



Sven Van den Berghe, CEO

A Better Fight for Life

A large-scale production facility for ^{225}Ac in Belgium

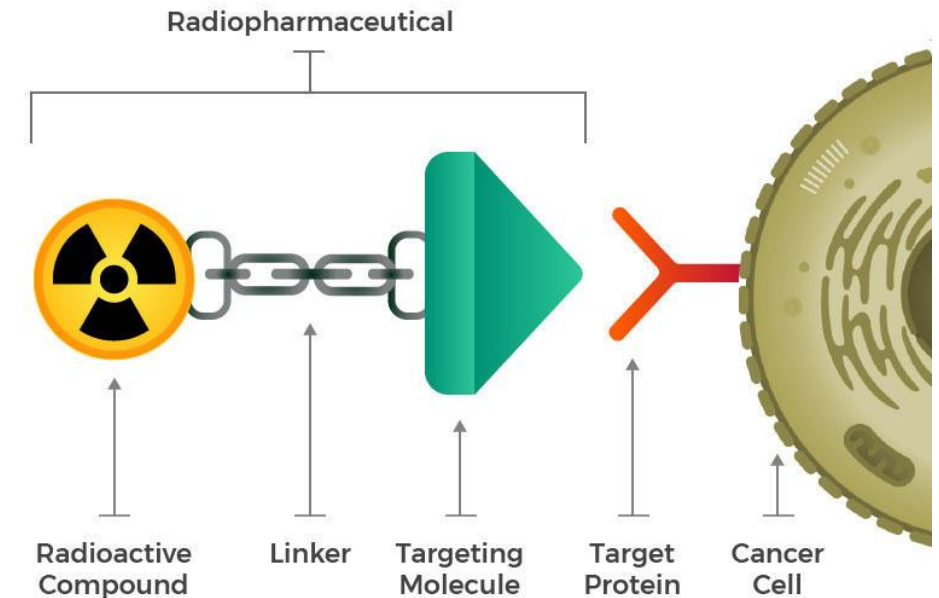
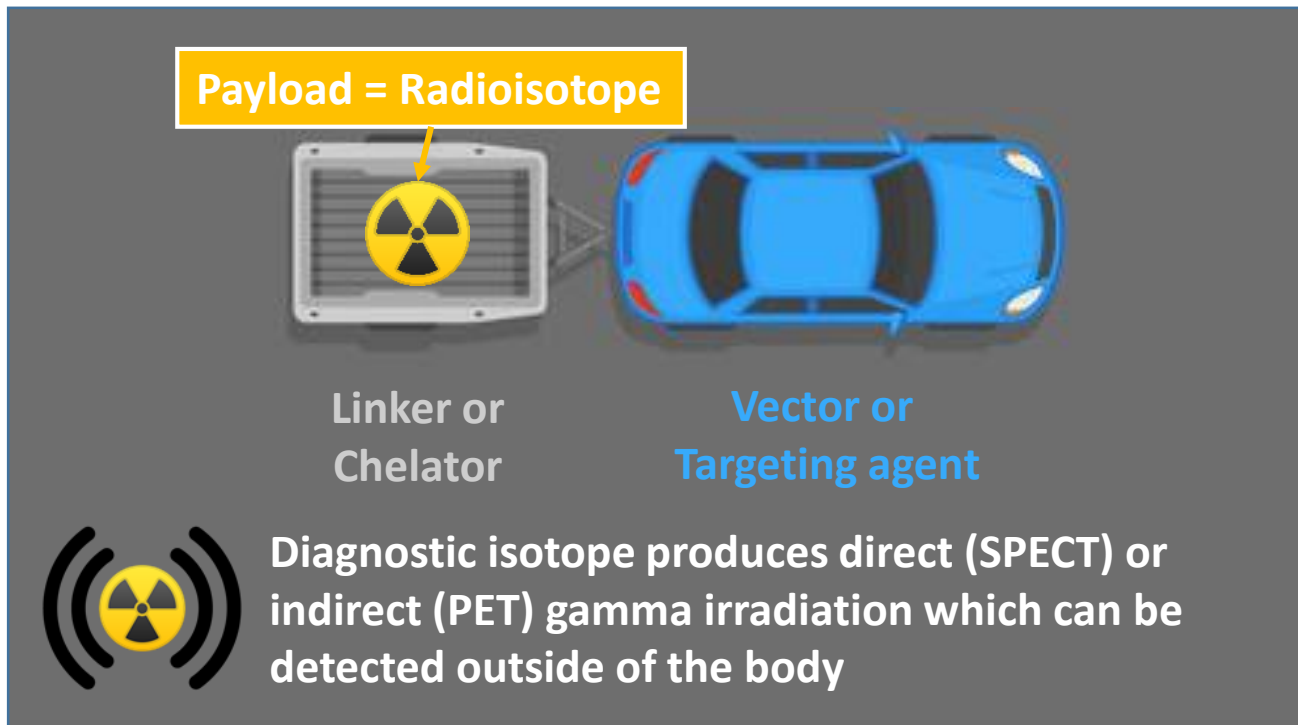
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Nuclear Medicine – the start

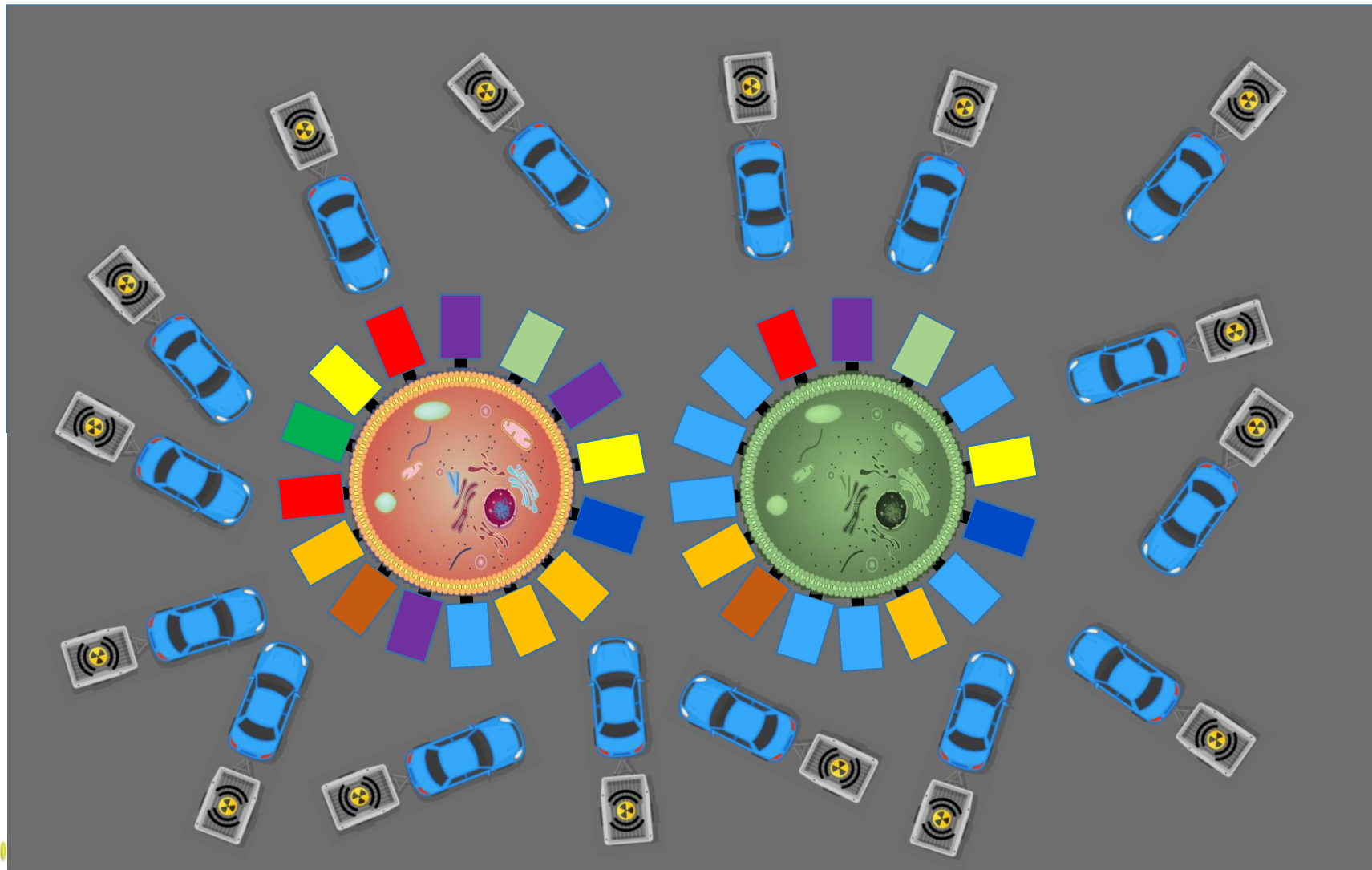
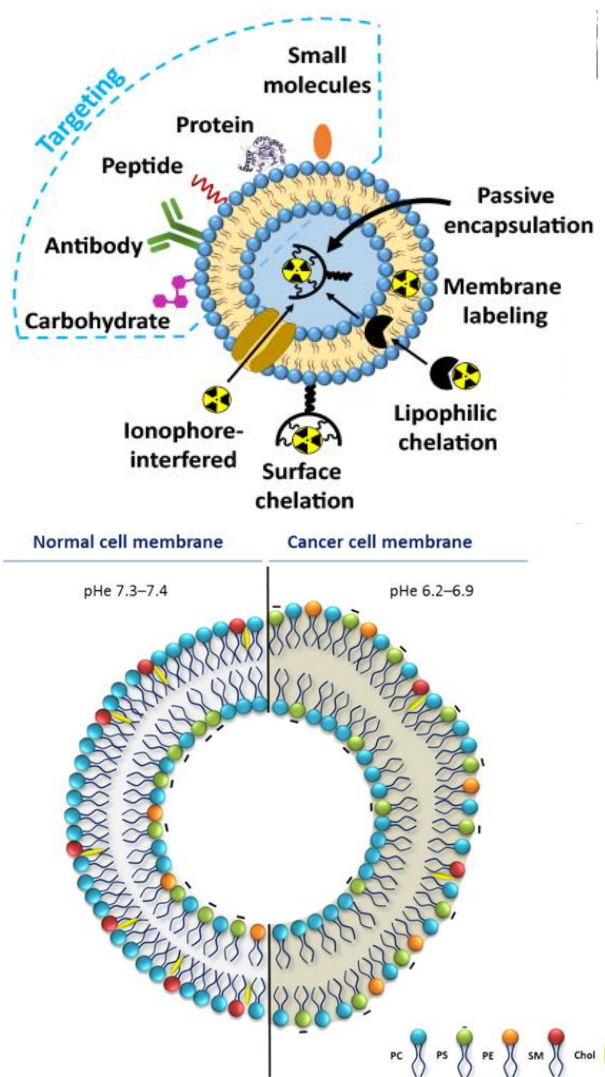
- Use of external radiation (or implantation of radioactive sources) is not considered nuclear medicine, but radiology and radiotherapy
- Nuclear medicine starts when mankind learns to make artificial radioactive elements by irradiating non-radioactive materials in 1934
 - Joliot-Curie ^{27}Al (α, n) ^{30}P ($t_{1/2}=2,5$ min) $\rightarrow$ Lawrence cyclotron
 - 1935 Nobel Prize
- Georg Charles de Hevesy uses ^{32}P as a tracer element in 1934 to follow biochemical processes in animal and human bodies
 - Later on ^{45}Ca , ^{42}K , ^{24}Na , ^{38}Cl , ...
 - 1943 Nobel Prize
- Saul Hertz starts using radioactive iodine in 1936 as the first targeted radiotherapy (TRT) $\rightarrow$ iodine exclusively processed by thyroid
 - First human treatment in 1941 with 2,1mCi ^{131}I , then 29 patients treated with publication of results in 1946

