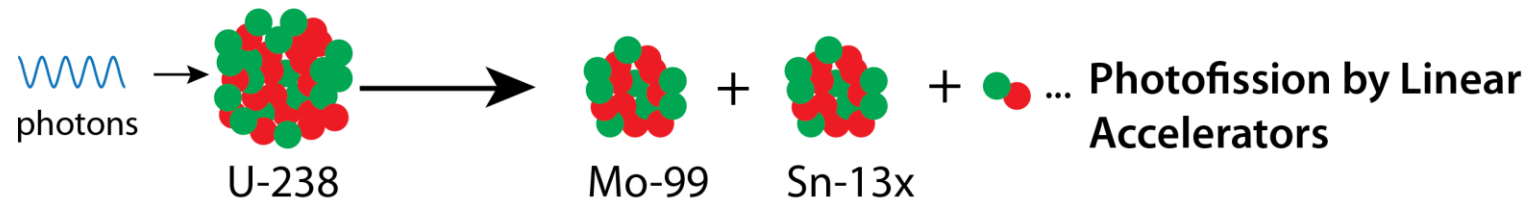
NUCLEAR REACTORS



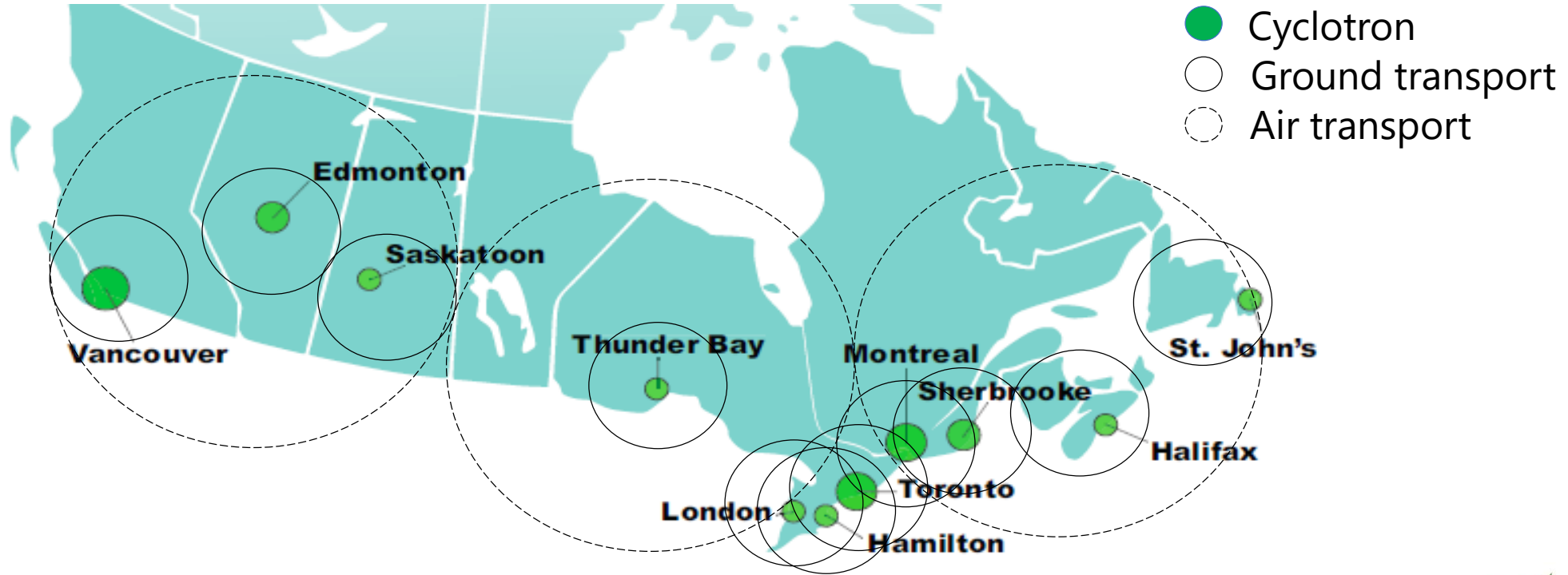
CYCLOTRONS



LINEAR ACCELERATORS



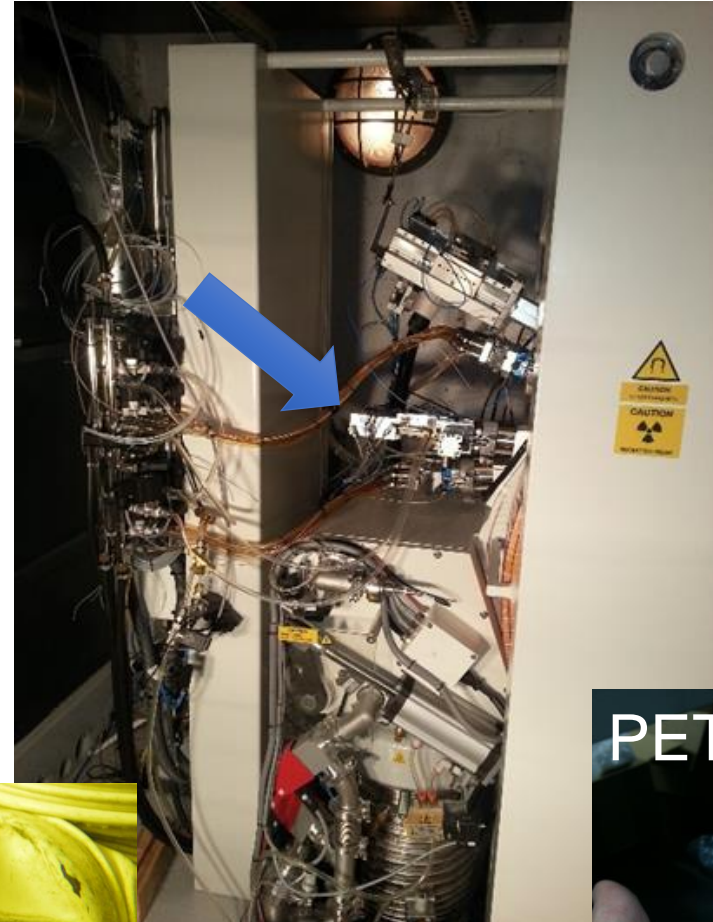
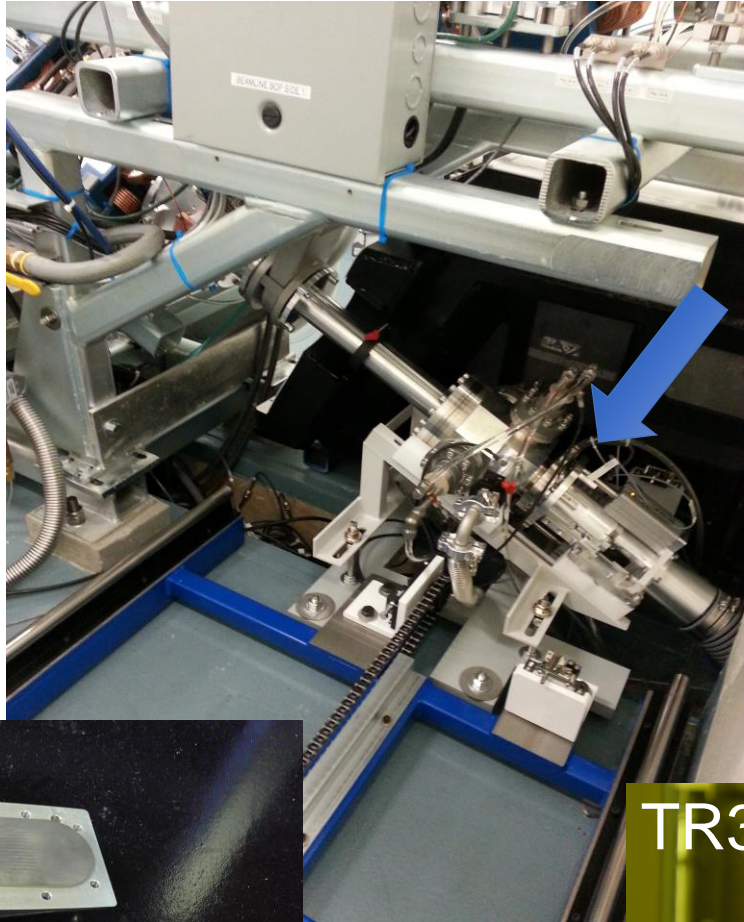
Alternative ^{99m}Tc Production



