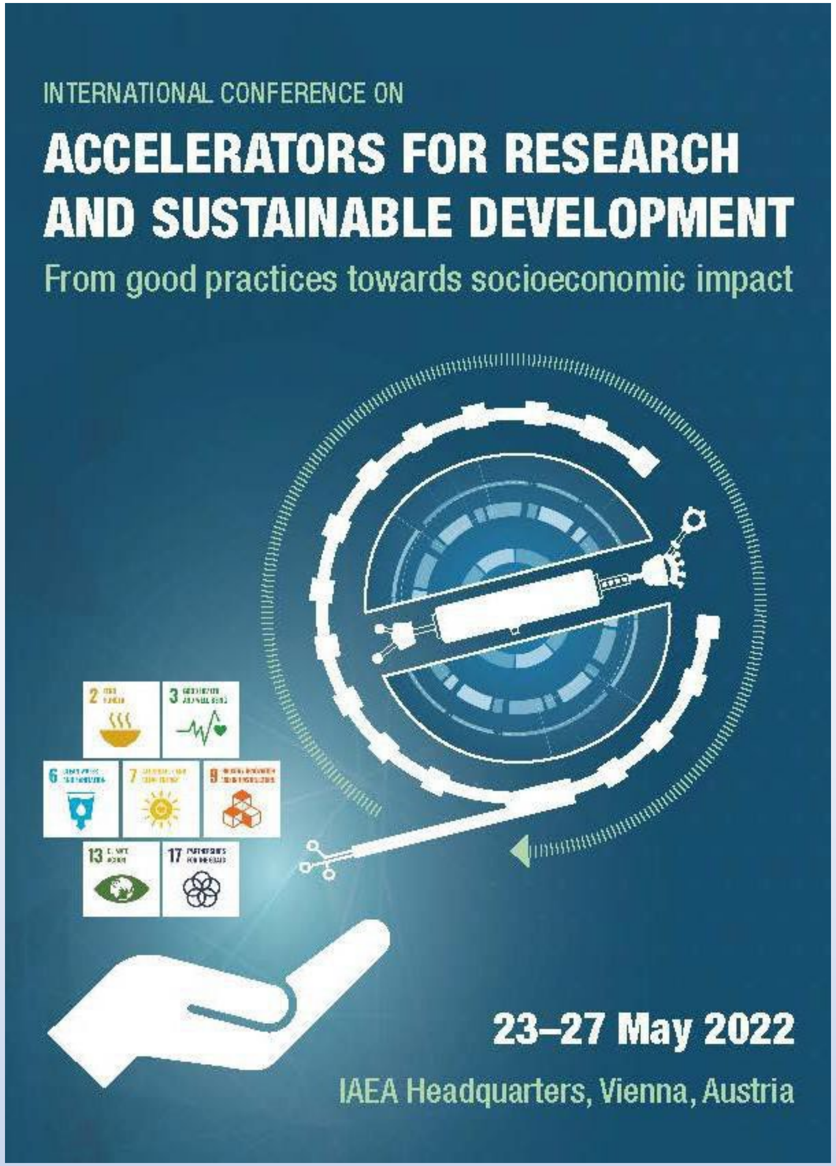
Increasing Medical Isotope Production with Accelerators



Dr. Cathy S. Cutler

Director of Medical Isotope Research & Production Program (MIRP)
Brookhaven National Laboratory
Department of Energy USA
July 2022

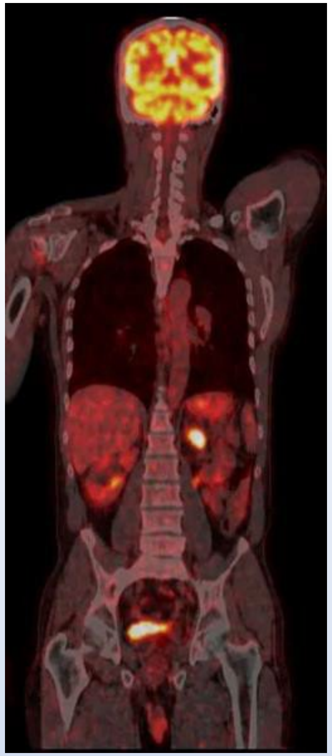
Outline

- Overview of medical radioisotope need and production
- Why are radionuclides used for medical applications
- Gap in demand and production capabilities
- Developing production capabilities in countries that have limited access
- Impacts of the growth
- Large accelerator facilities