Nuclear Medicine – Diagnostics

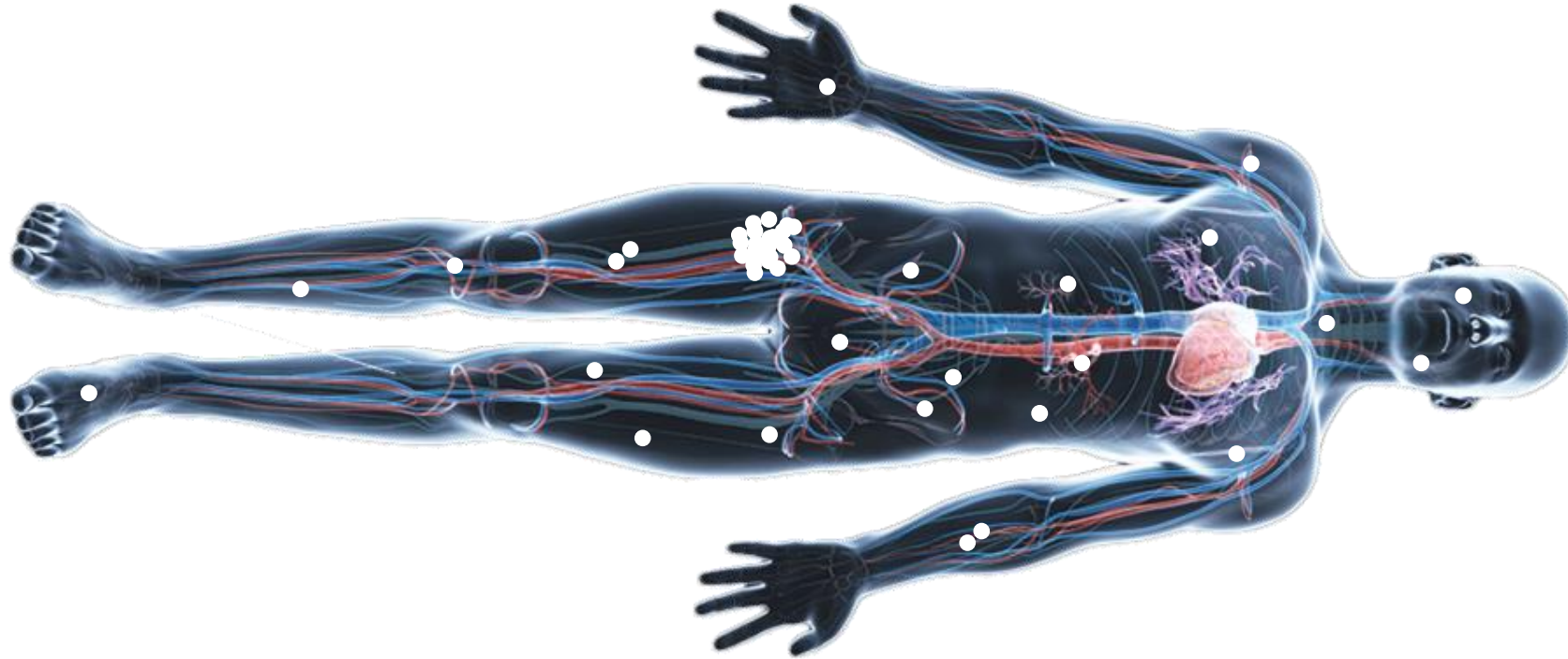
- Imaging tumors : how to get the radioactive product to concentrate at the tumor location ?
 - Tracers : replacing stable elements in bio-active molecules by radioactive ones
 - Vectorisation : designing vehicles to bring radioactive atoms to tumor cells



Nuclear medicine - Diagnostics

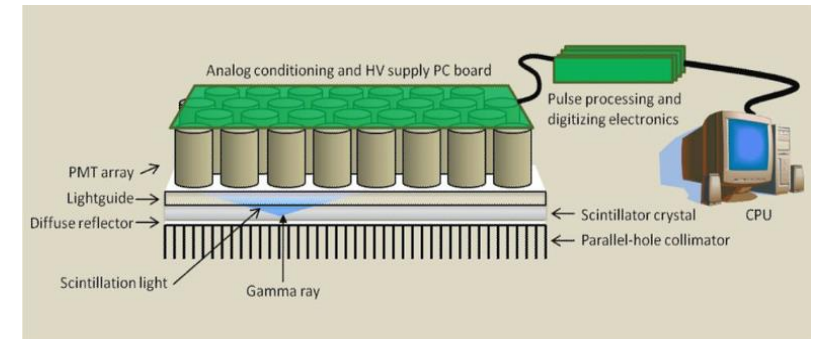
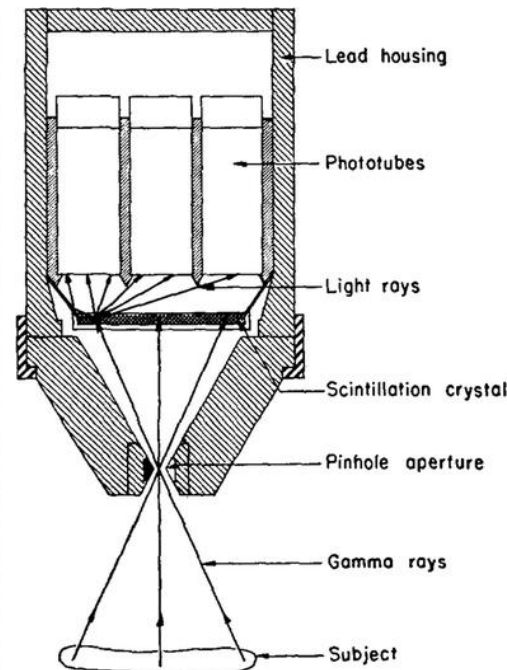
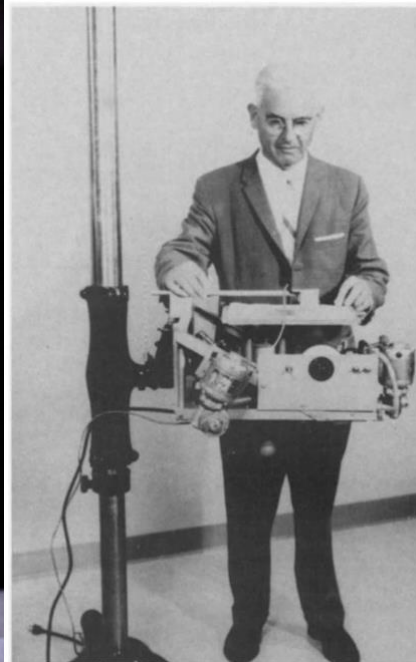
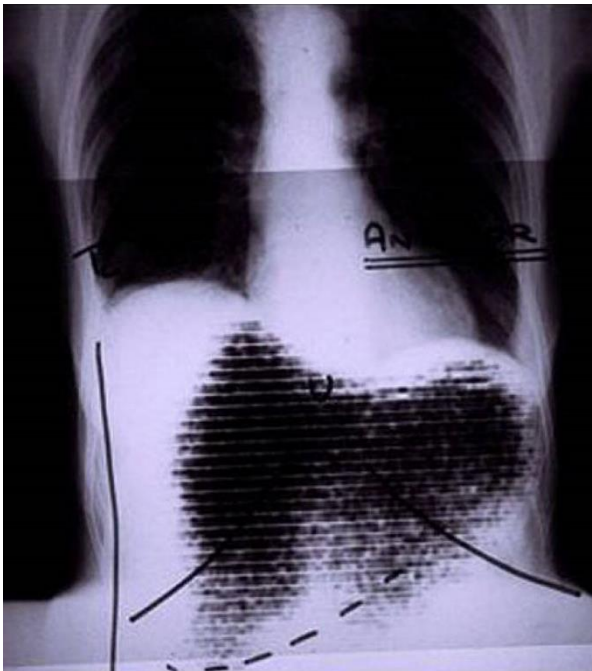


Nuclear technology in medicine



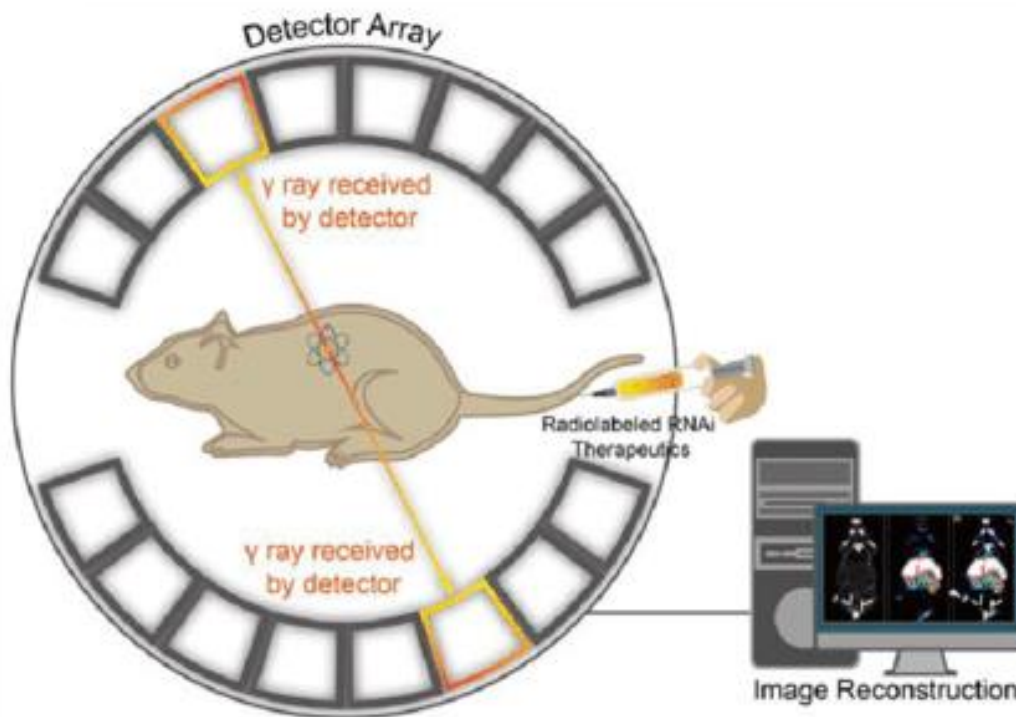
Nuclear Medicine – Diagnostics

- How to determine and image the distribution of radioactivity in the (human) body ?
 - Rectilinear scanner (1950)
 - Anger camera (pinhole, similar to camera obscura) (1952)
 - Gamma camera with photomultipliers and scintillator NaI crystal(s) (1956)