- 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



Cyclotron Production of ^{99m}Tc



TR19

300 μA , 18 MeV, 5.4 kW



TR30

450 μA , 24 MeV, 10.8kW

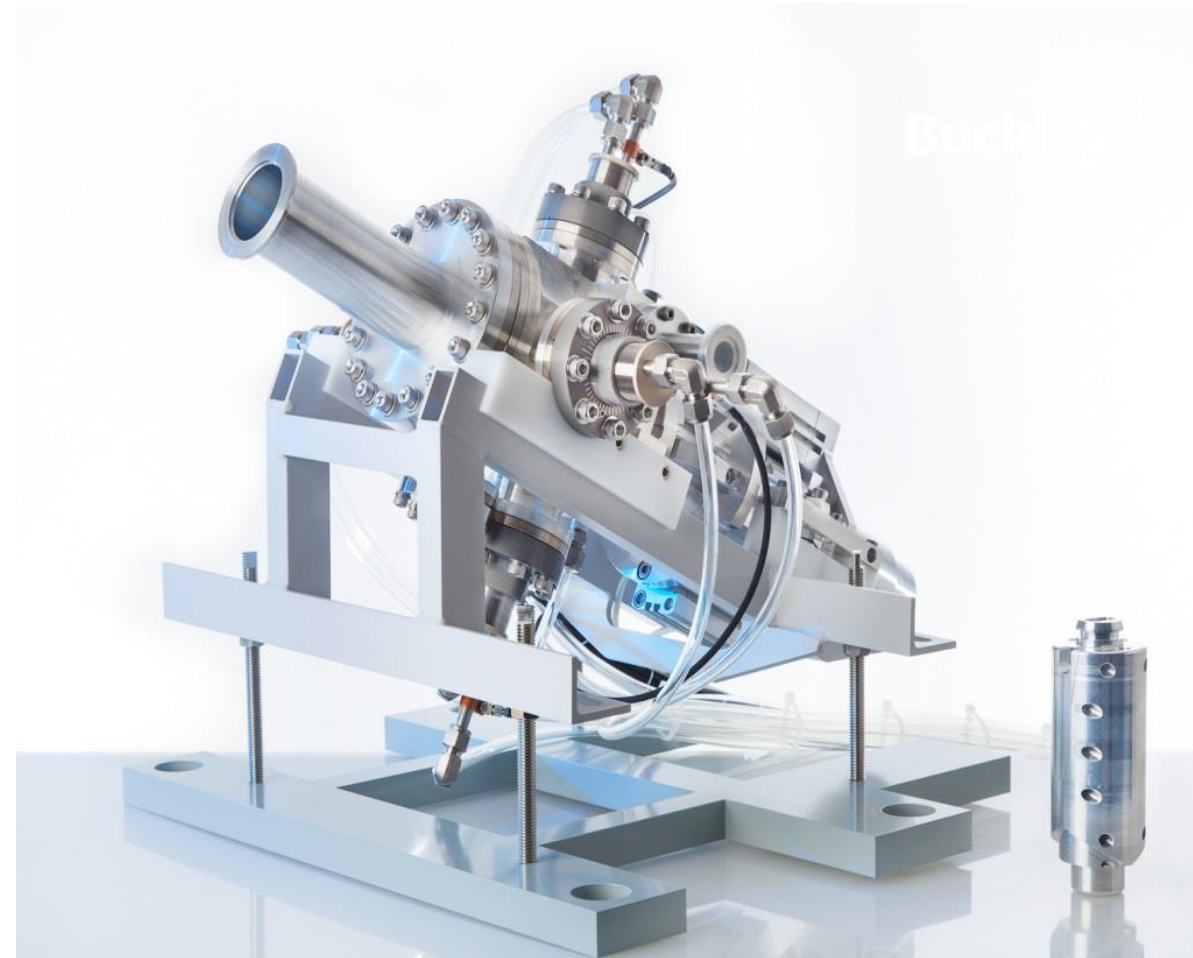


PETtrace

130 μA ,
16.5 MeV,
2.1 kW

^{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

Positron Emission Tomography

Radioactive tracer injected into body,
Uptake into different organs

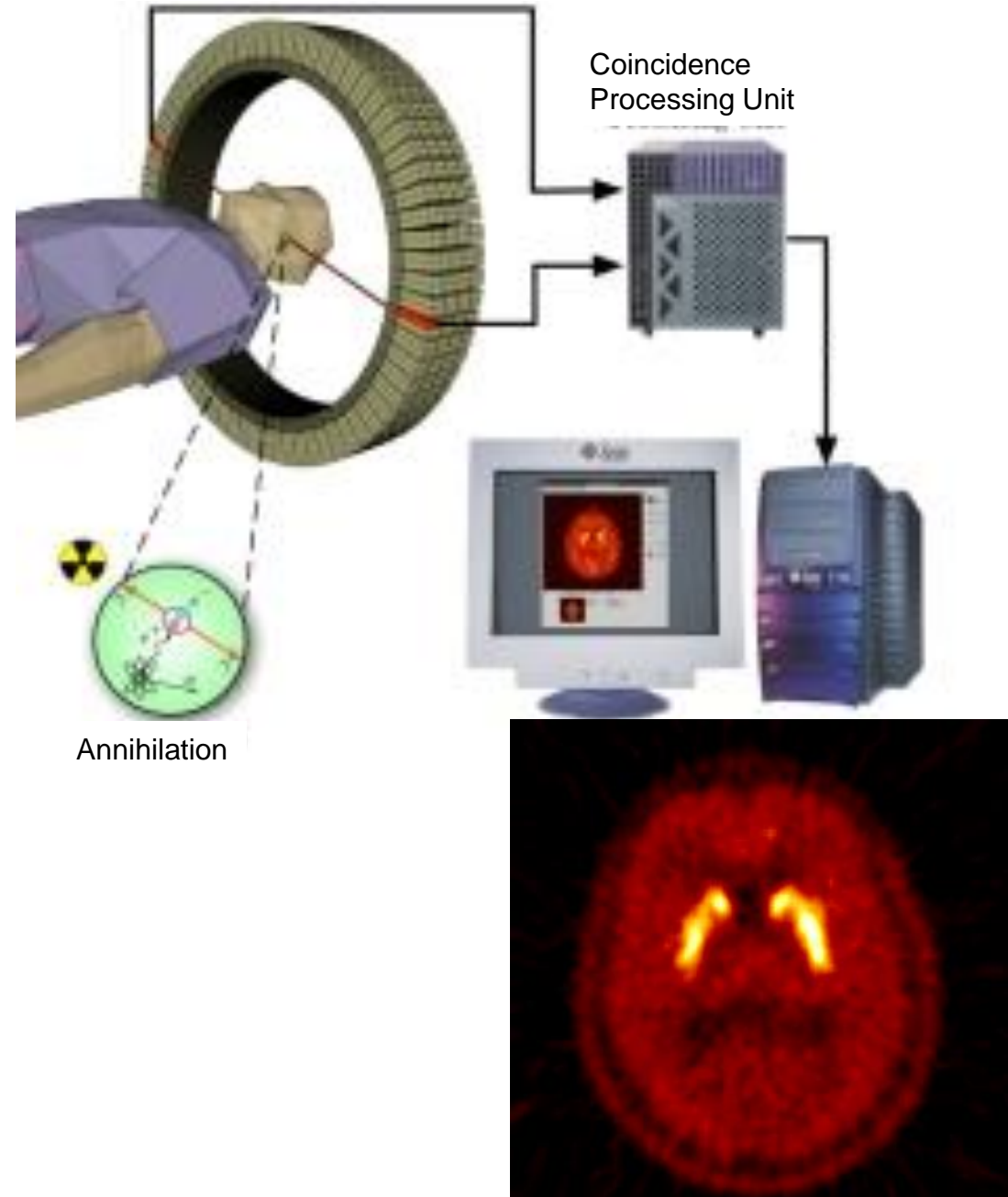
Positron decay



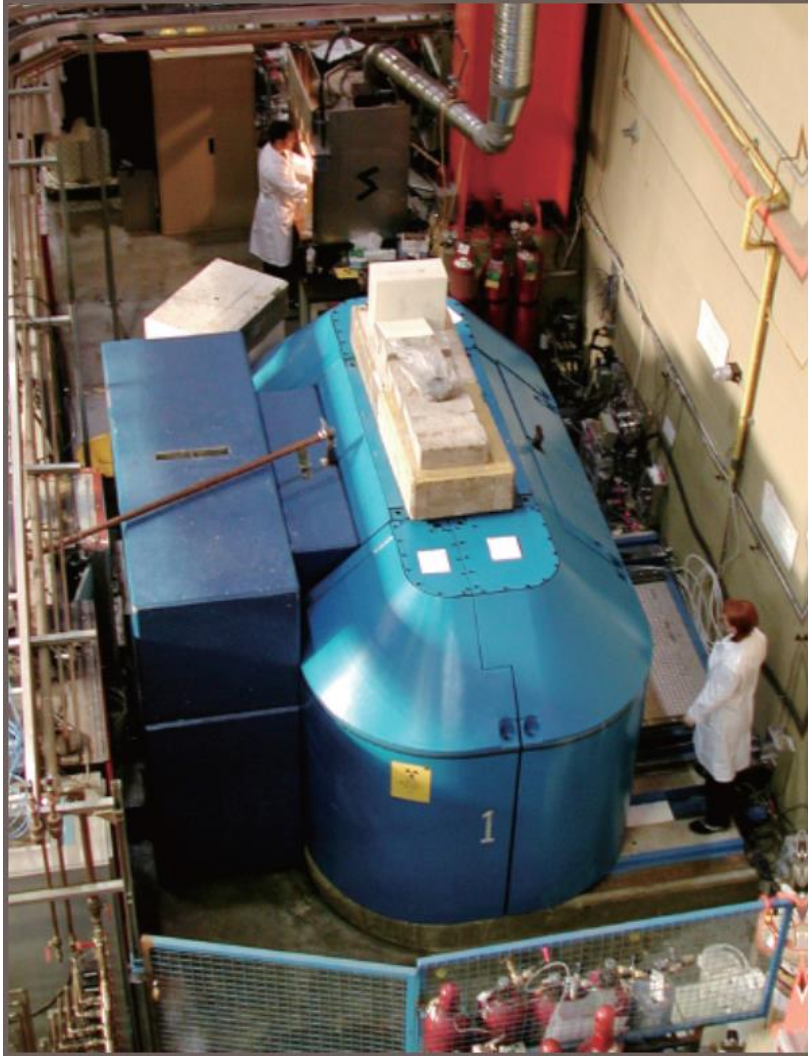
Two 511keV gammas

Measured in coincidence

Function rather than structure



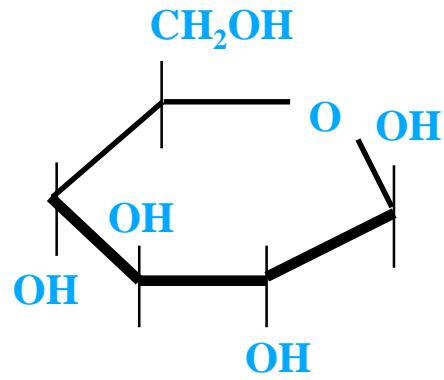
TR13 Cyclotron



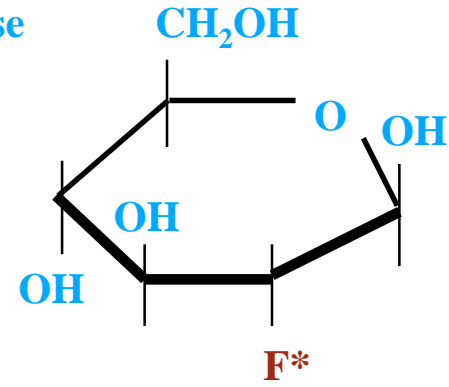
- 13 MeV (19 MeV)
- Negative hydrogen ions
- Dual beam extraction
- Eight targets

FDG

Glucose



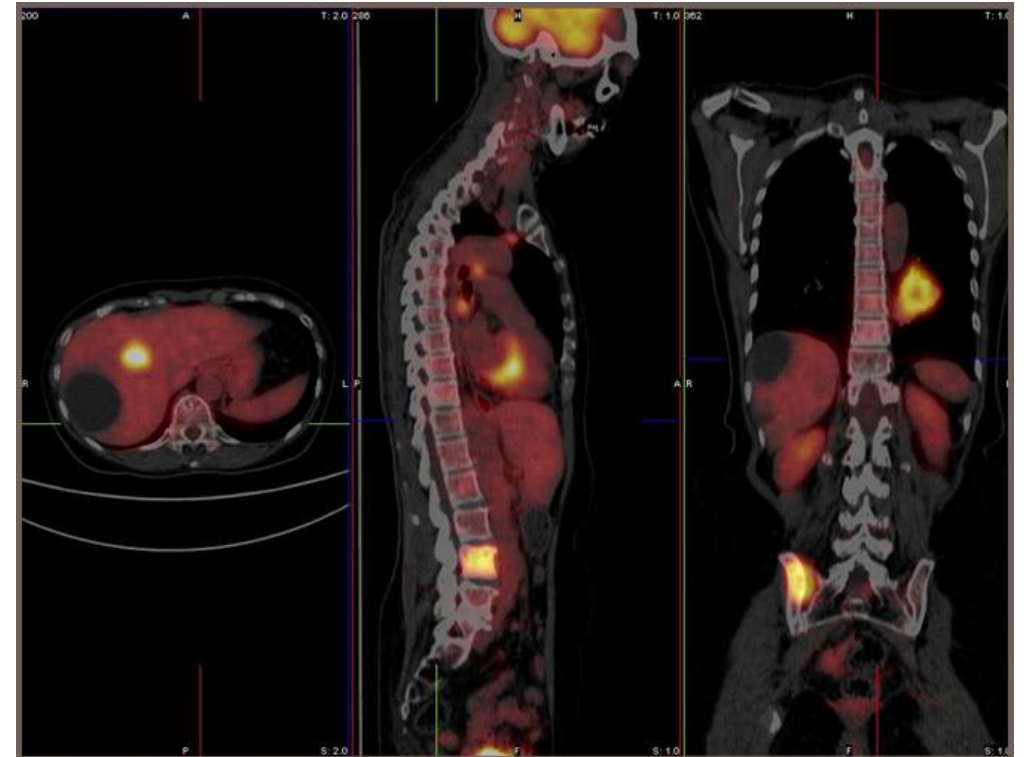
Fluorodeoxyglucose (FDG)



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

THE first successful transmutation of the chemical elements was performed by Rutherford¹ in 1919, not by chemical means, but by the physical process of driving one type

By **JOHN J. LIVINGOOD, Ph.D.**

*Radiation Laboratory
Department of Physics
University of California*

or porcelain tubes by high speed electrons.

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

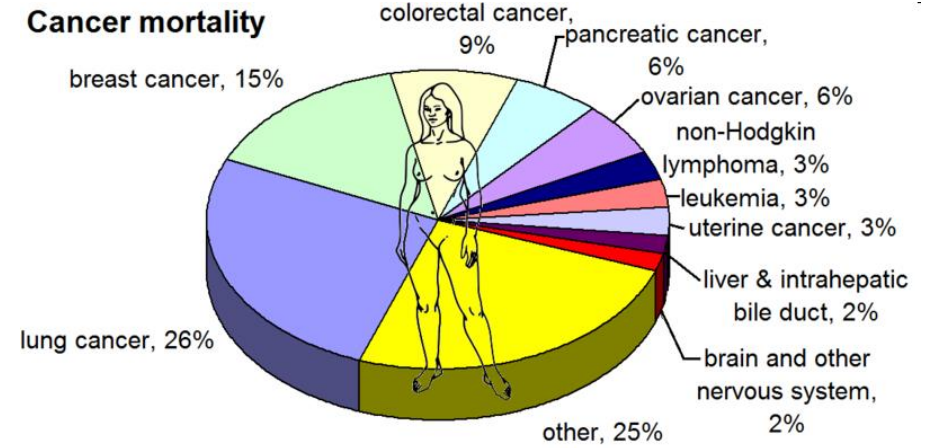
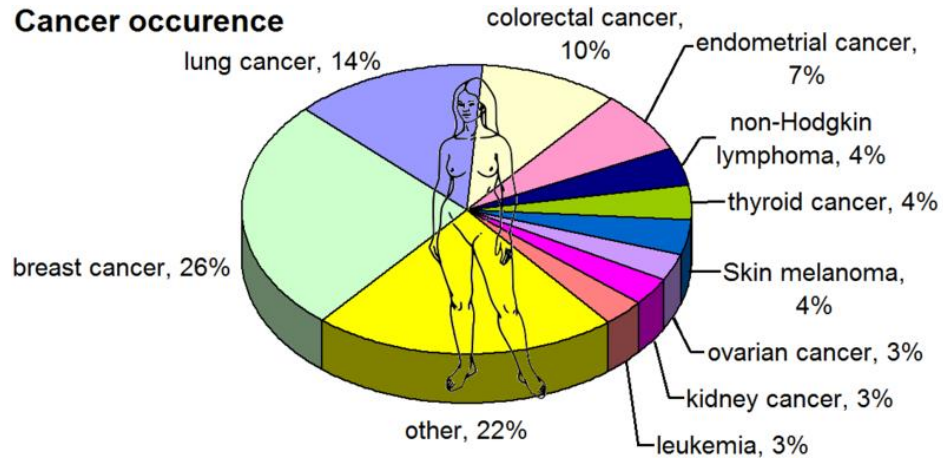
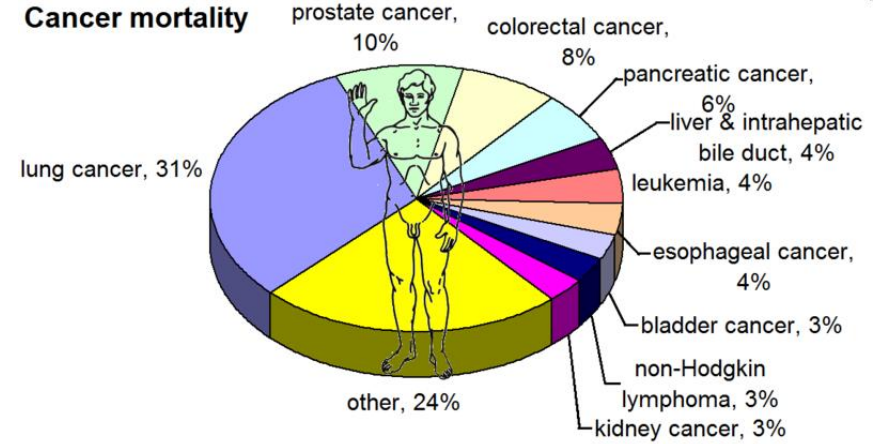
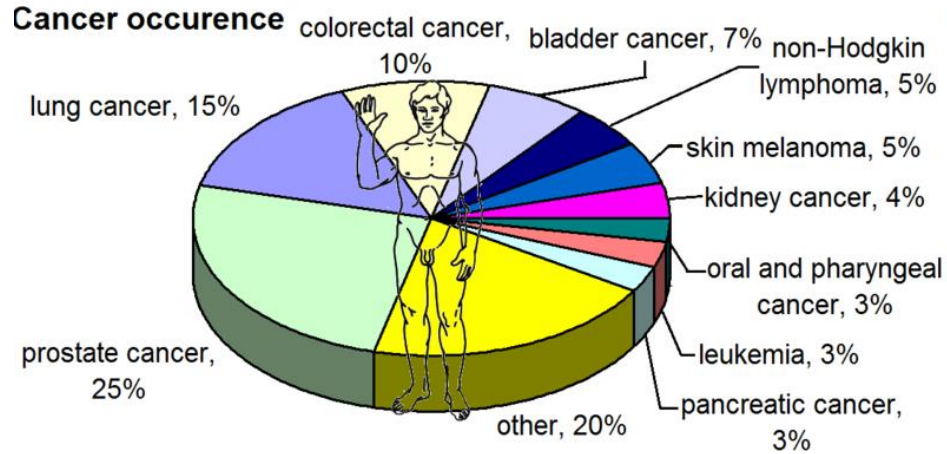
Uses in Biology