Radiopharmaceuticals

- Radiopharmaceuticals - Drugs that contain radioactive atoms
- Radiopharmaceuticals are used for imaging and therapy
- Diagnostic radiopharmaceuticals have no pharmacological effect
  - Examples:
    - Heart disease (e.g., ^{99m}Tc, ^{18}F, ^{82}Rb)
    - Cancer (e.g., ^{18}F, ^{68}Ga)
- Therapeutic radiopharmaceuticals deliver radiation therapy directly to a lesion
  - Examples:
    - Seeds for prostate cancer therapy (^{192}Ir)
    - Targeted therapy (^{90}Y, ^{131}I, ^{223}Ra, ^{177}Lu)
- More than 20 million nuclear medicine procedures are performed each year in the US, ~ 50% of the global market
- Nuclear medicine is ~ $2 billion USD/year industry
- **The health benefits and economic impact are enormous**

Applications of
Nuclear Medicine
Imaging



Detection of
cancer and its spread

Detection and monitoring of
cardiovascular diseases

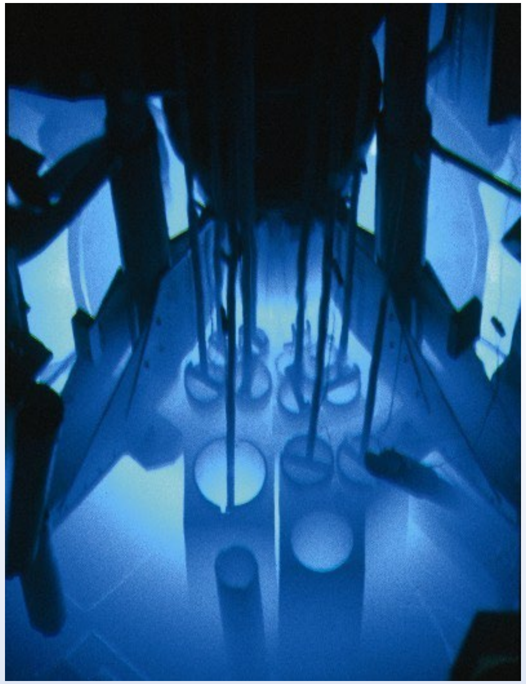
Identification of
neurologic and psychiatric diseases