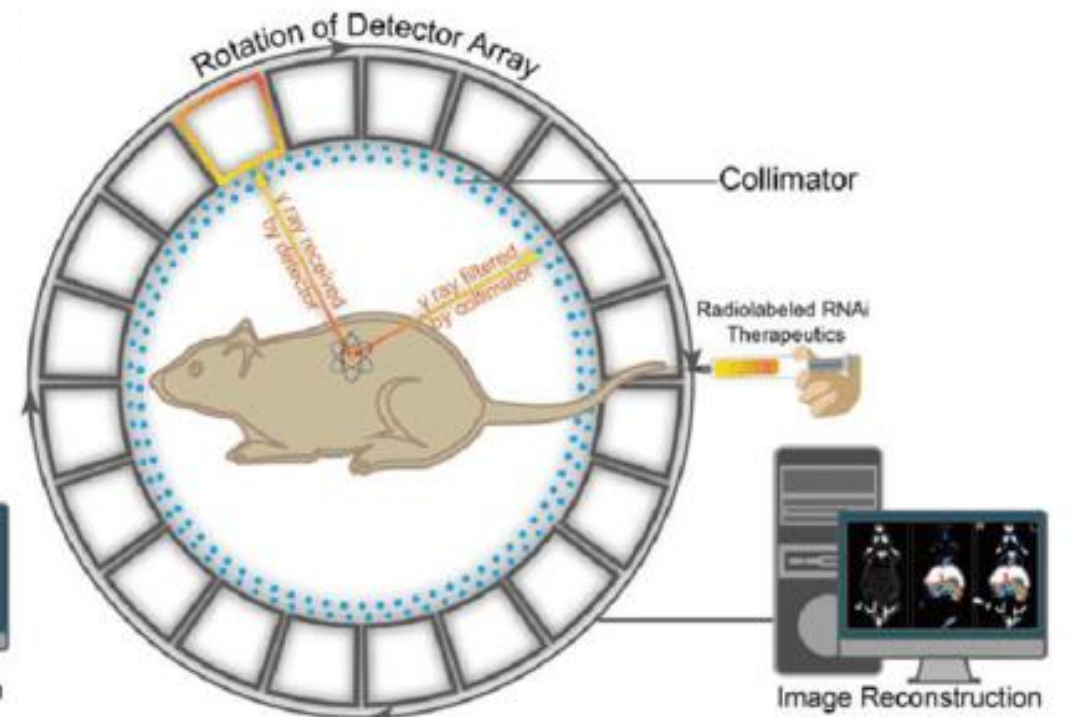


Nuclear Medicine – Diagnostics

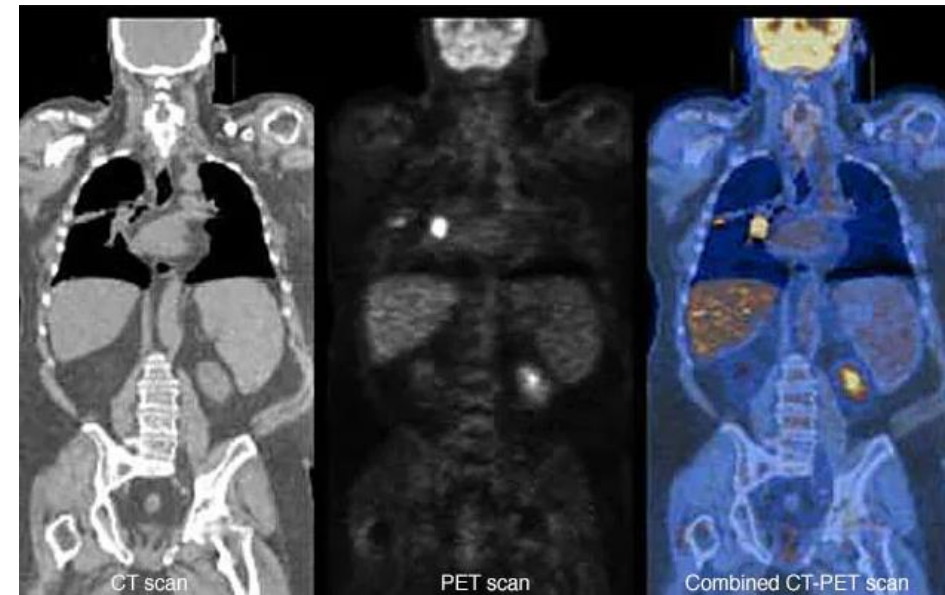
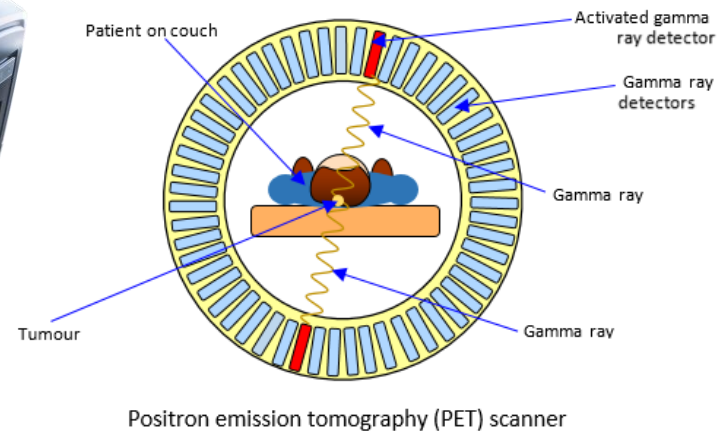
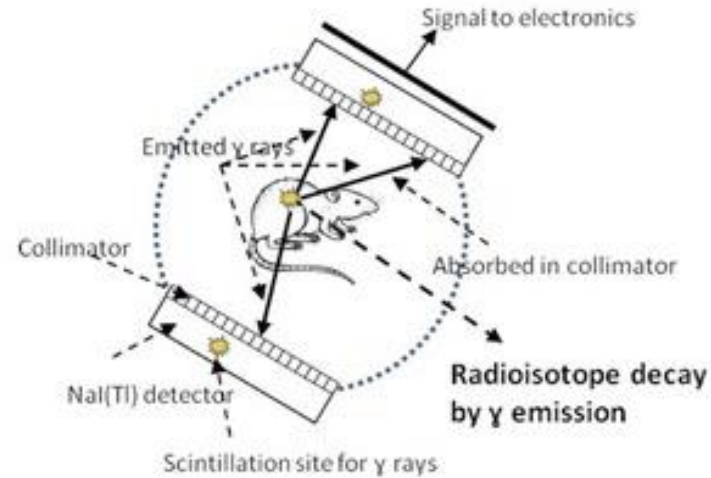
Positron Emission Tomography (PET)



Single Photon Emission Computed Tomography (SPECT)



Nuclear Medicine – Diagnostics



Nuclear Medicine – Diagnostics

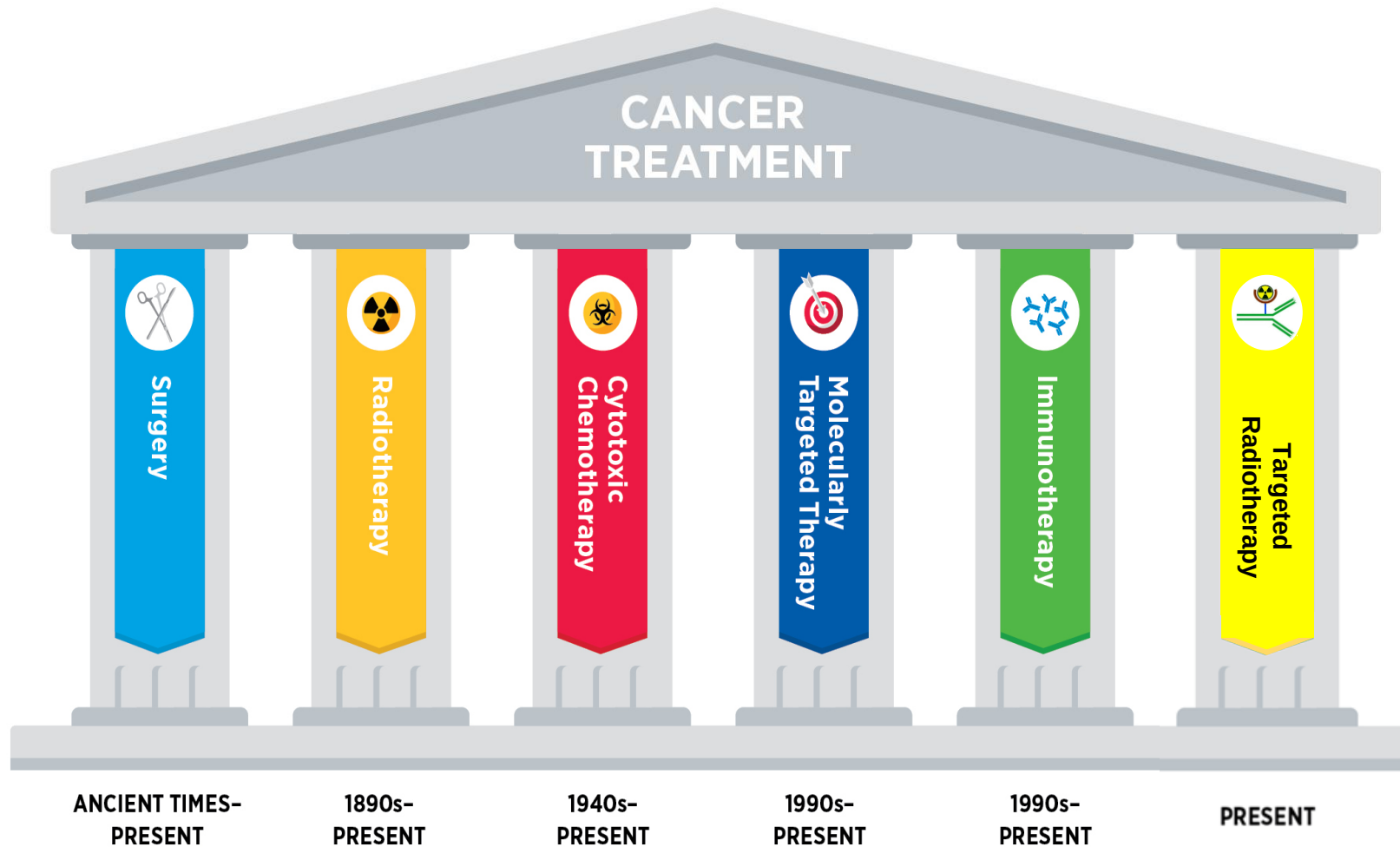
- Which isotopes to use and how to produce them ?
- SPECT isotopes → preferably pure gamma emitters (metastable)
 - ^{99m}Tc → produced from generator in hospital as decay product of ^{99}Mo
 - Swiss knife of SPECT, dozens of cold kits available
 - ^{99}Mo production as fission product of ^{235}U extracted from targets (IRE, CURIUM)
 - Main reactors BR2, HFR, SAFARI, OPAL, LVR-15 and MARIA
 - New production methods by $^{98}\text{Mo}(n,g)^{99}\text{Mo}$ (BWXT) and $^{100}\text{Mo}(g,n)^{99}\text{Mo}$ (NorthStar)
 - ^{111}In and ^{123}I sometimes used (electron capture decay=non radiative)
- PET isotopes → proton rich isotopes + short $t_{1/2}$ = typically cyclotron

Isotope	^{11}C	^{13}N	^{15}O	^{18}F	^{68}Ga	^{64}Cu	^{52}Mn	^{55}Co	^{89}Zr	^{82}Rb
Half-life	20 min	10 min	2 min	110 min	67.8 min	12.7 h	5.6 d	17.5 h	78.4 h	1.3 min

- ^{18}F as radiotracer in FDG (Fluorodeoxyglucose) = traces sugar consumption
- ^{68}Ga combined with cold kits (mainly DOTATOC)

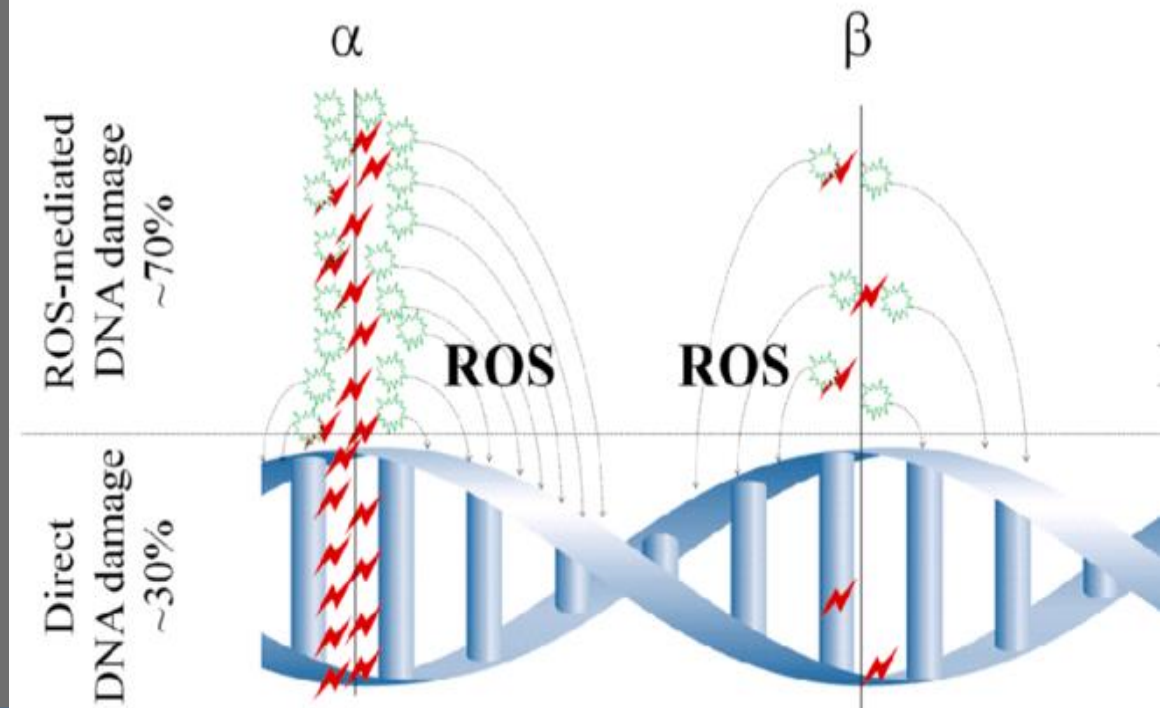
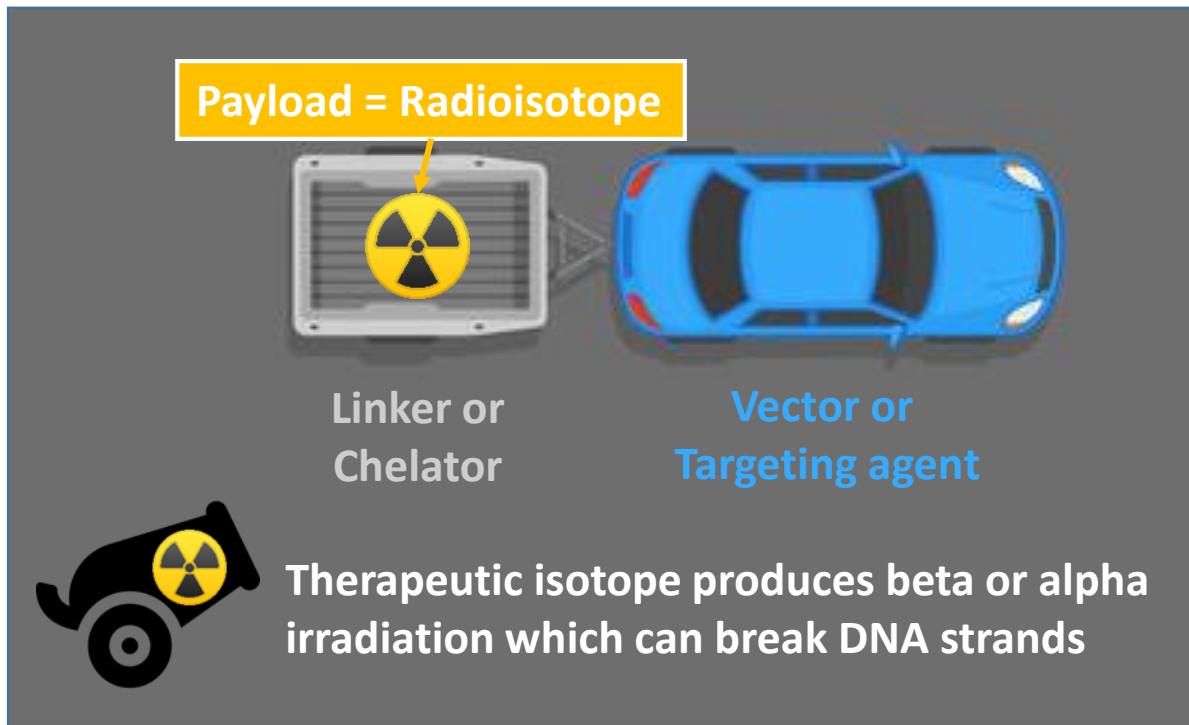
Nuclear Medicine – Therapeutics

OK, so now we know where the tumor cells are, but how to treat it ?