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 deuterons¹². 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



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

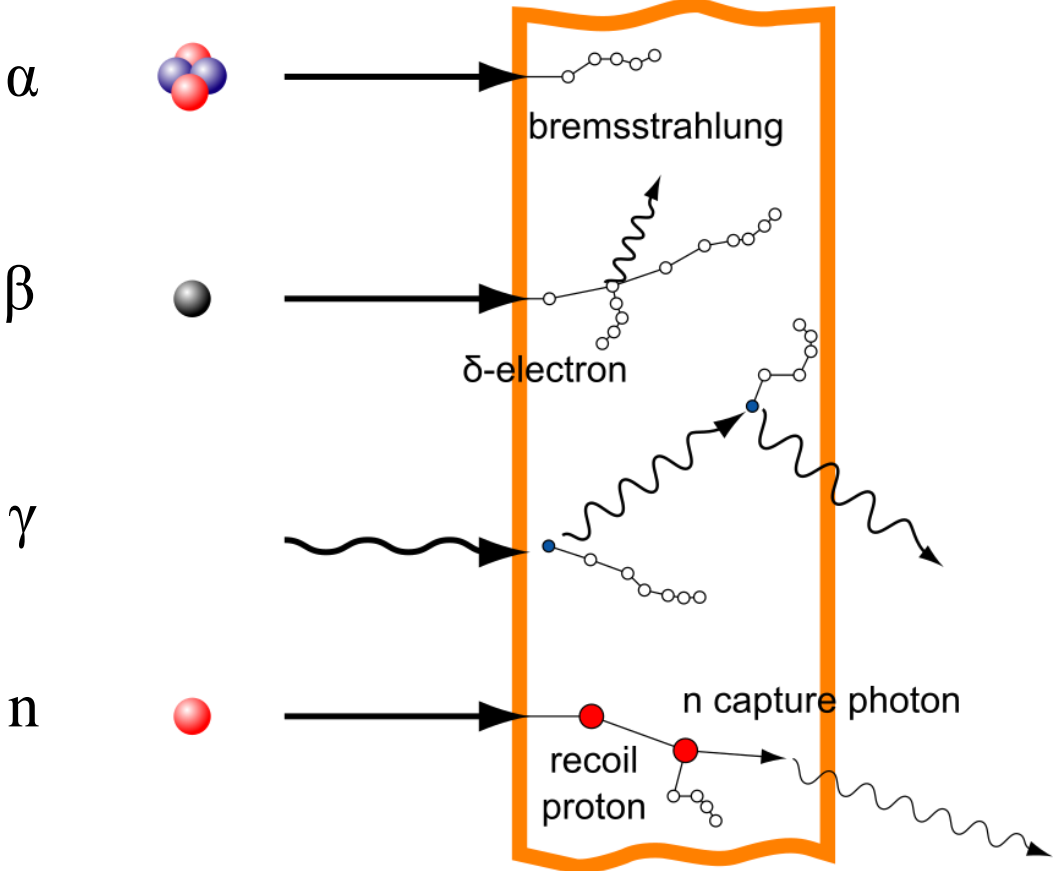
- * External beam therapy – photons, neutrons, protons, ions

- * Internal therapy – brachytherapy (radioactive isotopes)

Success: Tumor control vs. complications

Destroy/remove tumor without damaging healthy or normal tissue nearby

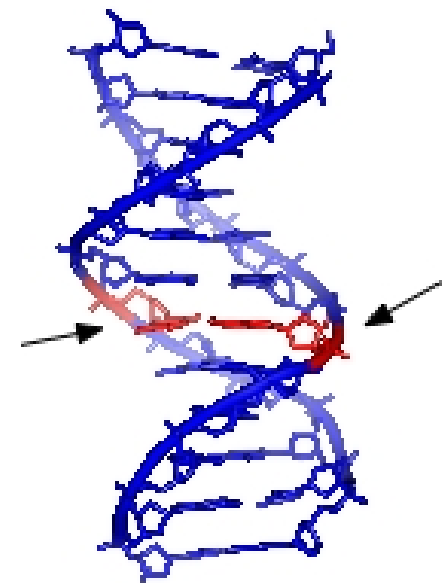
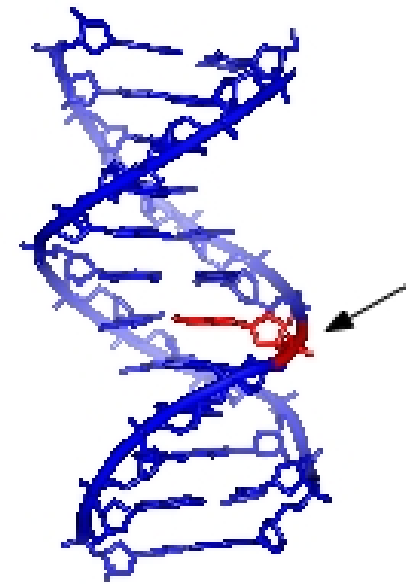
Ionizing Radiation



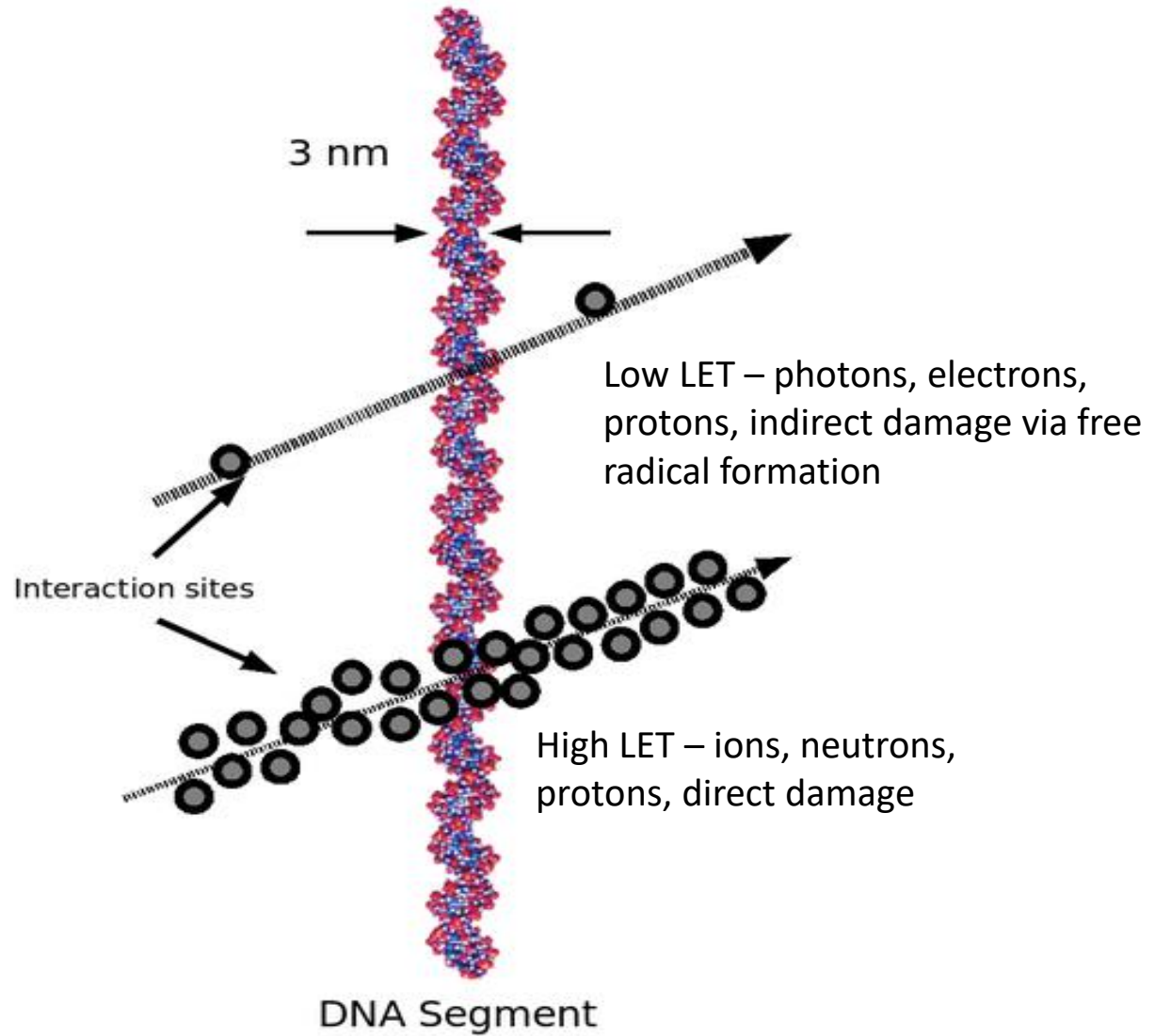
Radiation Therapy

- 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

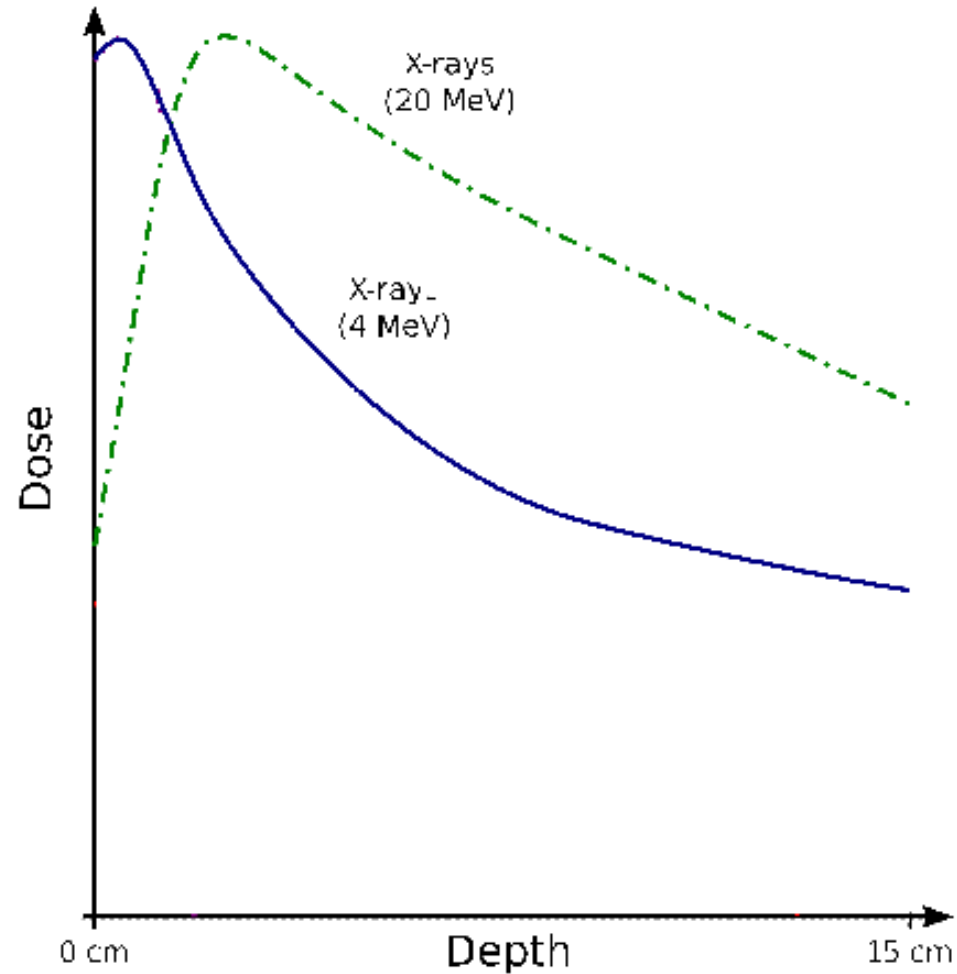
Radiotherapy: as many double helix breaks in cancer cells as possible with as few double breaks as possible in healthy cells