Imaging of normal and abnormal functions of
excretory organs

Identification of regional tissue damage due to
infection ortrauma

Identification and quantification of
endocrine disorders

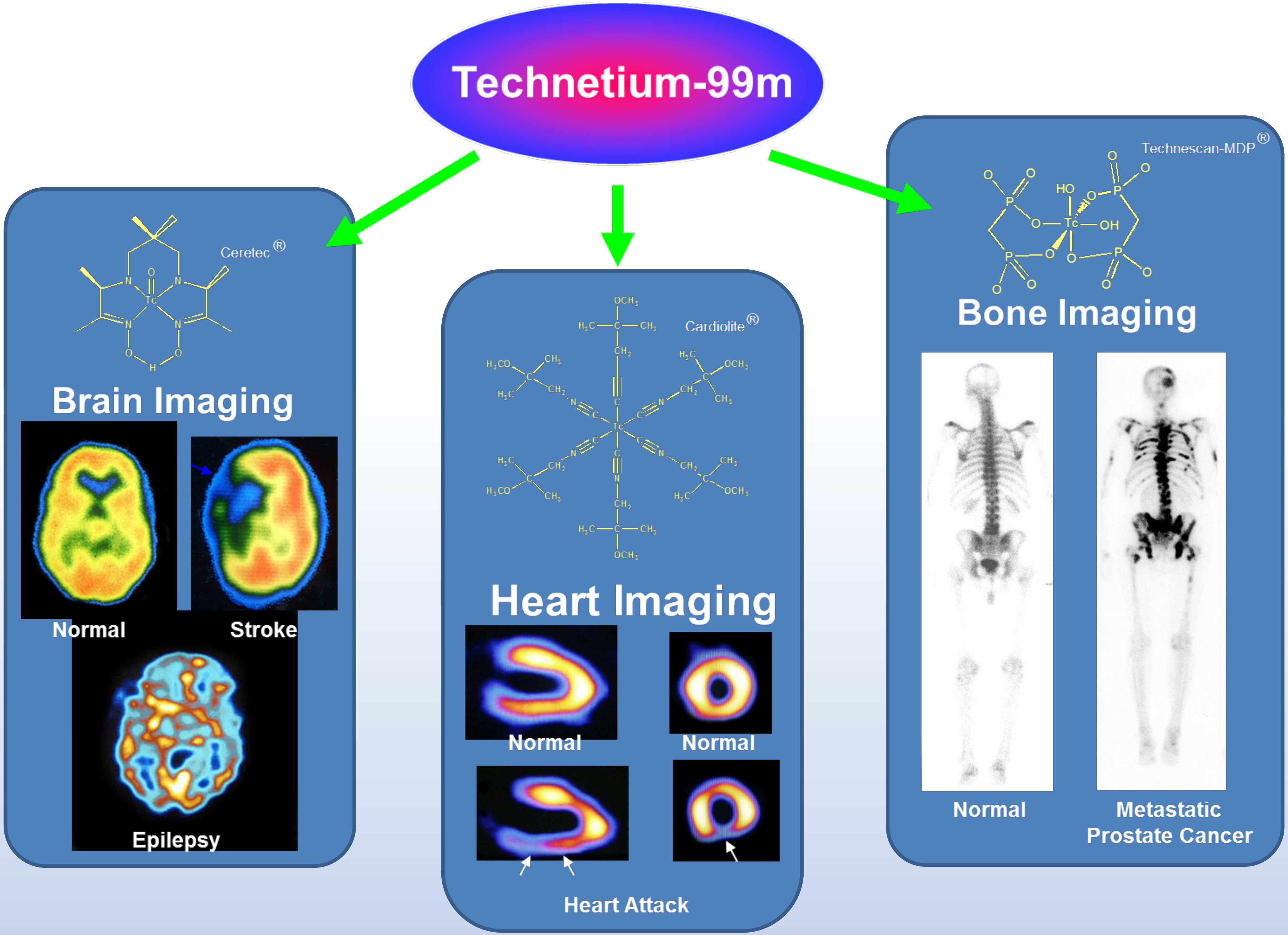
How are radioisotopes produced?



Reactors

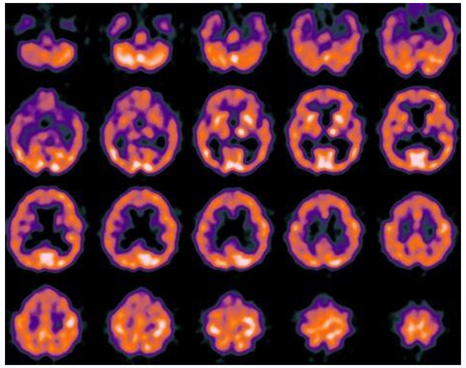
Accelerators

Generators

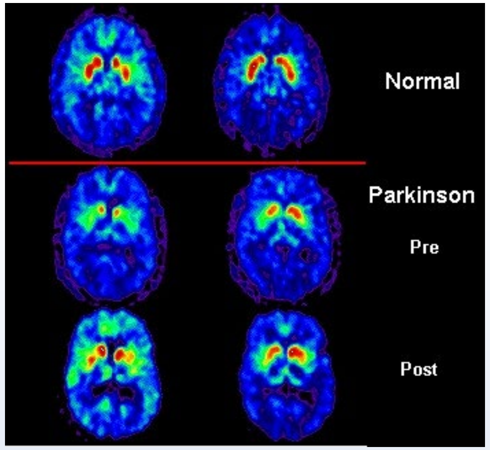

Technetium-99m
Ceretec®
Brain Imaging
Normal
Stroke
Epilepsy
Cardiolite®
Heart Imaging
Normal
Normal
Heart Attack
Technescan-MDP®
Bone Imaging
Normal
Metastatic Prostate Cancer

What Is Molecular Imaging?