Nuclear Medicine – Therapeutics

- Targeted RadioTherapy (TRT) = local irradiation of the tumor cells
 - Bring the radioisotope to the cancer cell and attach it there
 - When it emits its radiation, it damages the cancer cell (DNA) causing cell death
 - Individual cancer cells and metastasis also treated, not just solid tumors



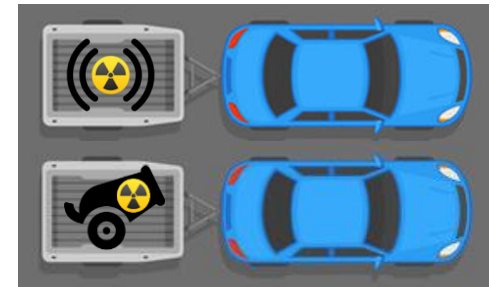
Nuclear Medicine – Therapeutics

- Which isotopes to use and how to produce them ?
- Beta isotopes
 - ^{177}Lu : basis for Lutathera and Pluvicto (Novartis)
 - Reactor production on basis of ^{176}Lu (ca) or ^{176}Yb (nca), also at BR2
 - ^{161}Tb : next generation
 - Reactor production on basis of ^{160}Gd (nca), also at BR2
 - Others : ^{67}Cu , ^{188}Re , ^{90}Y , ^{131}I , ^{153}Sm , ^{166}Ho
- Alpha isotopes
 - ^{223}Ra : decay product of ^{227}Ac for Xofigo (Bayer)
 - SCK CEN and radium connection
 - ^{225}Ac
 - Others : ^{211}At , ^{212}Pb

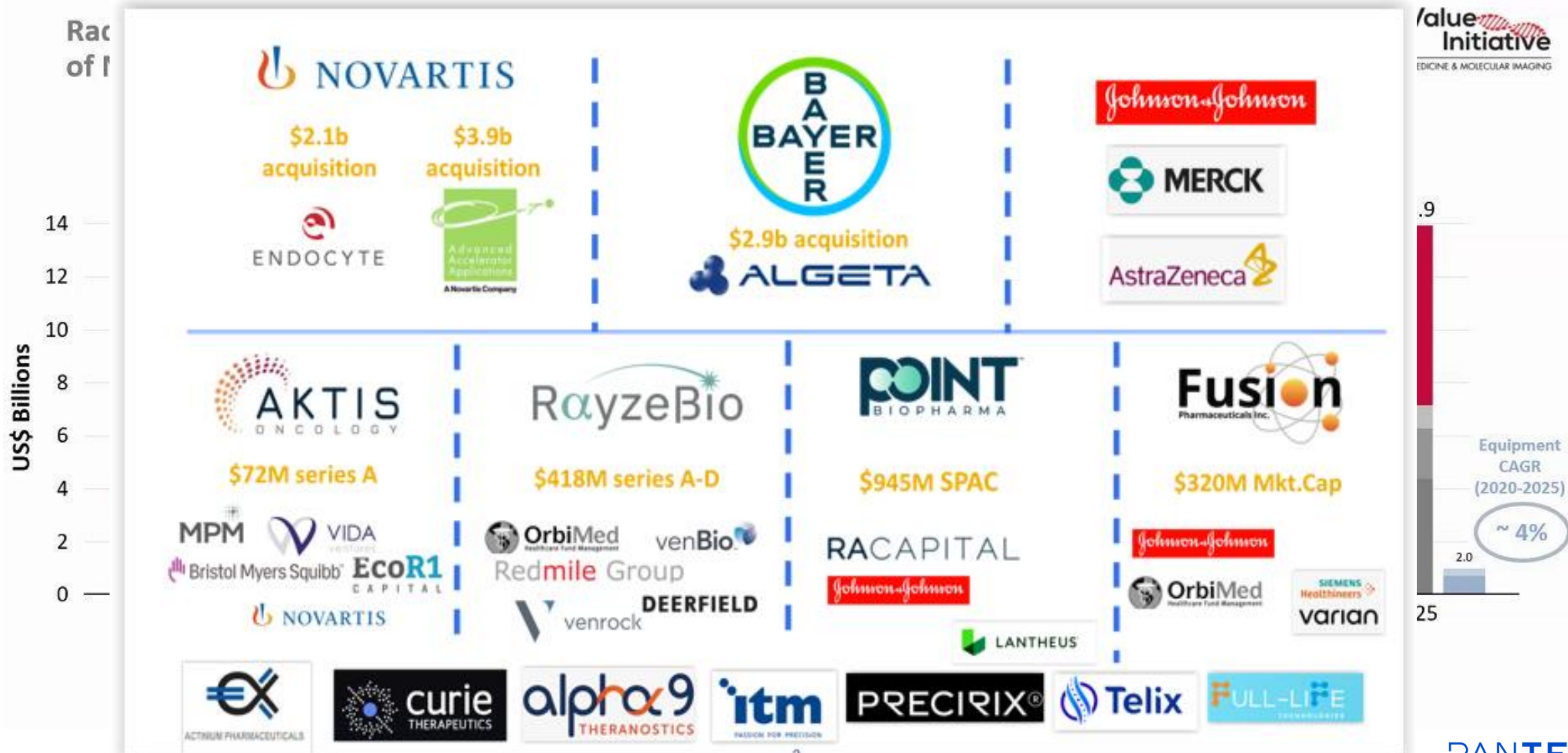


Nuclear Medicine – Theranostics

- Combination of diagNOSTICS and THERApeutics
 - Use the same isotope for therapy and imaging
 - Most beta and alpha emitters also have gamma emission, but not optimized for imaging. Follow-up of treatment possible
 - Use same vector for 2 isotopes of same element (same chemistry)
 - Ideal theranostic pair, but very rare to have 2 isotopes of the same element with optimal properties: one for therapy and one for diagnostics → ^{64}Cu and ^{67}Cu
 - Use same vector for 2 isotopes of different elements
 - Most common situation : optimize for diagnostics and for therapy
 - Different vectors and different isotopes
 - No theranostics, still useful !
- Goal : reconnaissance mission (diagnostic) before attack (therapeutics) = see if therapy will work before injecting high dose
 - Different from chemotherapy or hormone therapy = trial and error



Nuclear Medicine – Theranostics

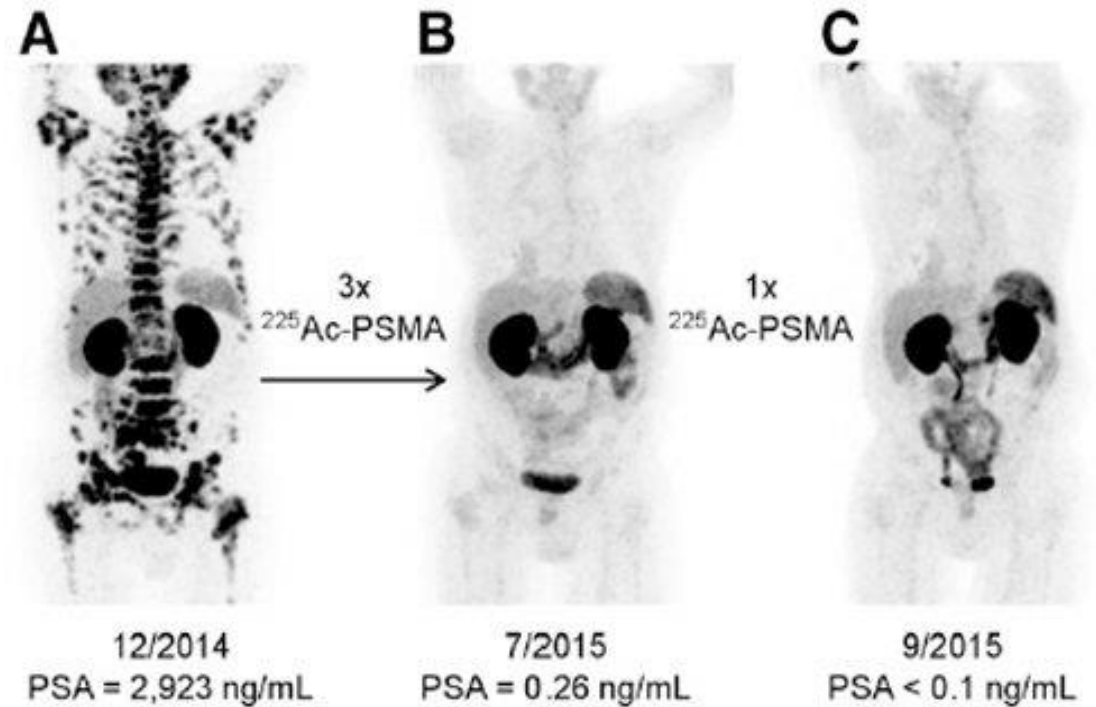


^{225}Ac – General consensus - promising isotope

α -radiation emitter

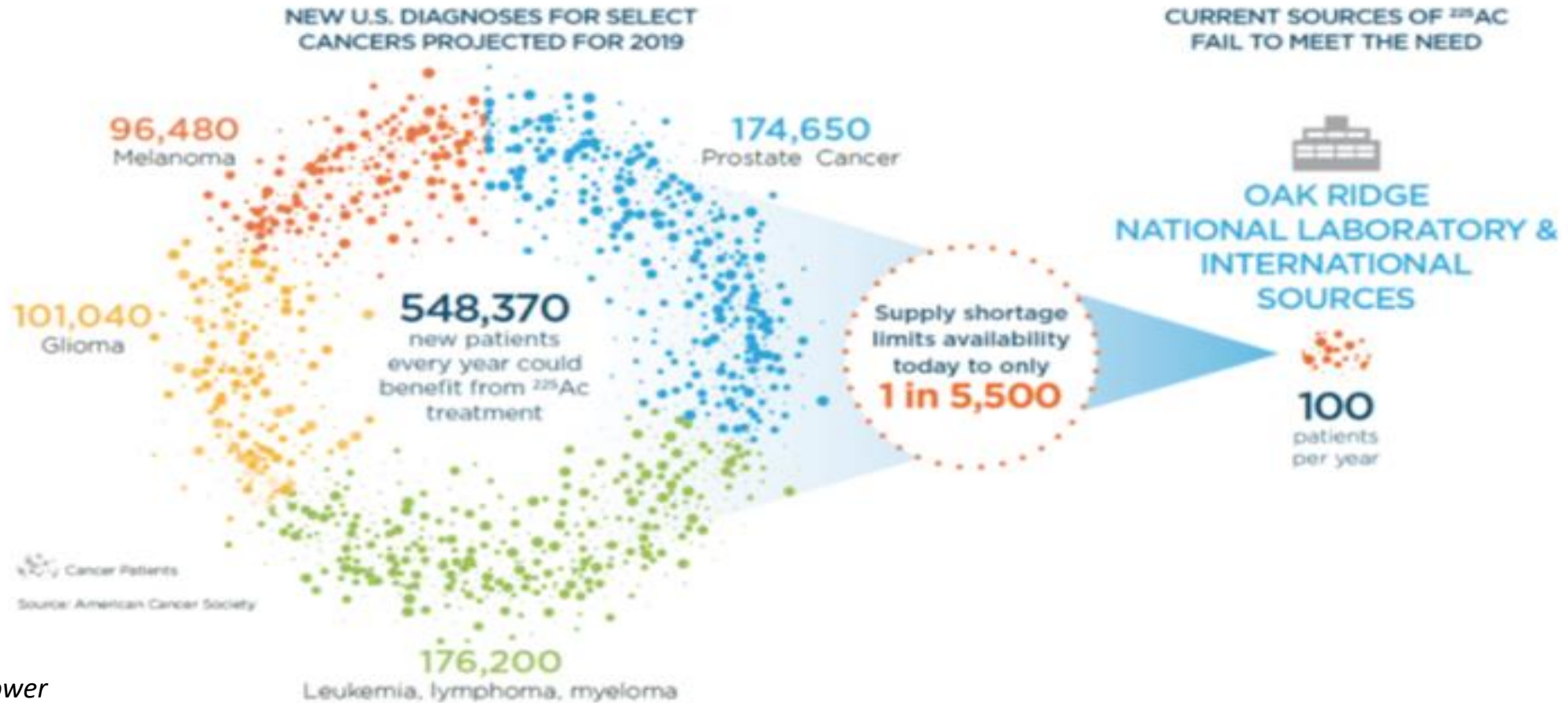
- ✓ deposits very high energy radiations within the cancer cells (DNA double strand break)
- ✓ has an action range of only a few cells (thereby reducing the impact on healthy tissue)
- ✓ has a 10-days half-life (facilitates logistics)