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

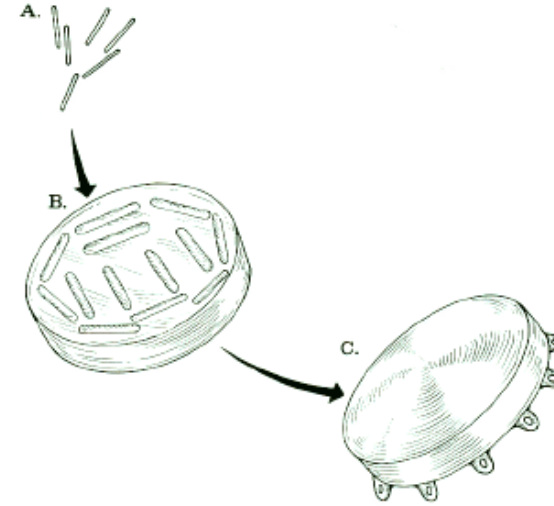
From the Greek word *brachys*, meaning "short-distance", most isotopes used are gamma emitters

Advantages

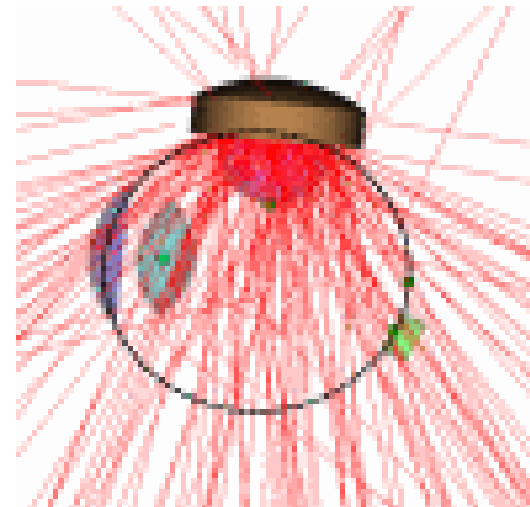
- Very localized
- Can have shorter treatment times
- Moves with tumor
- Can be permanent or temporary

Disadvantage

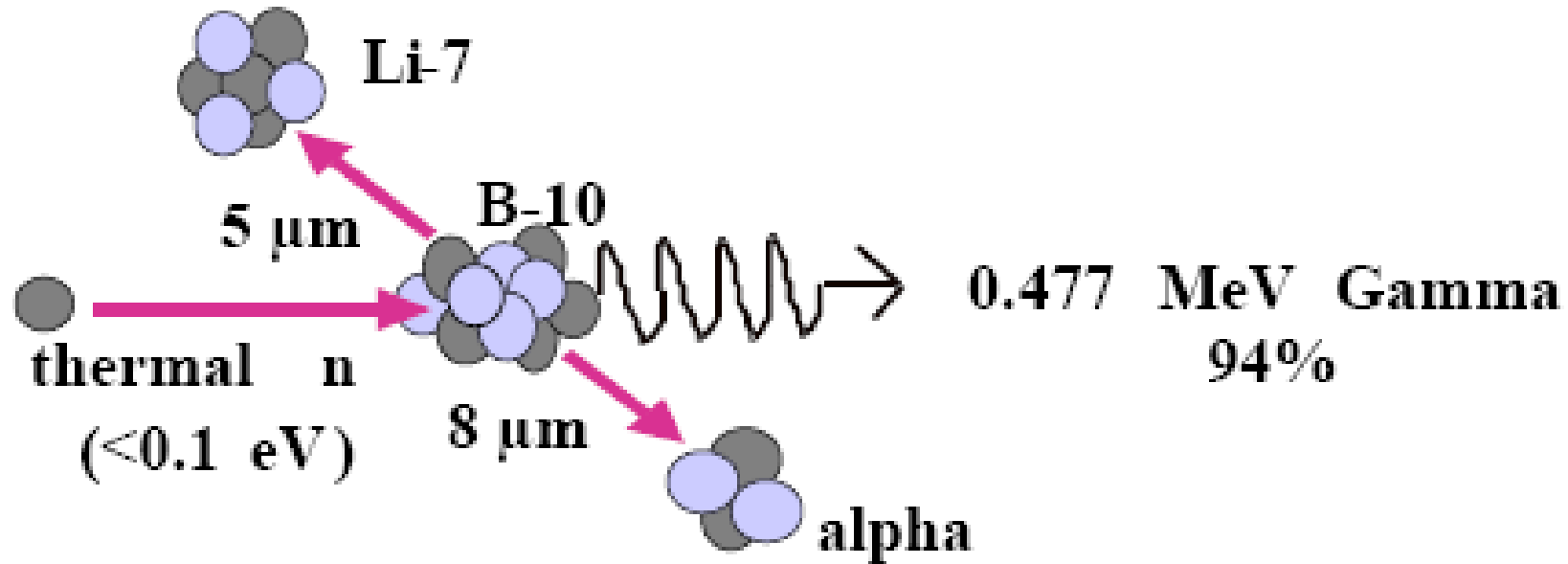
- High dose to medical personnel
- Dose not homogeneous (in some cases 40% of dose can be deposited in 15% of tumor)
- Tumor-size dependent



© The EyeCare Foundation, Inc.



External/Internal: Boron Neutron Capture Therapy (BNCT)



- BNCT (thermal $<0.1\text{ eV}$)
- Only experimental (treatment for hours)
- Tracer development still in beginning