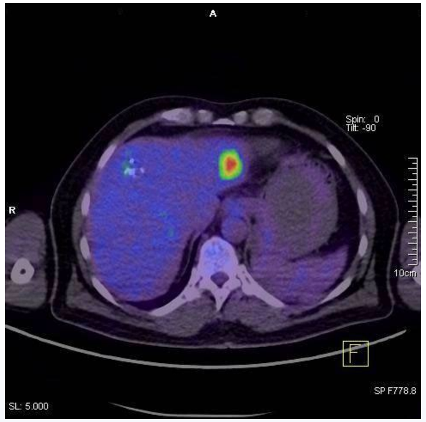
Visualization



Characterization



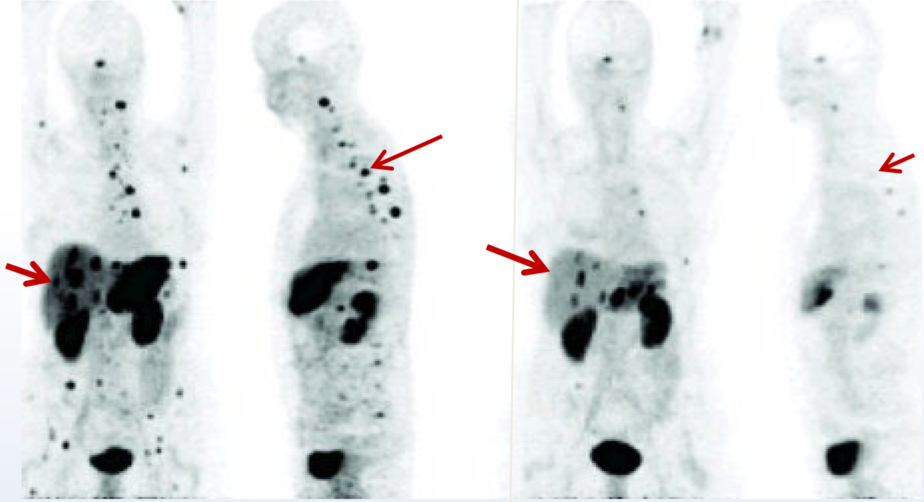
Measurement



of biological processes at the molecular and cellular levels in humans and other living systems

"Remarkable response to Bi-213-DOTATOC observed in tumors resistance to previous therapy with Y-90/Lu-177-DOTATOC"

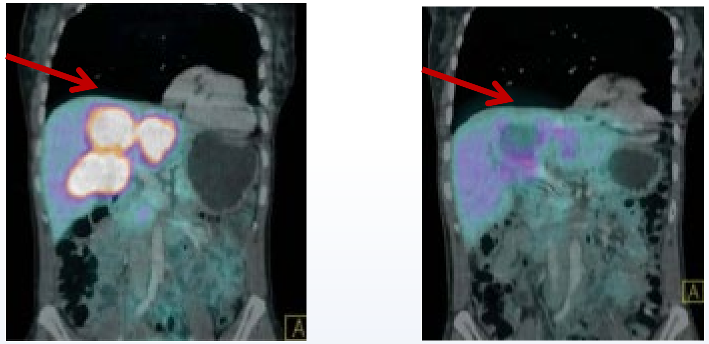
Before After



Case I: Shrinkage of liver and bone metastases after i.a. therapy with 11 GBq ^{213}Bi DOTA-TOC

Ga-68 DOTA-TOC

Before After



Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq ^{213}Bi DOTA-TOC

Abbreviated decay chain: ^{225}**Ac**→ ^{221}Fr→ ^{217}At→ ^{213}**Bi**

GEP-NET = Gastroenteropancreatic neuroendocrine tumors

Ref. Morgenstern et al. J. Nucl Med 2012; 53 (Supplement 1): 455.

High publicity: Study awarded Society of Nuclear Medicine Image of the year in 2012

SNMMI press release June 11, 2012

How are accelerator radiopharmaceuticals produced?