1.000+	Patients treated
100+	Pre-clinical studies
15+	Clinical trials
~10	Different cancers



This picture shows three different images of a single patient with end-stage prostate cancer. The first was taken before treatment with ^{225}Ac , the second after three doses, and the third after an additional dose. The treatment, performed at the University Hospital Heidelberg, was extremely successful. Credit: US Department of Energy.

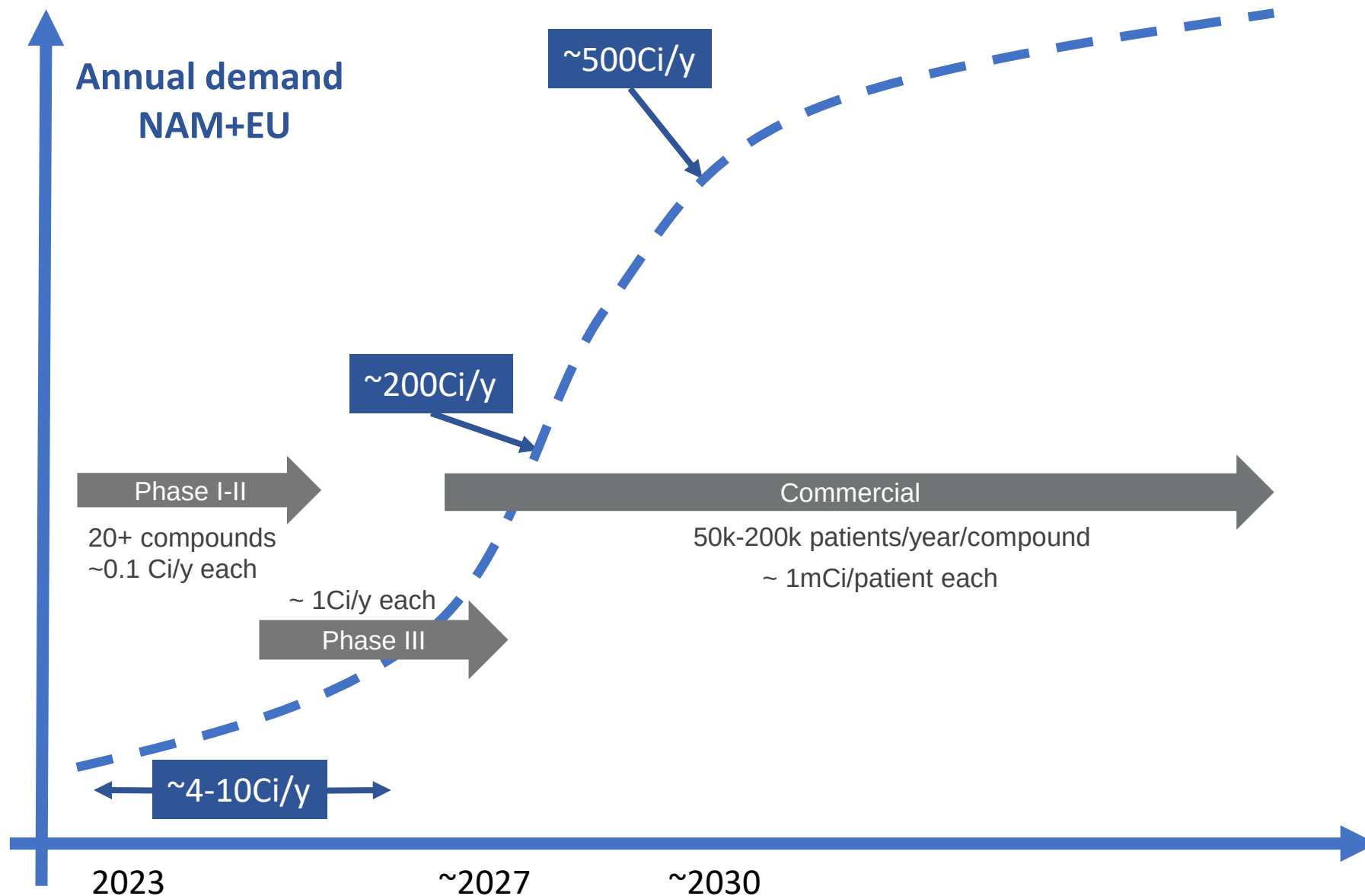
^{225}Ac – From 2Ci to hundreds of Ci by 2030



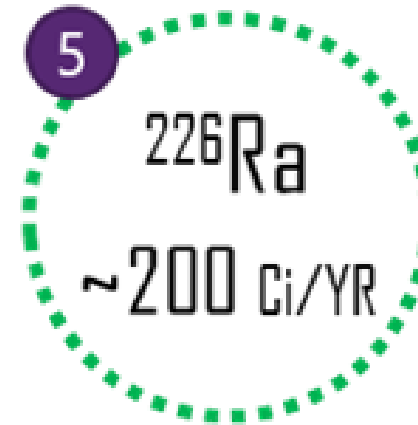
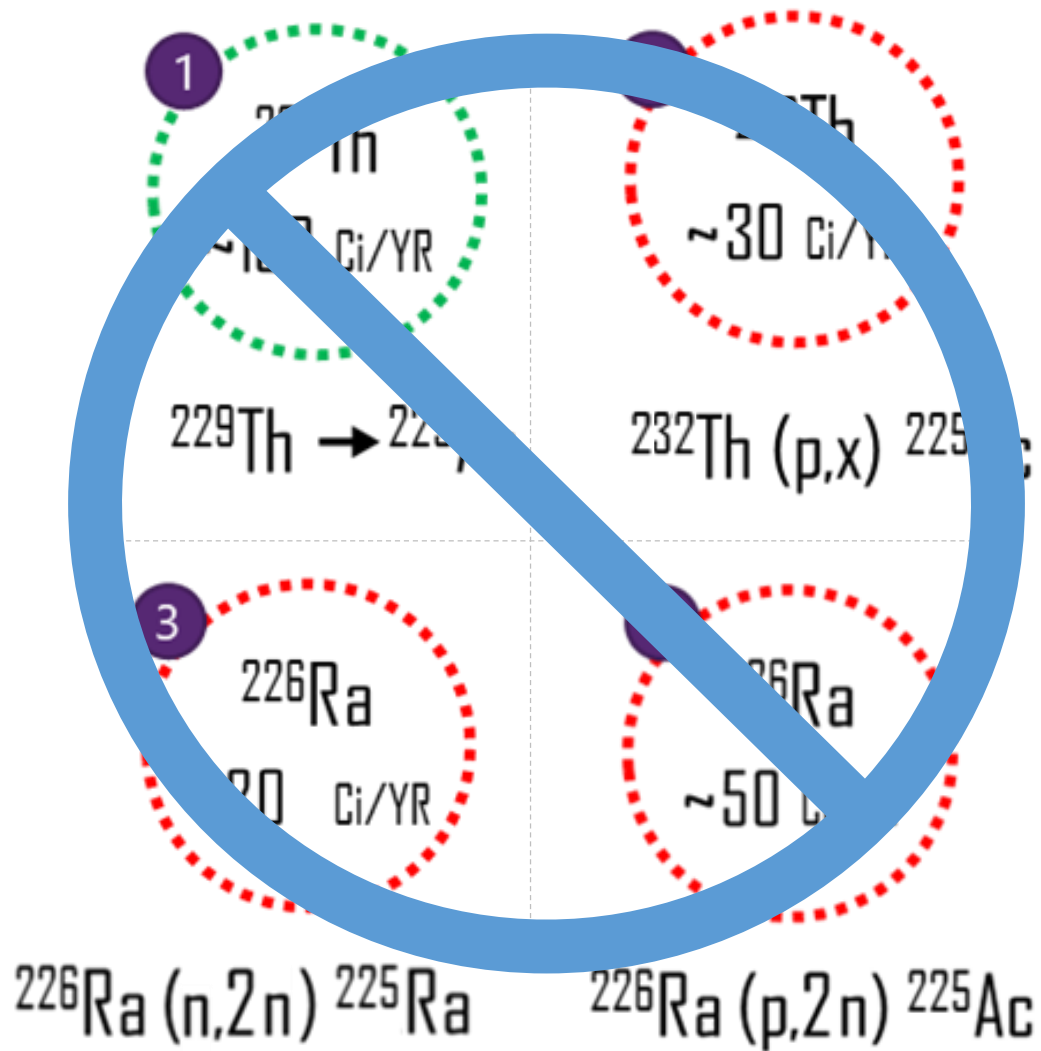
Source: TerraPower

with 1mCi/patient → ~550 Ci/y

^{225}Ac – Expected demand evolution



^{225}Ac – Production methods



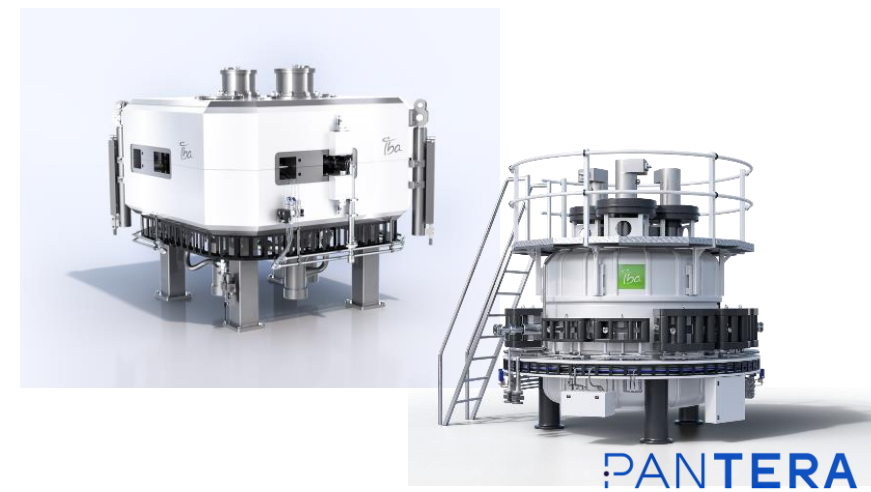
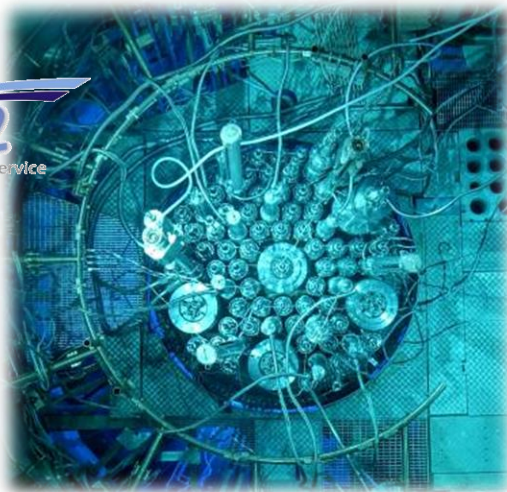
- Gamma route (electron)
- Pure product
- Requires high ^{226}Ra quantities



sck cen

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PAN

PAN – prefix from the Greek παν, meaning "all", "of everything", or "involving all members" of a group, such as in pan-demic or pan-theon, but also pan-cancer = across different/all cancers