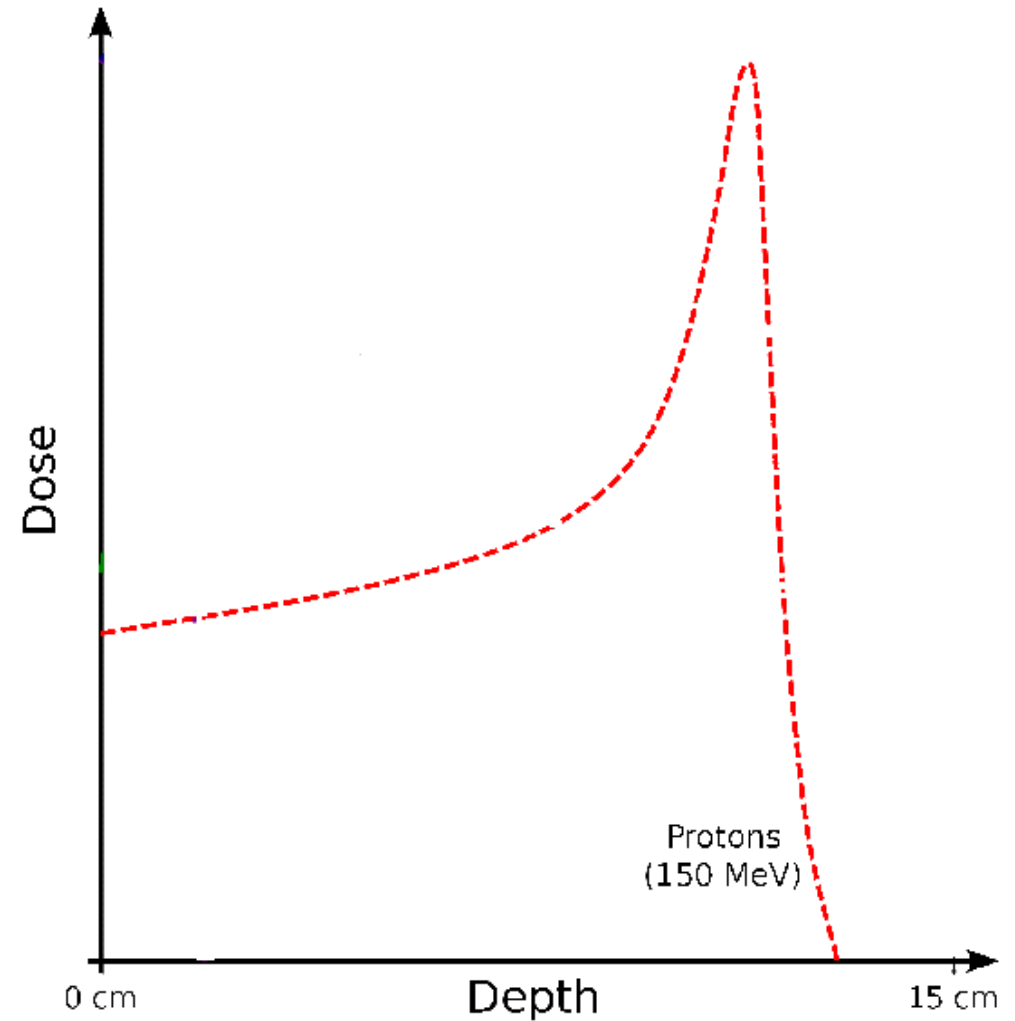
External: Ion Beam Therapy

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

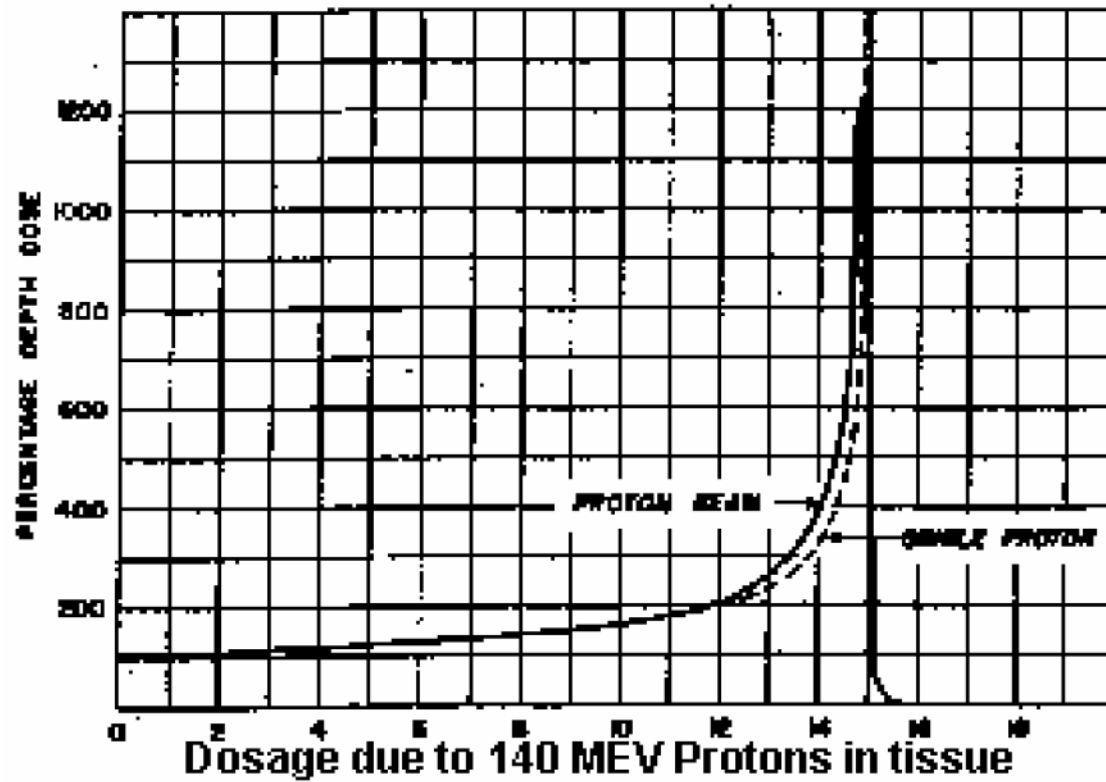


Hans Bethe,
1930 and 1932

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

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

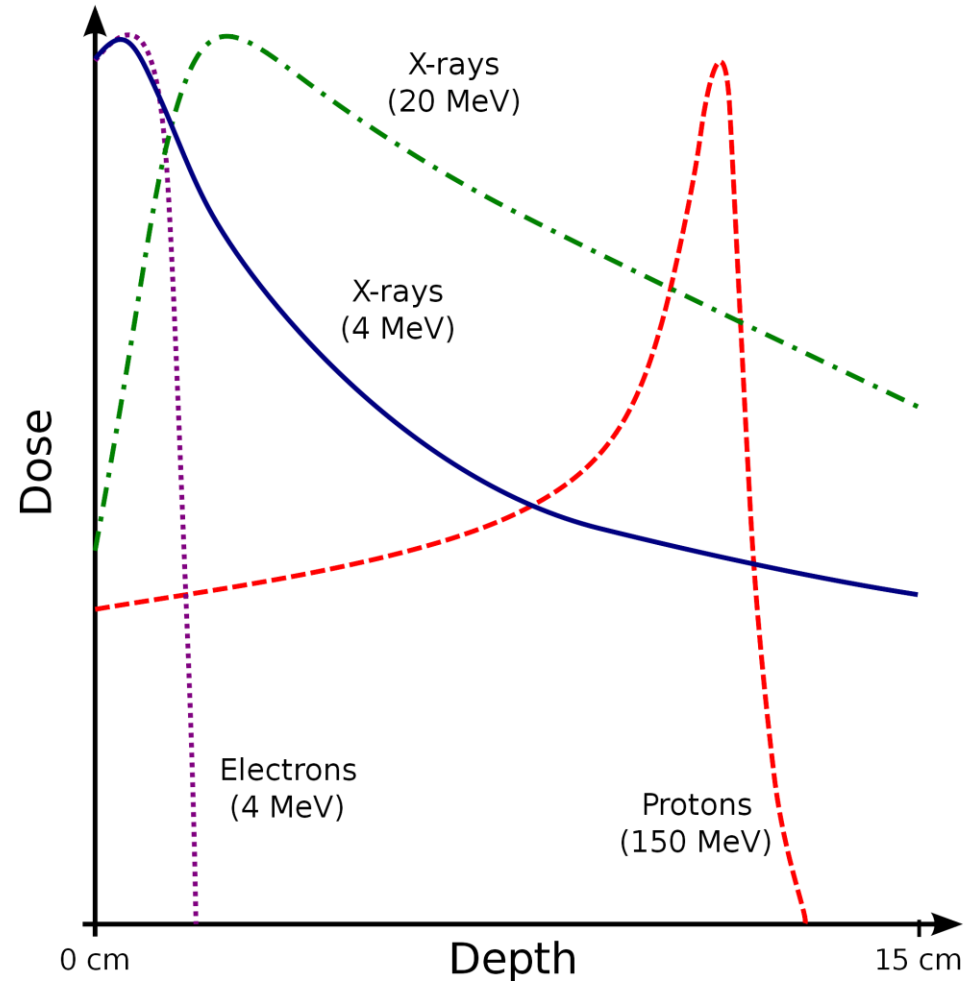
External: ion-beam therapy

Advantage

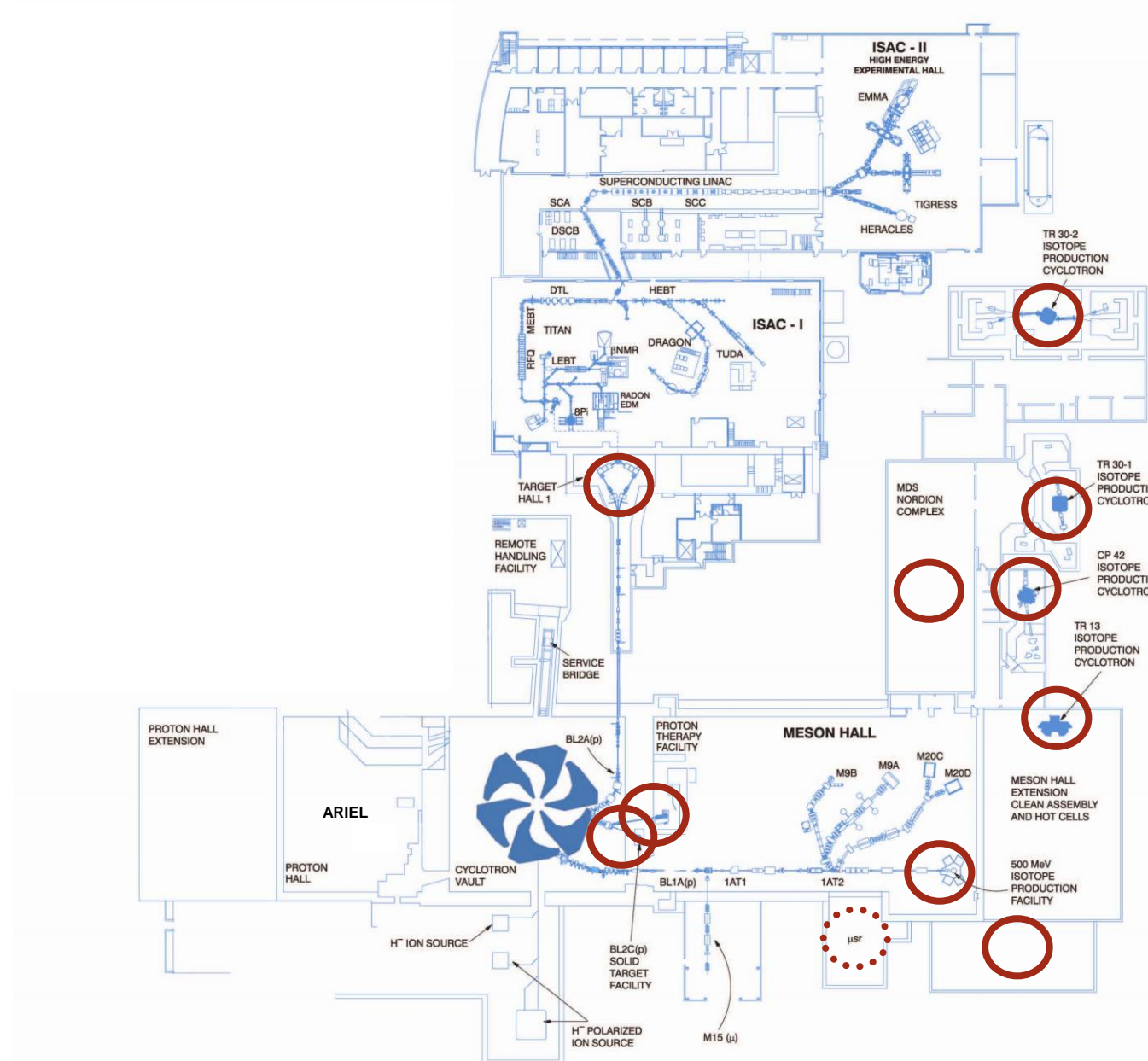
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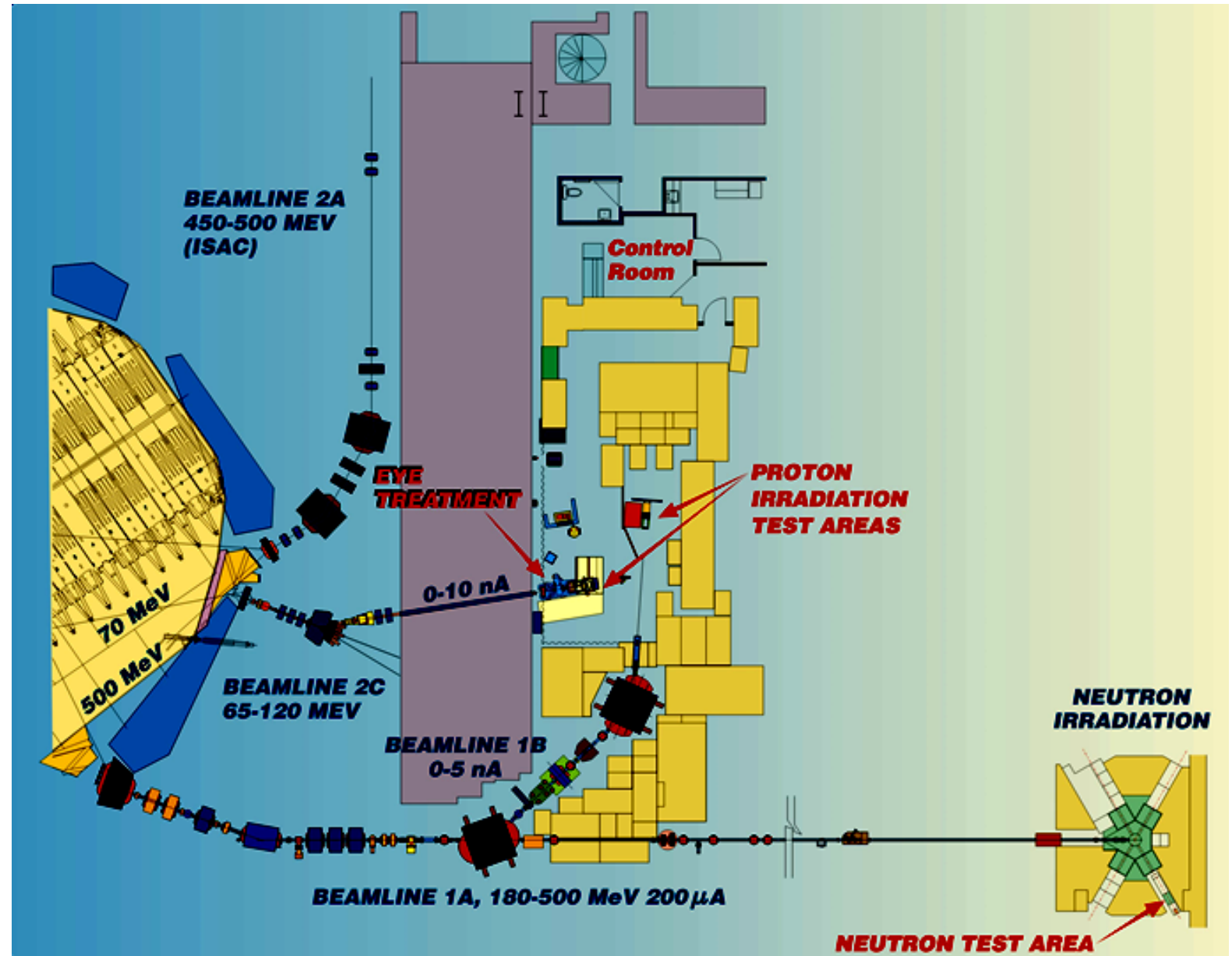


Medical Application @ TRIUMF



Proton Therapy at TRIUMF

- Since 1995
- Ended Feb 2019

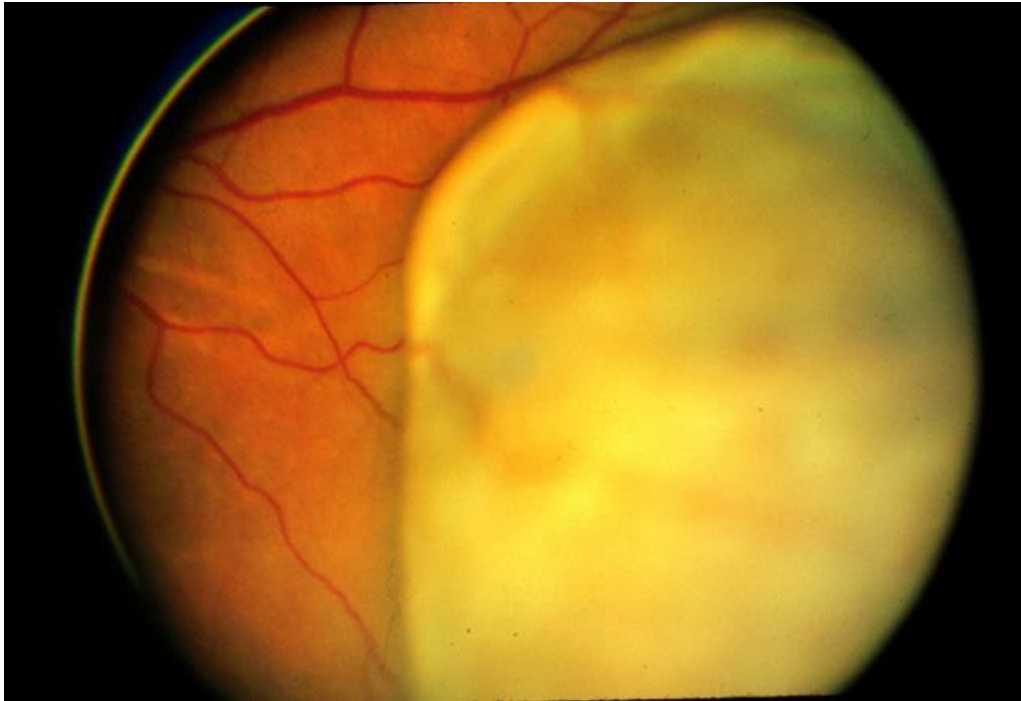


Ocular Melanoma

Frequency: 5 -6 cases/year per million population

Treatment protocols: Radioactive plaque therapy
Charged-particle radiotherapy
Enucleation