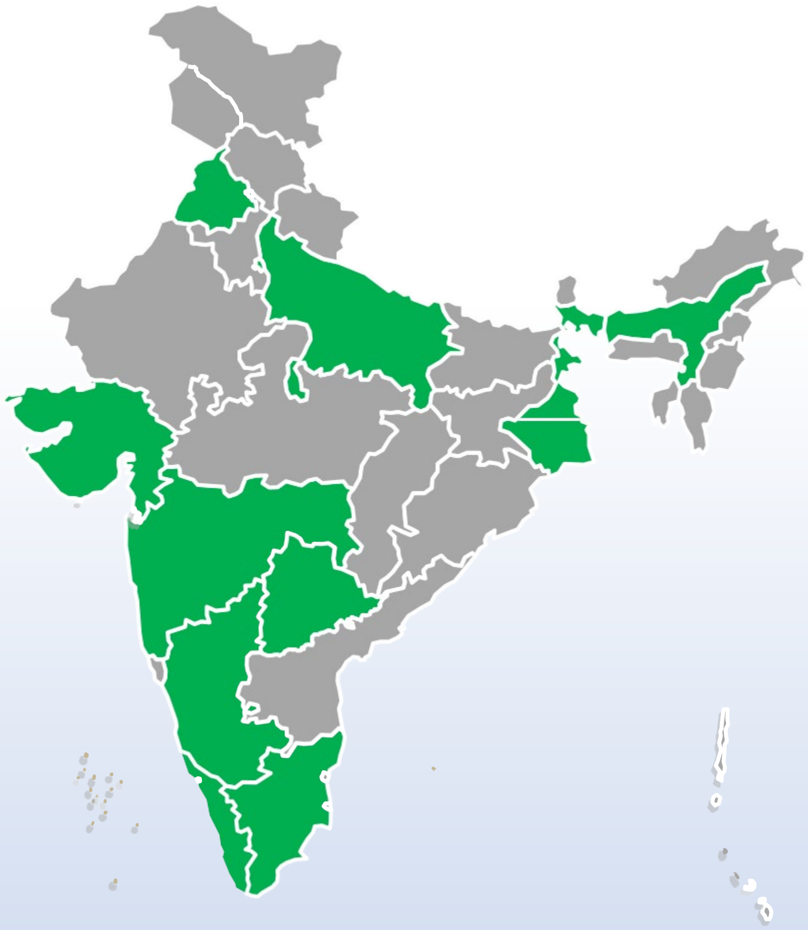
1200+
Cyclotrons

5600+
PET Scanners

IAEA | Accelerator Knowledge Portal

iMAGiNE

Cyclotrons & PET Scanners in India



21
Cyclotrons

333
PET Scanners

1.4 billion
Population

4.2

Millions are served by 1 PET Scanner

or

0.24

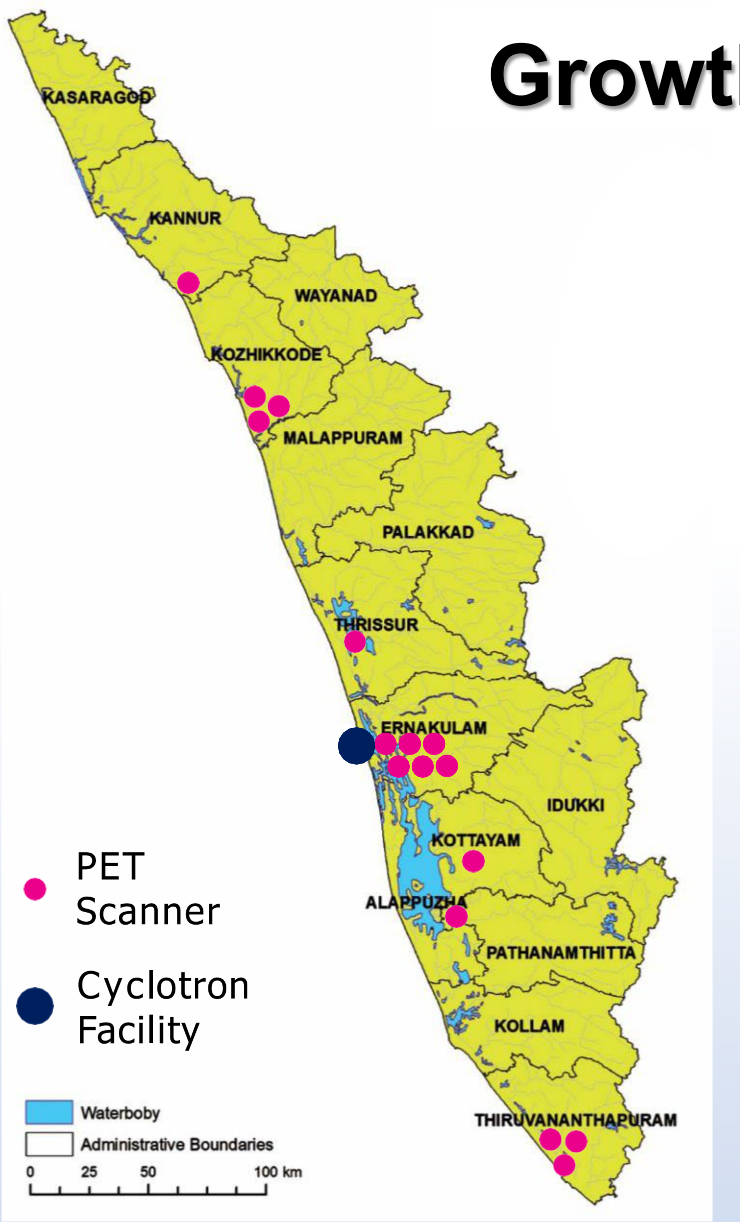
PET Scanners (per million)