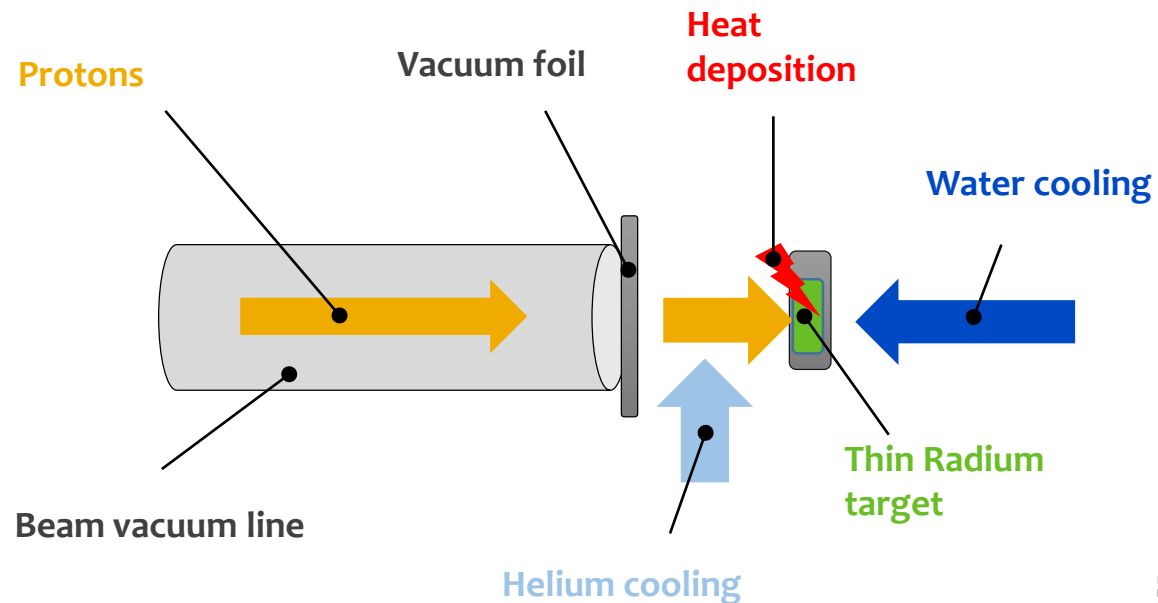
TERA

TERRA – the Latin name for the planet Earth
TERA – a unit prefix denoting multiplication by one trillion, originating from the Greek for “monster”
THERA – as in therapy-therapeutics

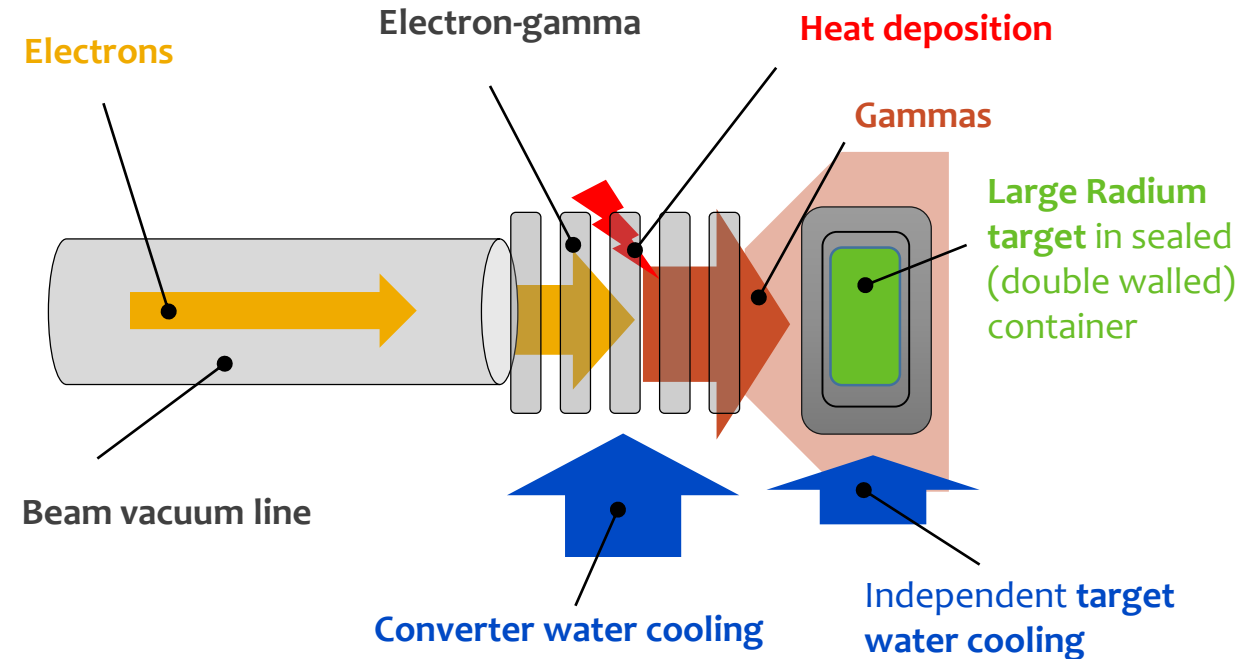
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^{225}Ac – Proton vs. Gamma route: safety first

PROTON ROUTE

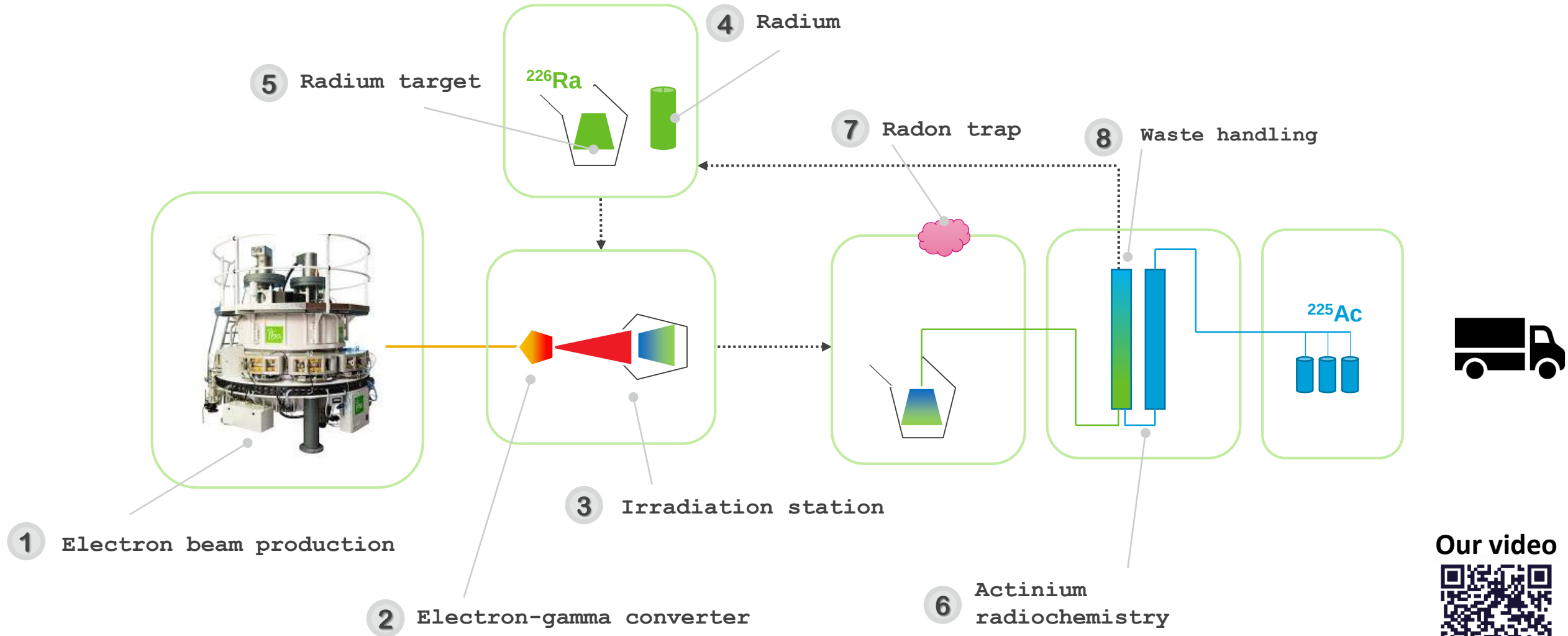


GAMMA ROUTE



–	Radium containment	+
–	Power deposition	+
–	Cooling	+
–	Failure impact	+

PanTera's gamma based ^{225}Ac production



PanTera's unique technology & IP

1

Rhodotron® HE

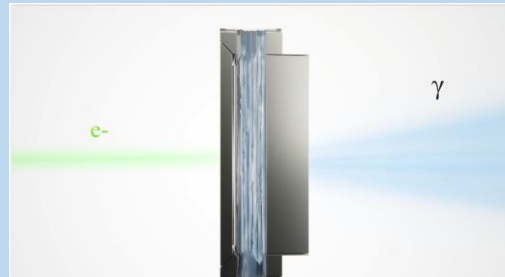
High performance,
high energy,
high reliability
electron accelerator



2

Electron-gamma converter

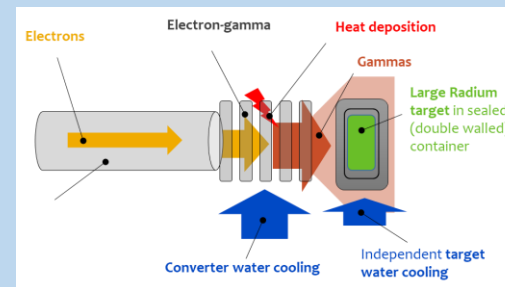
Technology with
well-known
thermohydraulics



3

Irradiation station

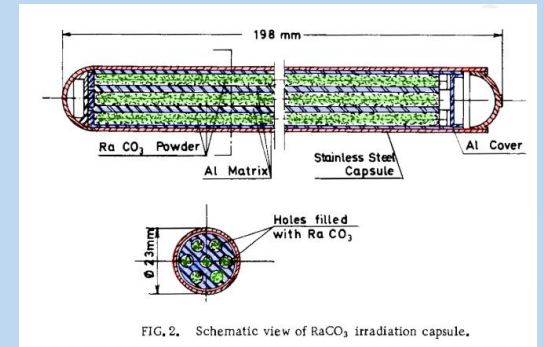
Hybrid technology
allowing low activation &
flexible access
for upgrade/maintenance



4

Radium

>100g pure RaCl_2 crystals
More Ra recoverable from
waste materials

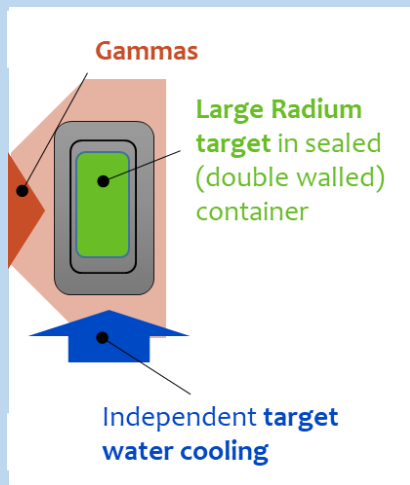


PanTera's unique technology & IP

5

Radium target

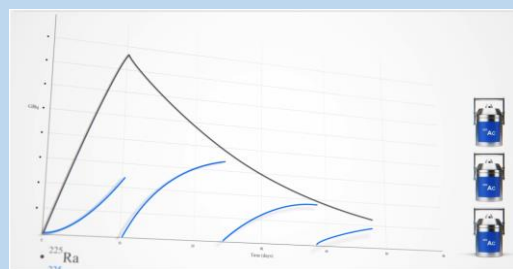
Technology for enhanced radium loading
3-6 Ci per irradiation run
High radium recovery capability (>99.9%)



6

Radiochemical extraction

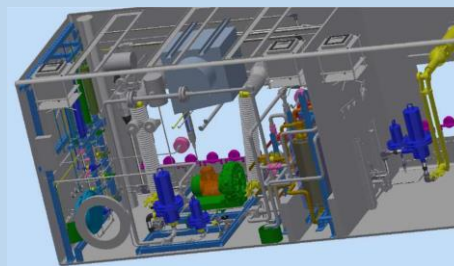
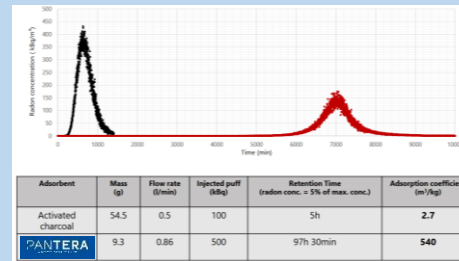
High performance separation chemistry
High (>99,9%) radium recycling efficiency



7

Radon trap

Experimentally demonstrated
High efficiency Radon trap



8

Waste

Radium waste route available
Waste handling by design
Low losses



Radium's history : Marie Skłodowska-Curie

'All medicine that relies on radioactivity – on irradiating people – goes back to Marie Curie.'