35

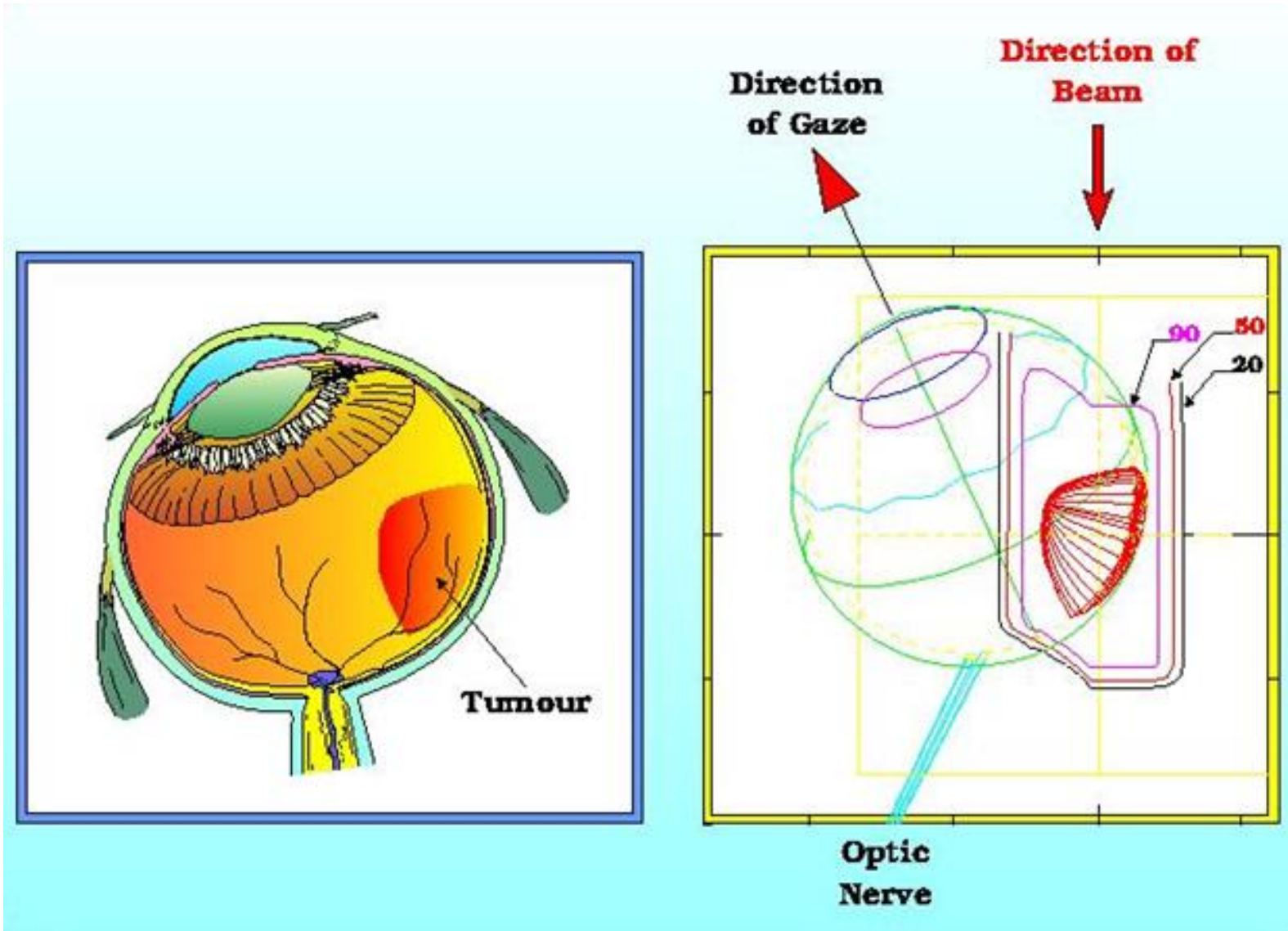


Uveal Melanoma before
proton beam treatment

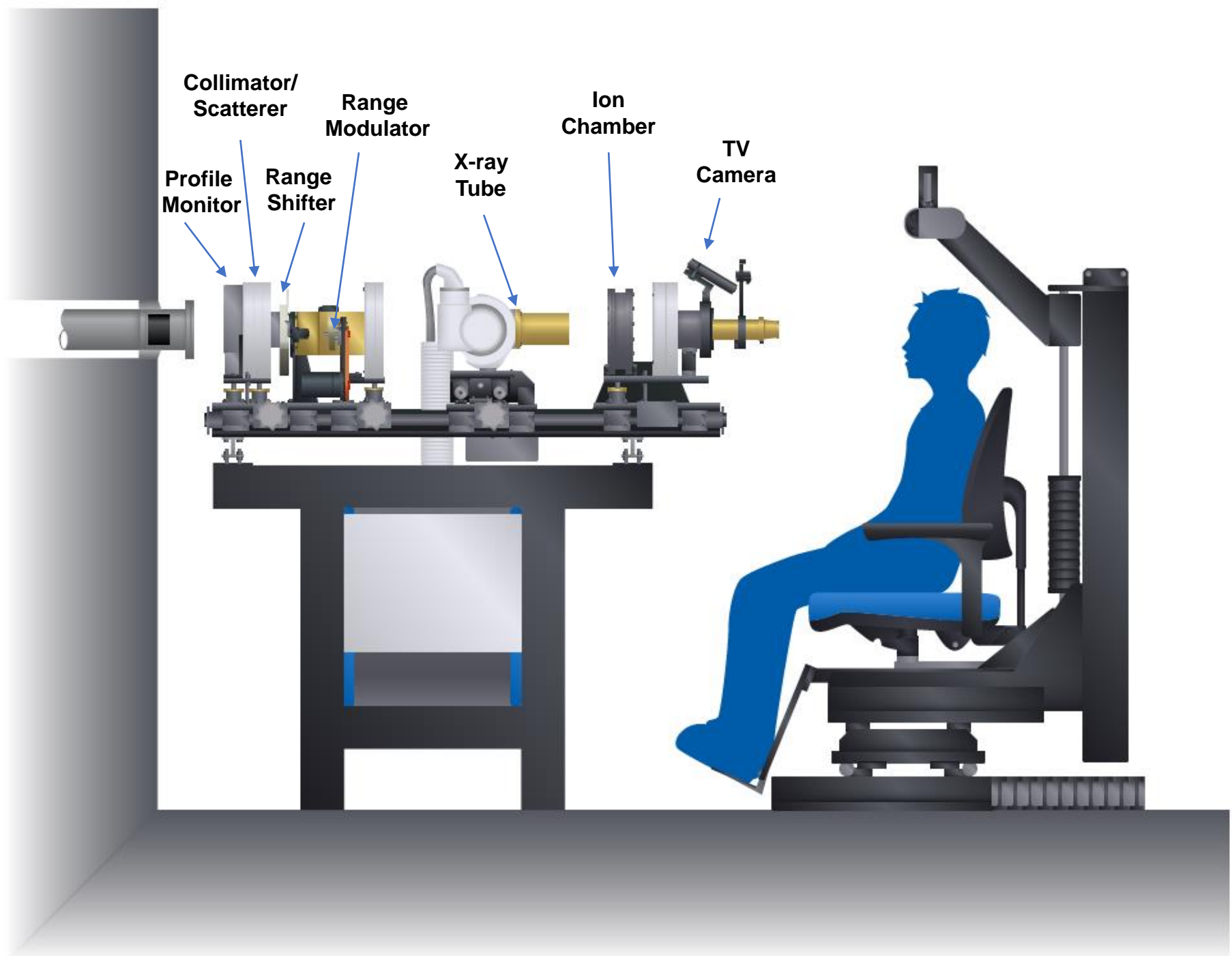


Uveal Melanoma after
proton beam treatment

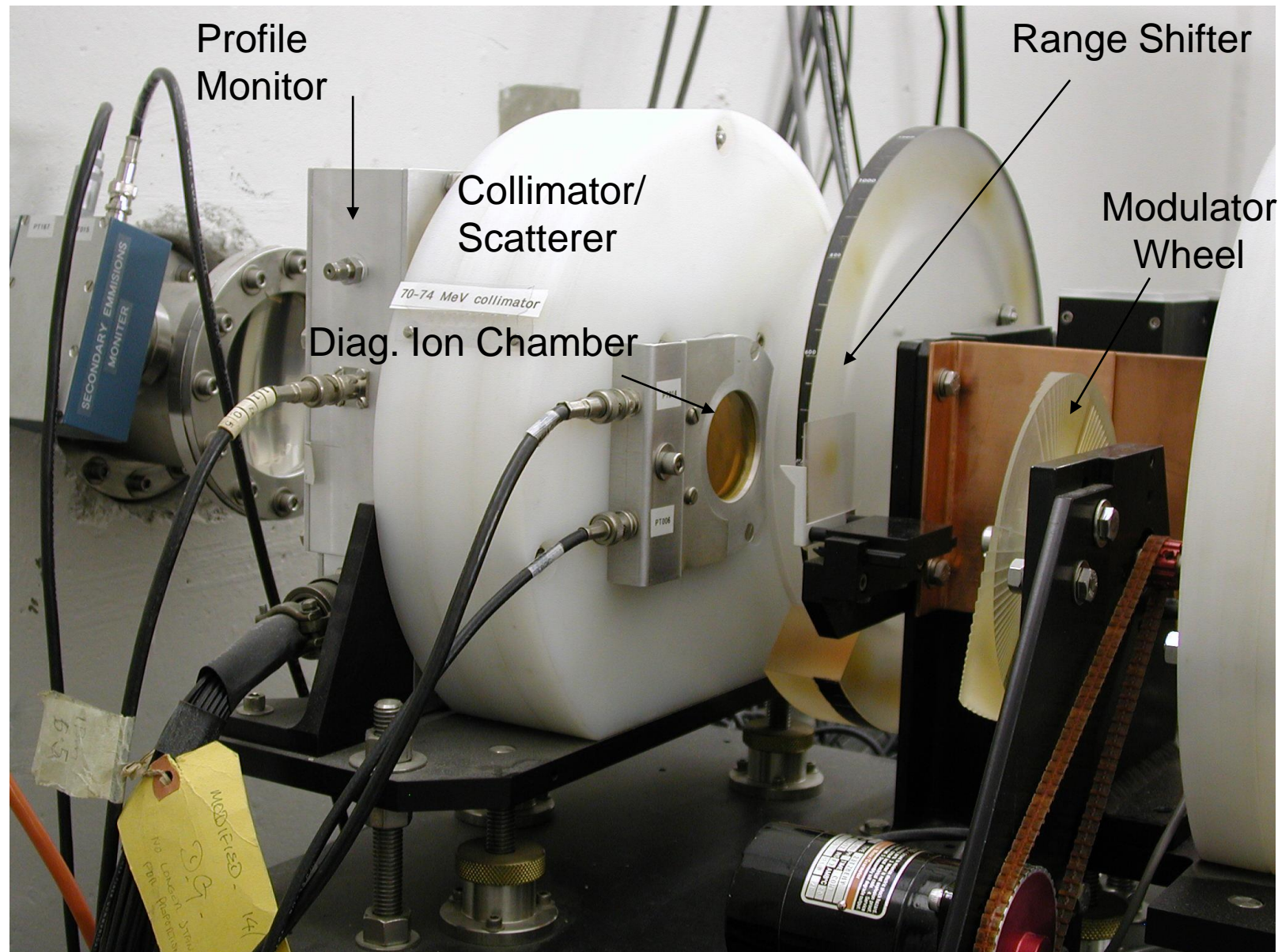
Treatment Planning



Beamline

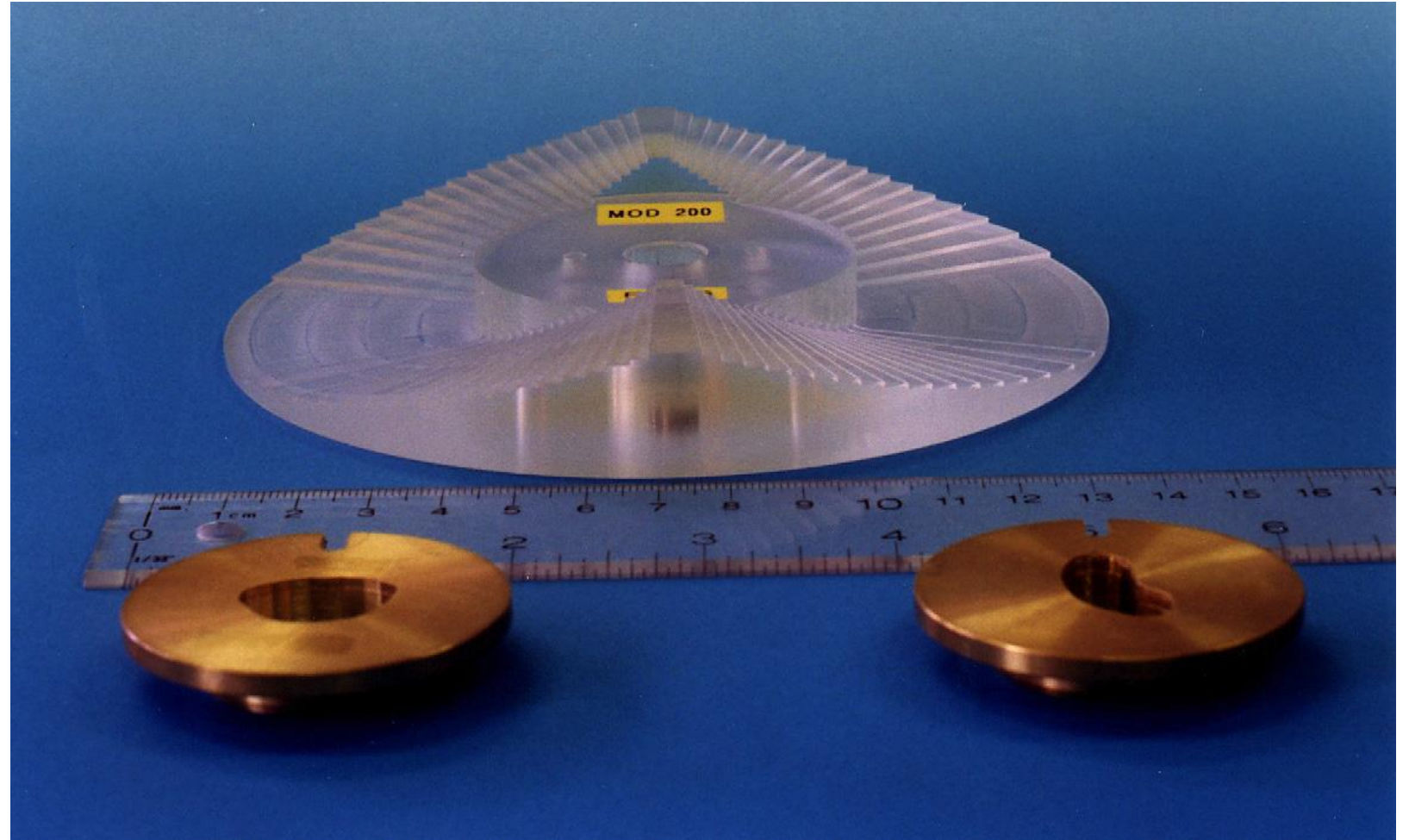


Beamline



Modulator and Collimator

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



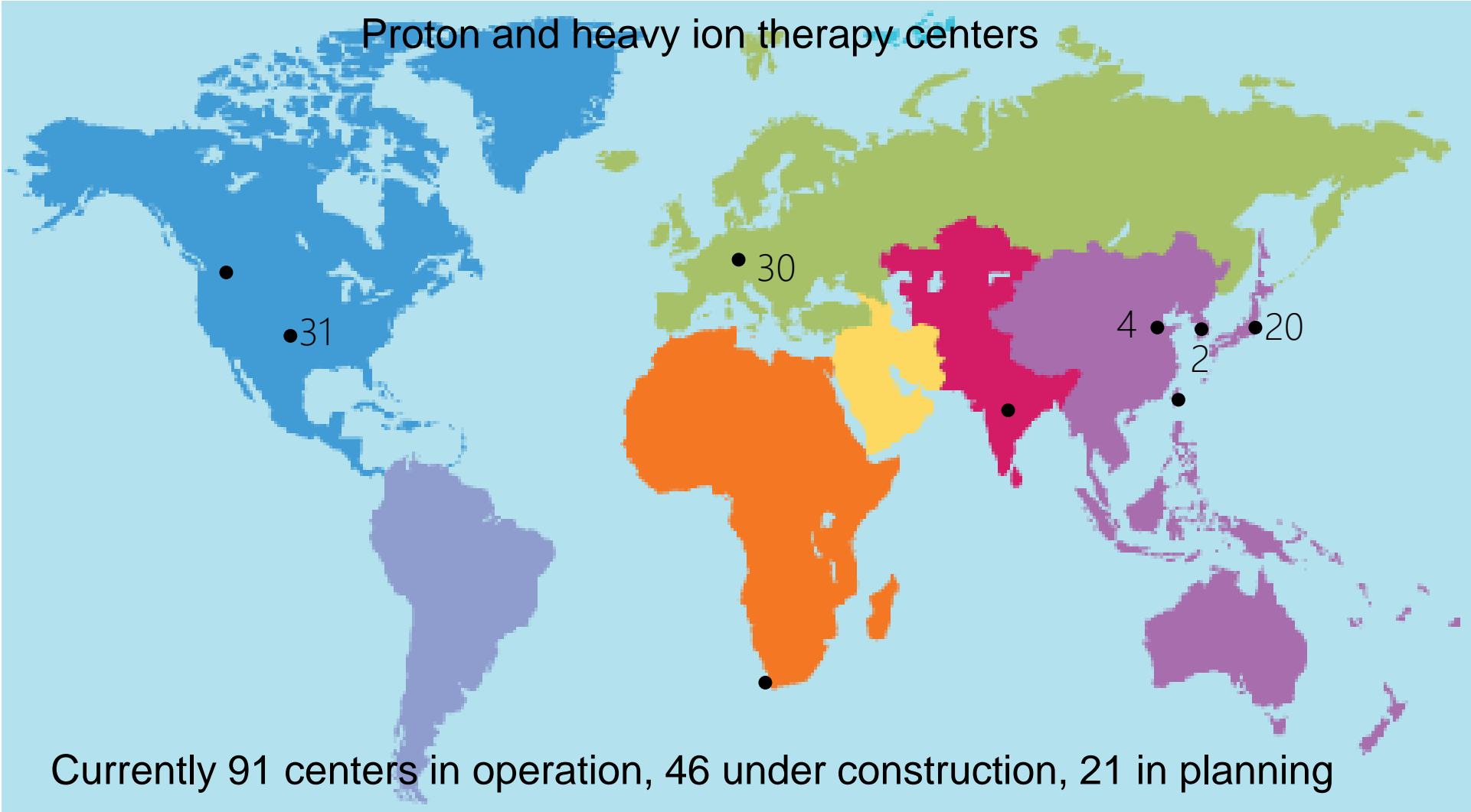
PT Treatment Results

Summary paper with 59 patients

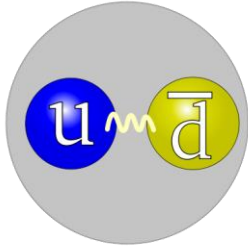