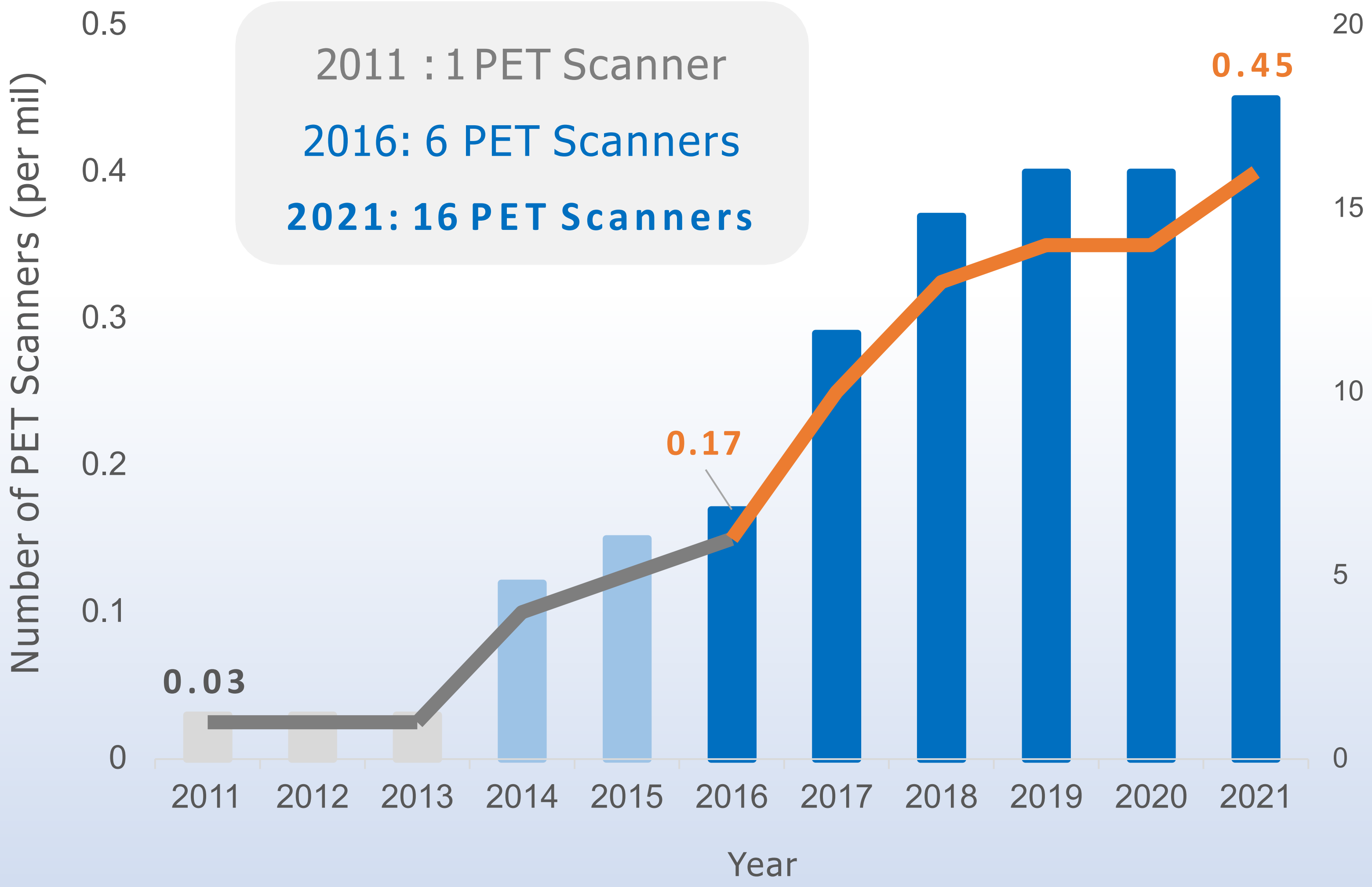
Molecular Cyclotrons, Kochi

MOLECULAR Cyclotrons Pvt. Ltd.