Dr. Spencer Weart, former director of the Center for History of Physics



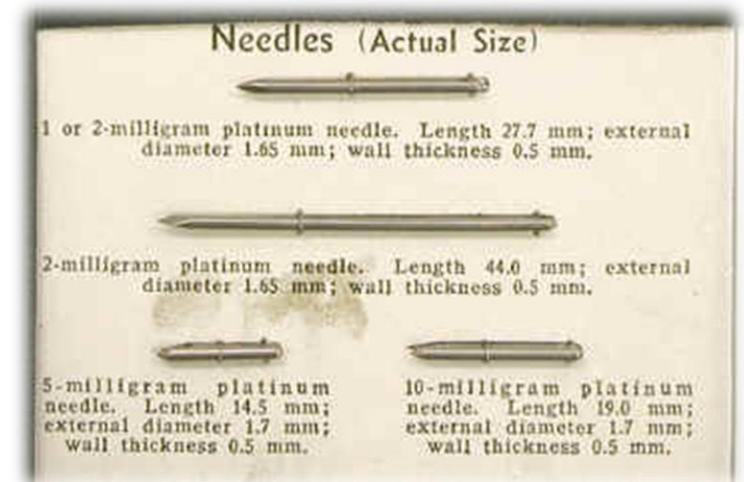
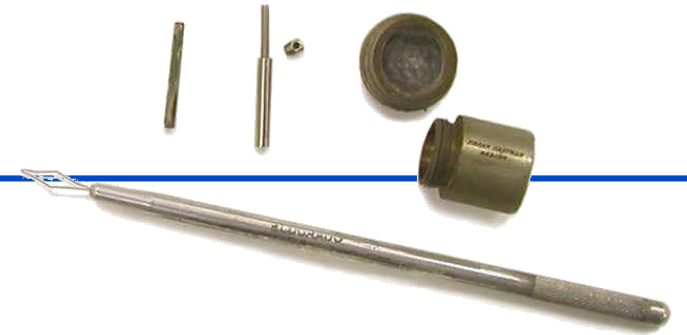
Radium's history : symbol of vitality

- Radioactivity is the ability of some materials to emit energy spontaneously, considered a source of vitalization for boosting health.
- The name “Radium” was commercialized: rare, mysterious and very expensive. Its was used to reflect health, status, quality, vitality and power

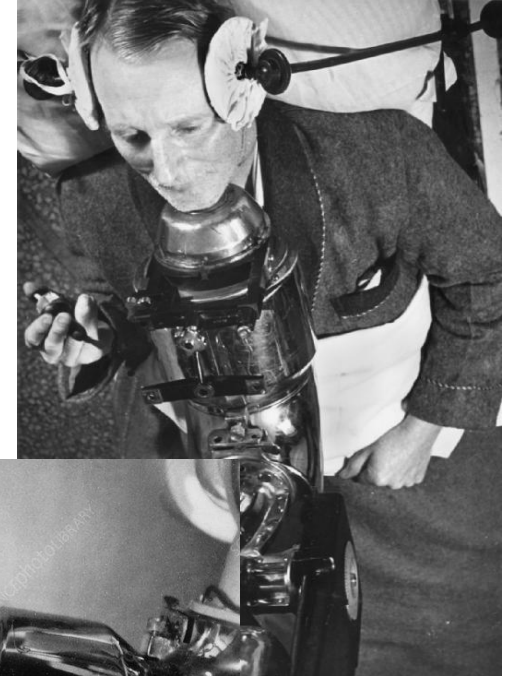
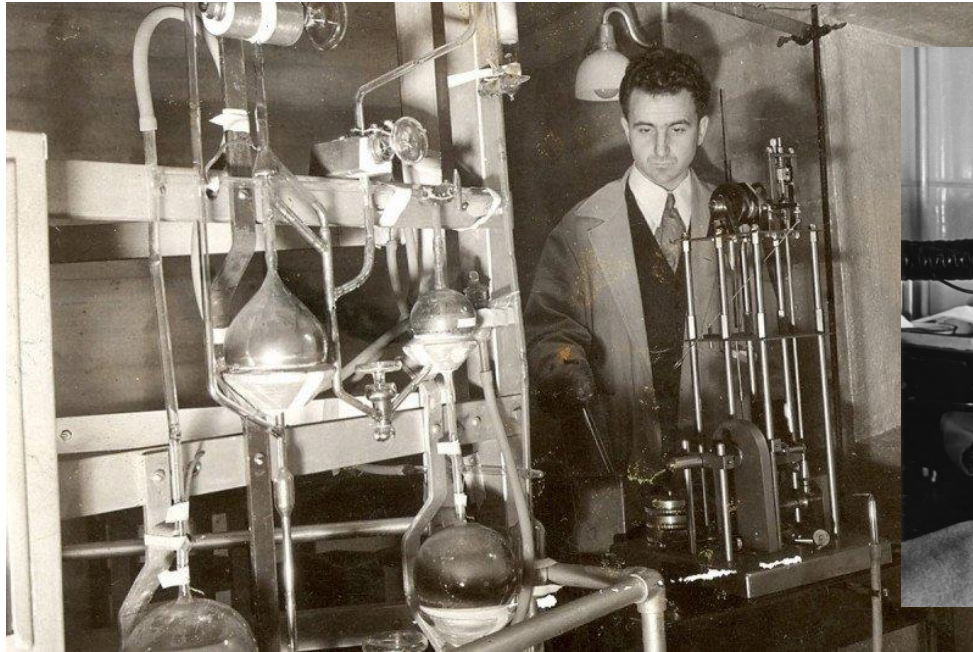


Radium's history : historic use

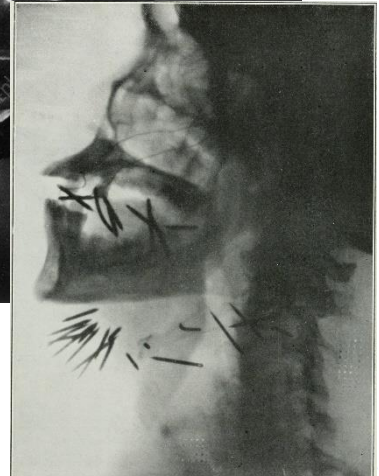
- Radium's 2 main real uses were
 - an ingredient in luminescent paint, used for dials in military and civil applications, such as watches, dials in airplanes, exit signs, etc.
 - A source of radiation in cancer treatment
 - external radiation source (curietherapy) more powerful than X-rays (sometimes even the radium daughter radon-222 was collected as an even more potent source of radiation)
 - internal irradiation source (brachytherapy) in the form of needles introduced in the patient's body, in or near the tumor.



Radium's history : medical use

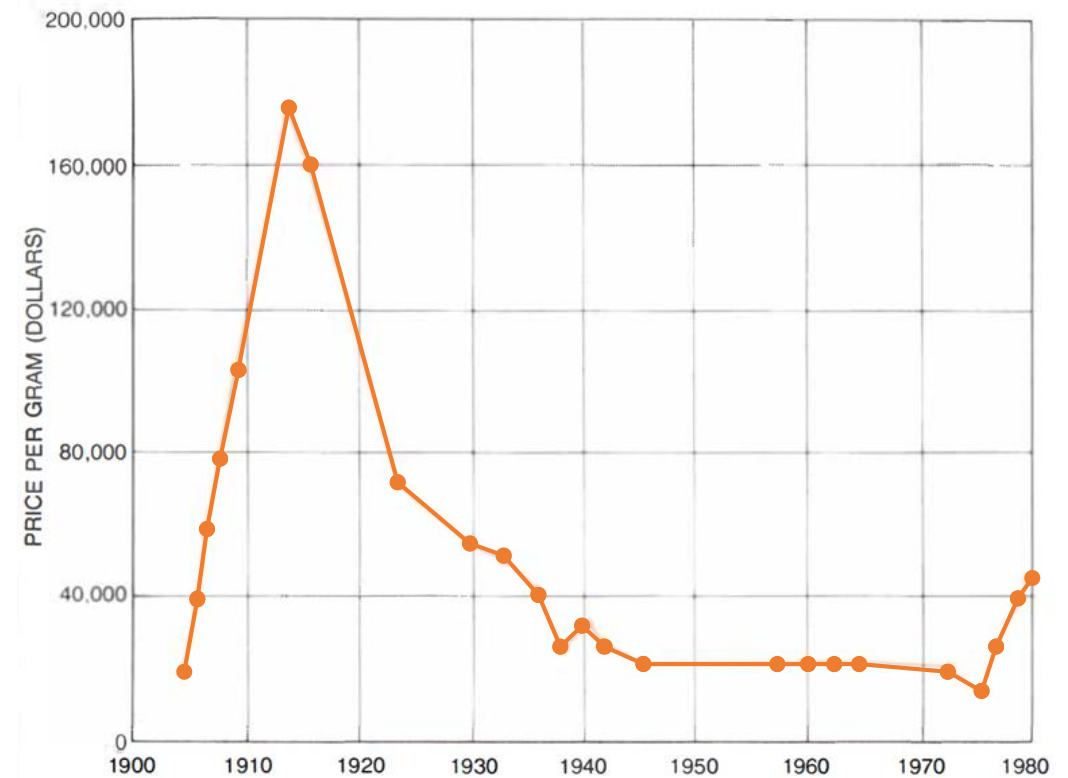
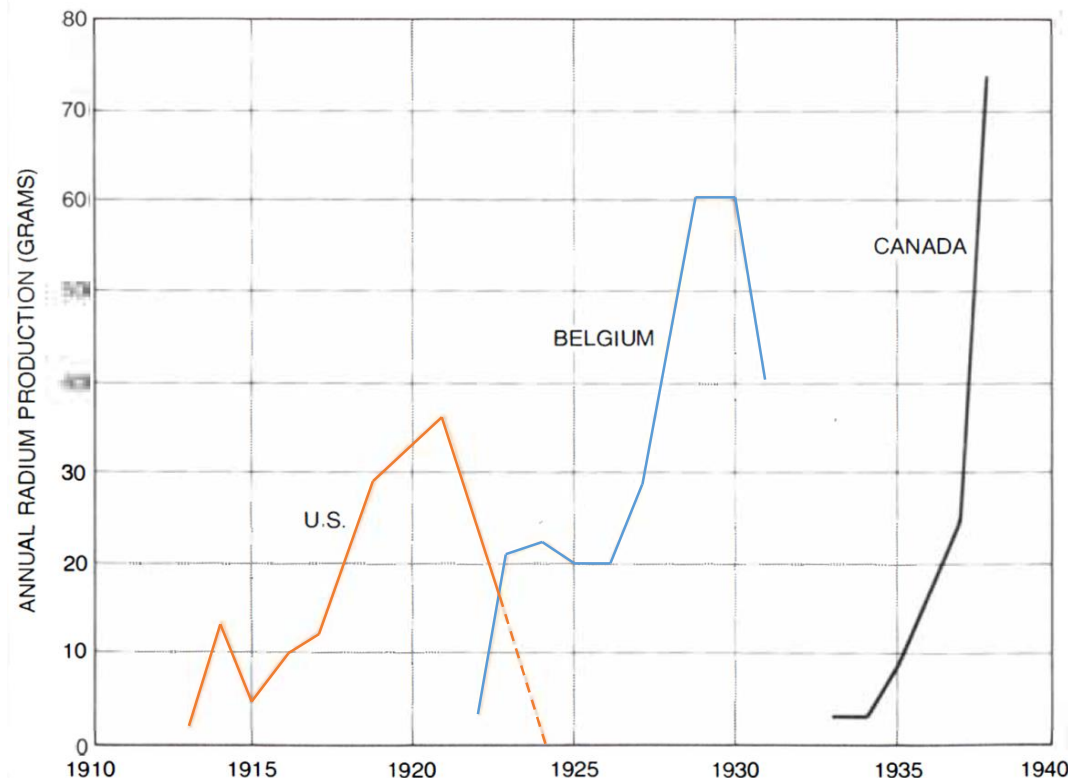


Radon gas capture apparatus
Memorial Sloane Kettering Hospital, ca. 1940
By 1926, 'The Radium Hospital' had 9 grams of Radium, more than anywhere else in the world.