(E. Tran et al., Int. J. Radiat. Oncol. Biol. Phys. [83](#) (2012) 1425)

- 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%

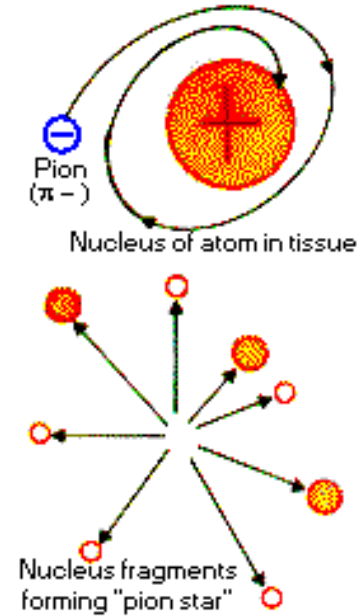
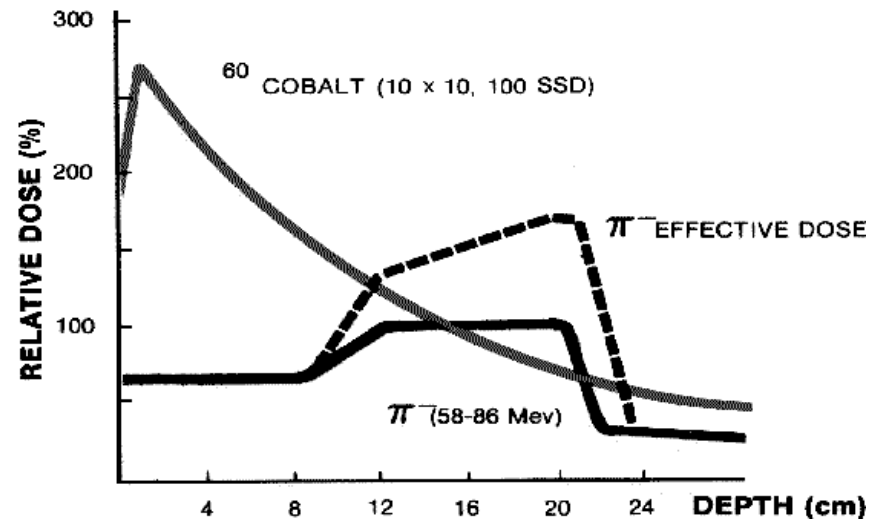
Hadrontherapy around the World



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

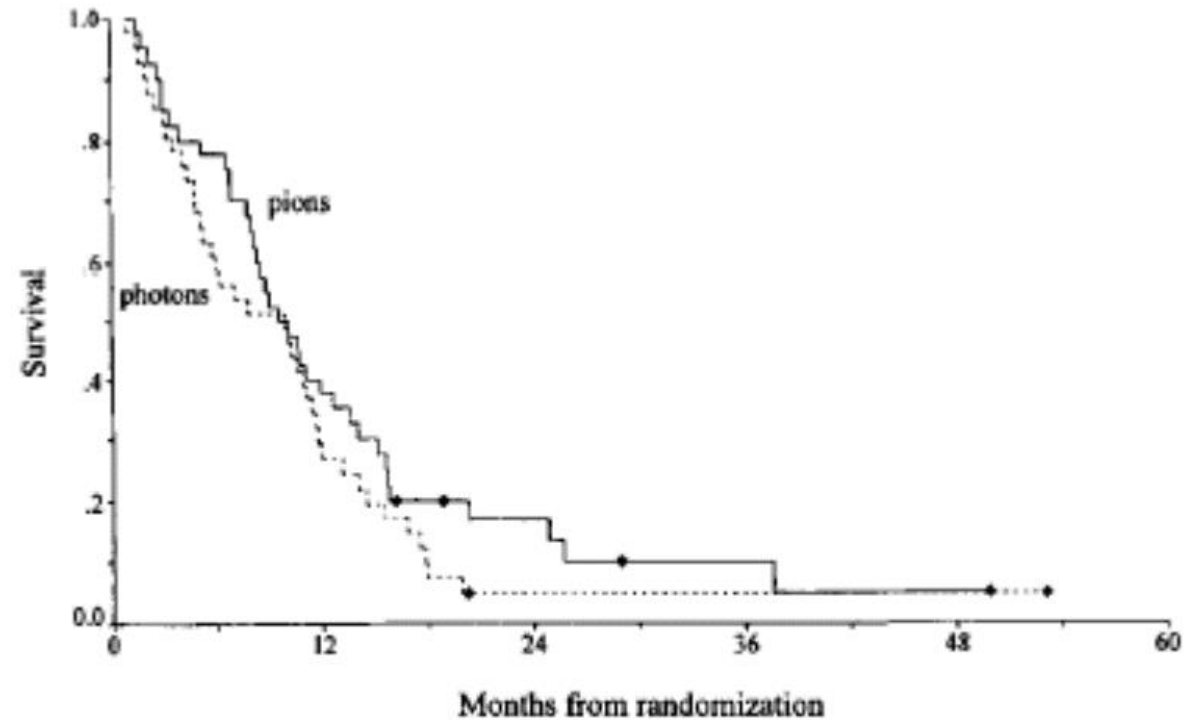


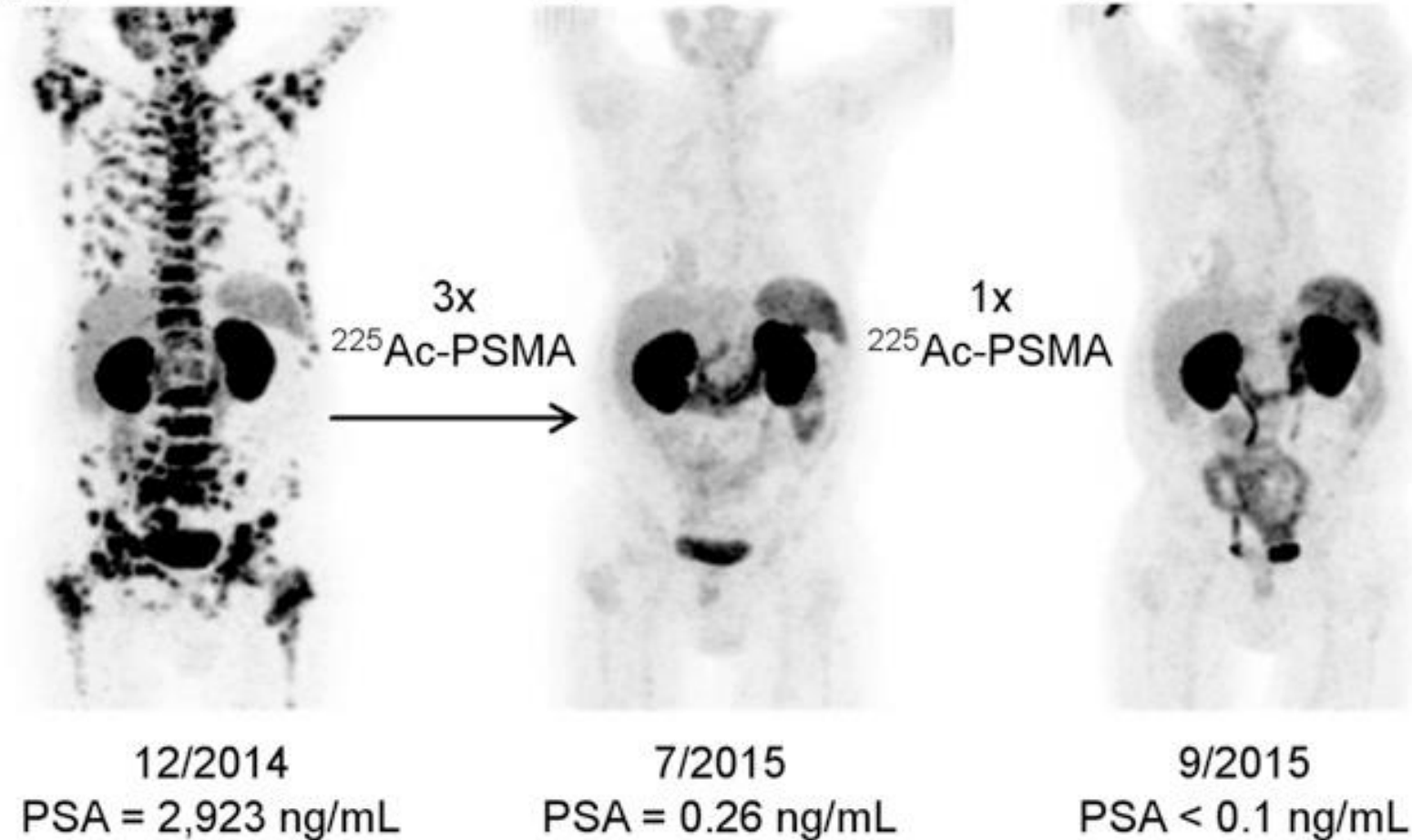
Fig. 2. Overall survival for both treatment groups. Median survivals are: photons, 10 months; pions, 10 months. Log rank: $p = 0.22$.