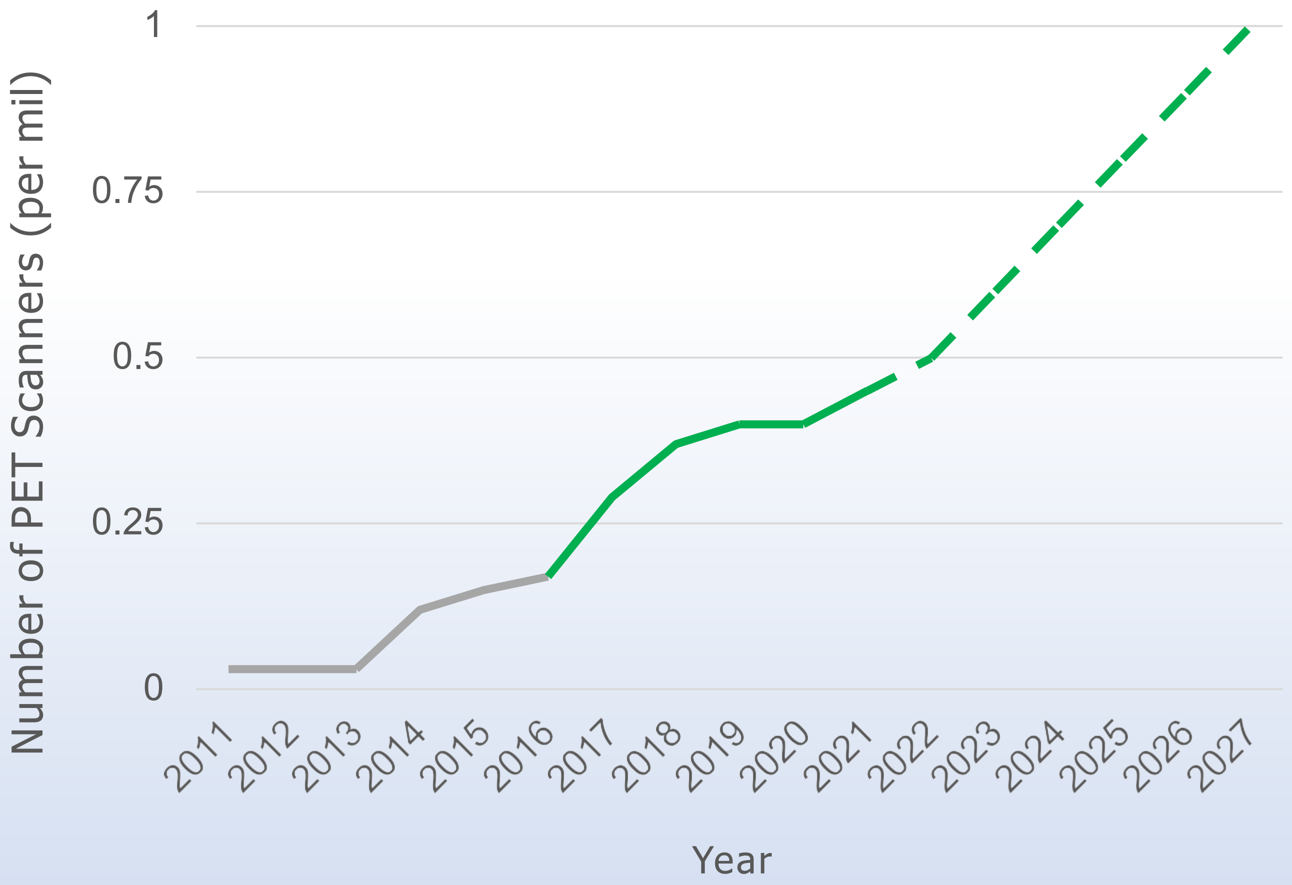
First and only medical cyclotron facility in the state of Kerala