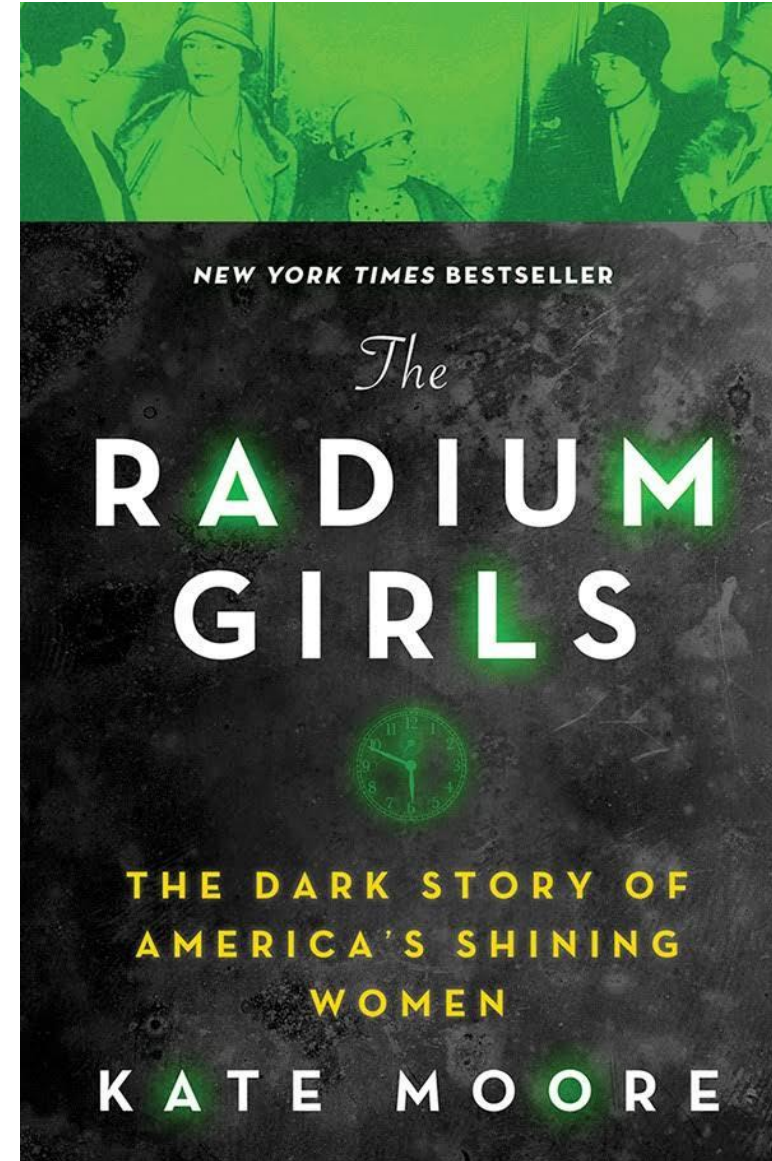


Radium's history : supply

- Radium's availability increased from the early 1920's from the Joachimsthal and Colorado mines to the 1930's from the Union Minière Shinkilobwe mines in Belgian Congo (up to 1960) and later the Canadian Great Bear Lake mines

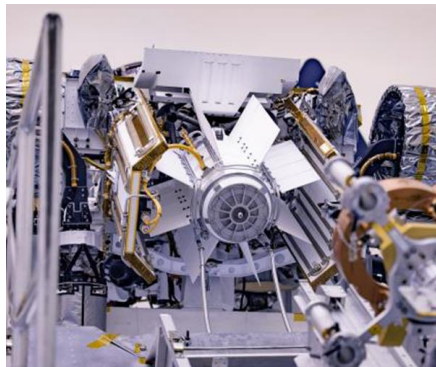
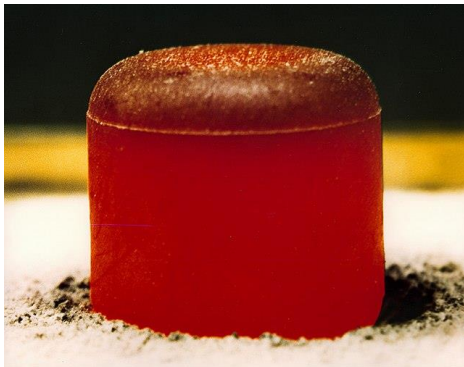


Radium's history : poisoned workers

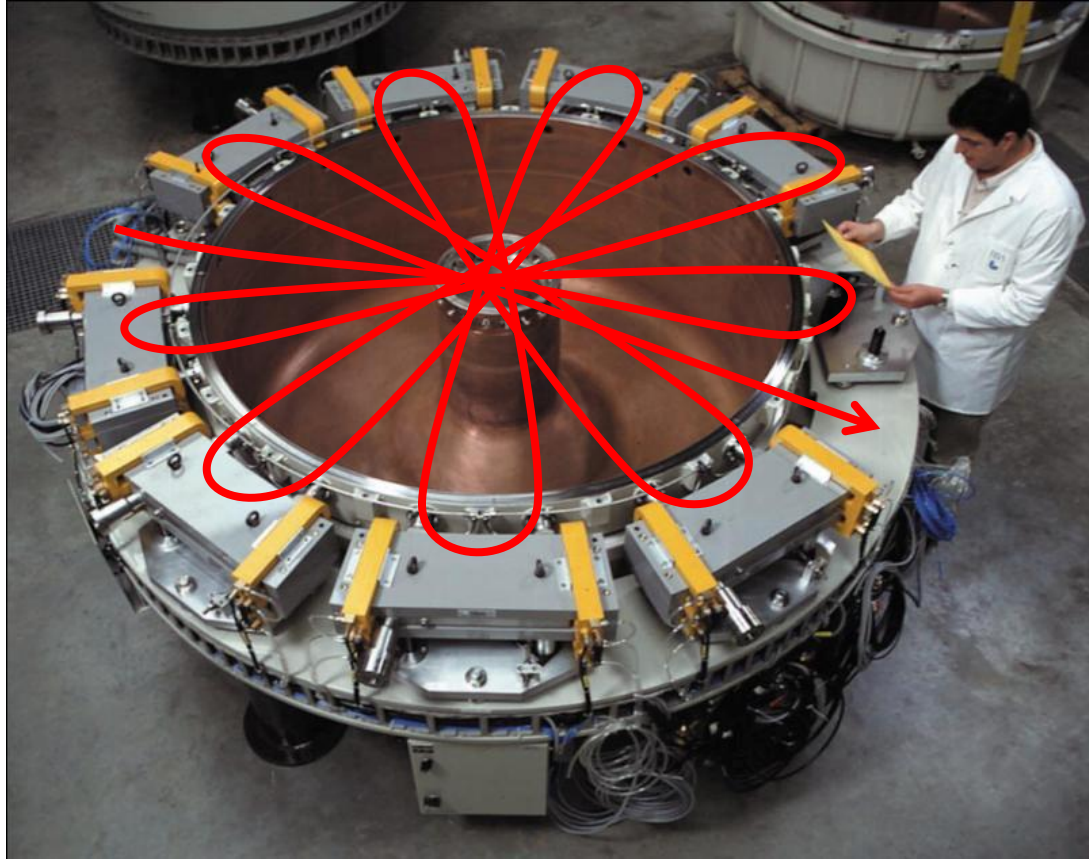


Radium's history : space power

- 1960's: 'The US will put a man on the moon before the end of the decade'
- European Space ambitions → use ^{227}Ac as source of heat for space power
 - European project for production through irradiation of ^{226}Ra
 - ^{226}Ra available in pure form and large quantities in Belgium, as well as BR2 reactor
- The BR2 reactor irradiated important quantities of ^{226}Ra from which ^{227}Ac was separated in a dedicated installation between the late 60's and 1976
 - ^{227}Ac was eventually never used, but provided to Algeta in 2009-2010 as the original source for Alpharadin, later Xofigo...



The Rhodotron: a unique e-beam accelerator



- Compact industrial accelerator:
 - From 2 to 10 MeV, 20 to 700 kW
 - 24/7 operations > 8000 hours
 - Focused beams & low energy spread
- 50 units worldwide: E-Beam & X-Ray sterilization, food, cargo imaging:
 - Versatile beam lines & transport
 - Linear high-power X-ray converters
- From 2018, new RF generators enable high-energy electron production (40 MeV)
 - Opens applications in the field of radionuclide production: ^{99}Mo , ^{67}Cu , ^{47}Sc , ^{225}Ac

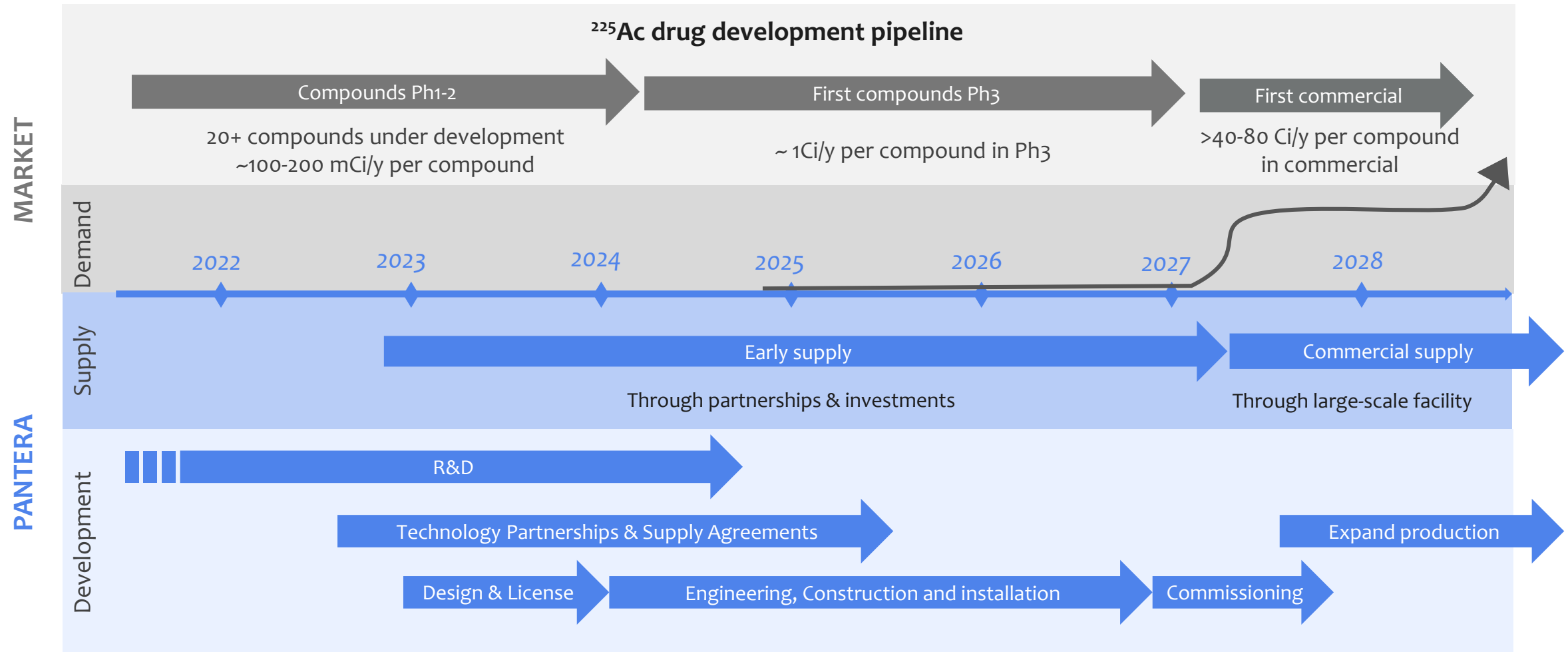
The Rhodotron[®] HE: unmatched e-beam power !

Photonuclear route requires high intensity gamma field to enable large scale production of ²²⁵Ac.



- A unique accelerator at the heart of the facility
- The Rhodotron[®] HE enables
 - Up to 40 MeV electron beam
 - Up to 125 kW of power (3.125mA average current)
 - 24/7 seamless operations
 - Very compact footprint (4mx4mx3m)
 - < 22 tons
 - Low electrical consumption

PanTera's (realistic) timeline



The PanTera Team



Samy Bertrand
CTO



Sven Van Den Berghe
CEO



Christophe Malice
CBO



PANTERA

A BETTER FIGHT FOR LIFE

A Better Fight for Life by providing the **know-how, services, material and infrastructure** needed to **supply the rarest drugs** in the world, **enabling the application of nuclear radiation** as a **dependable source of hope**, as a **precision tool for medicine** which **attacks the disease**, not the patient

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THANK YOU

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