Internal: Alpha Therapy



12/2014
PSA = 2,923 ng/mL

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)

Current ^{225}Ac Production

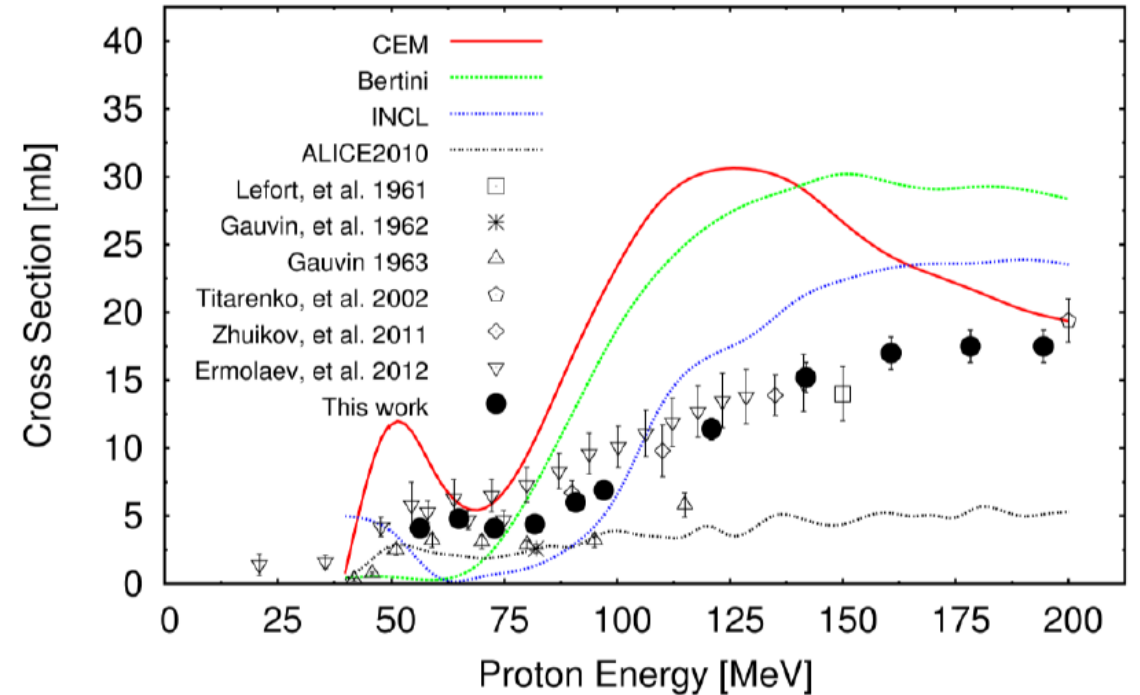
Primary ^{225}Ac sources:

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

Global production is $\sim 1\text{-}2$ 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

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



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

LANL

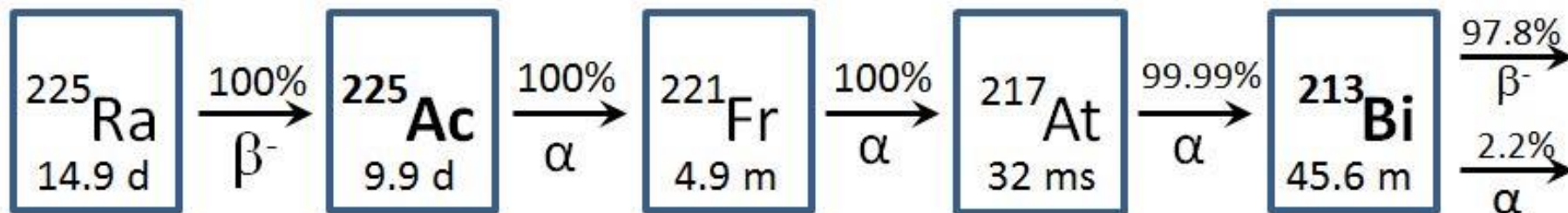
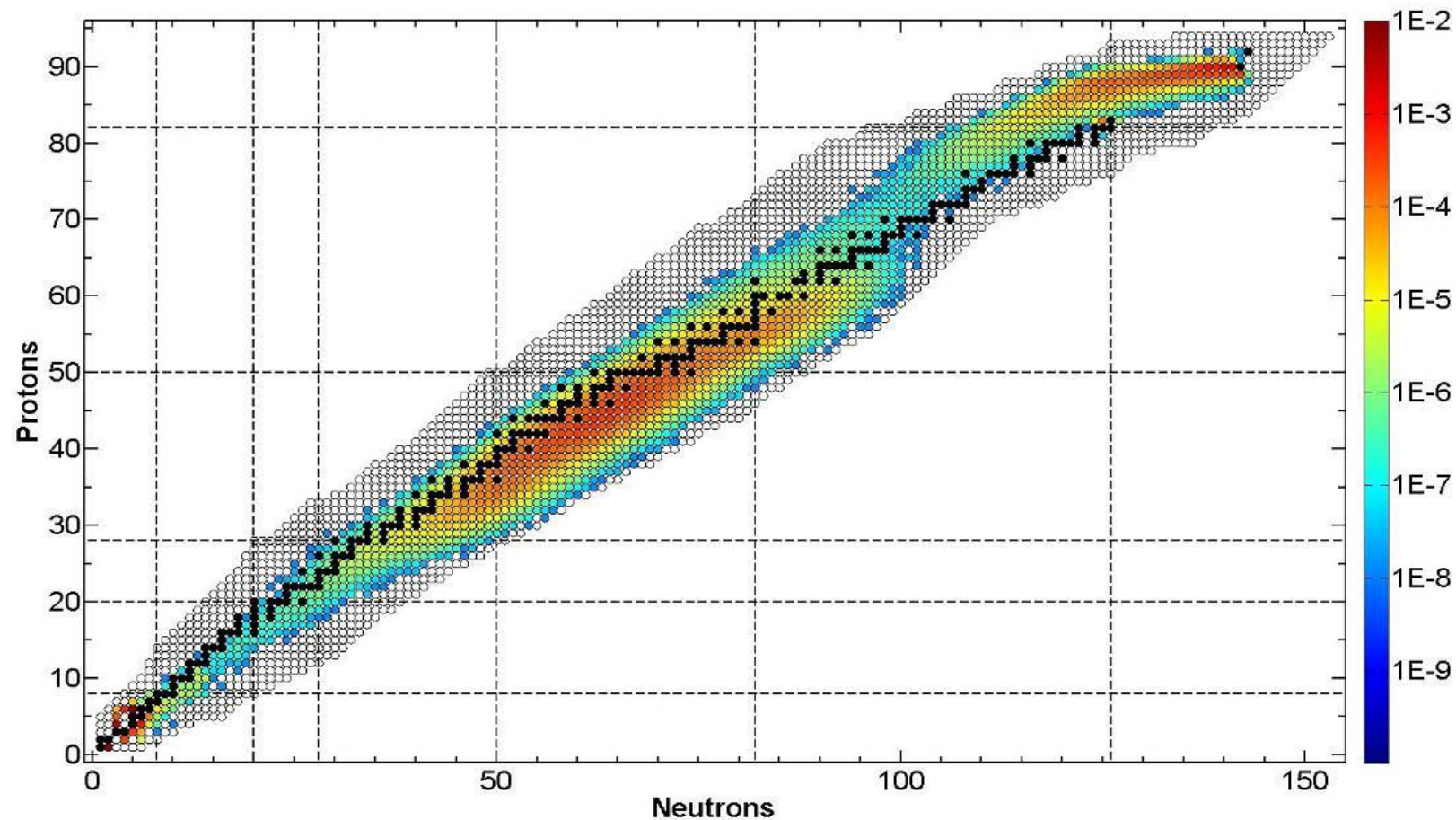
50 - 200, 800 MeV

INR RAS

40 - 90 MeV

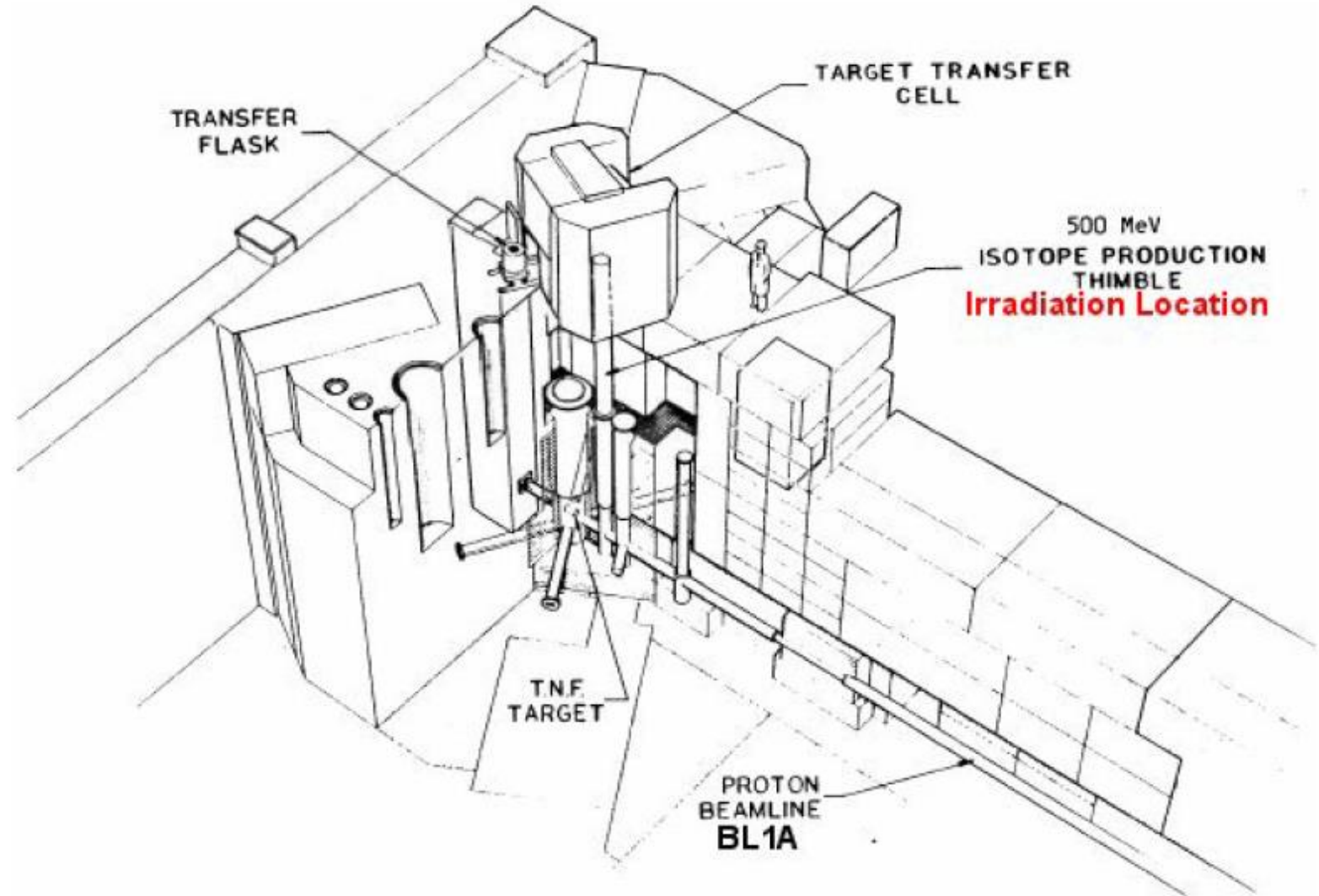
Spallation Reaction on ^{232}Th with 500 MeV Protons

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



α emitters

- 500 MeV – IPF (BL1A)
Intermediate activity (MBq),
spallation
- Routine, independent production



500 MeV Isotope Production Facility

Acknowledgements



Thank you
Merci

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