Growth of PET Scanners in Kerala



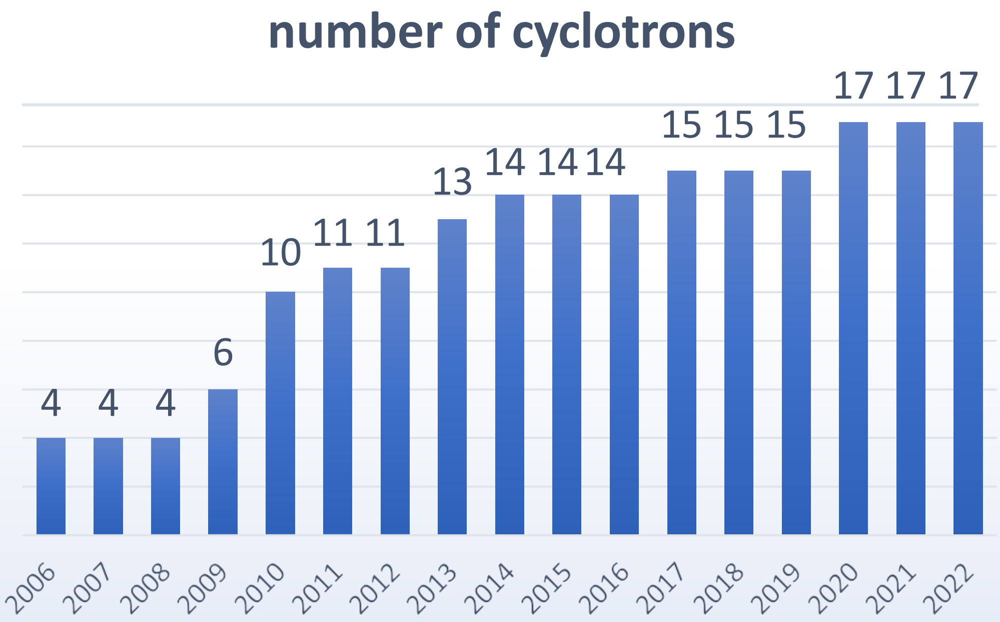


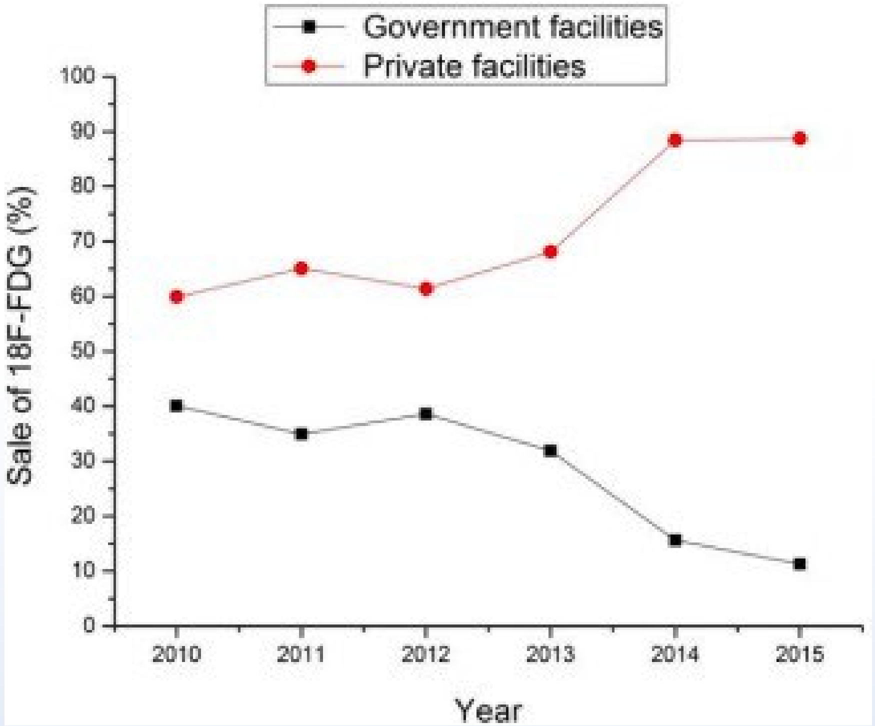
Looking forward to..



- Estimates 36+ million population in the state in 2027
- Kerala requires at least 36 PET scanners to reduce inequities in access to diagnostic nuclear medicine
- Our second cyclotron facility is under planning in another location

In 02/2006, with constitutional amendment, the monopoly for short half-life radioisotopes production (less than 2 hours) ended.



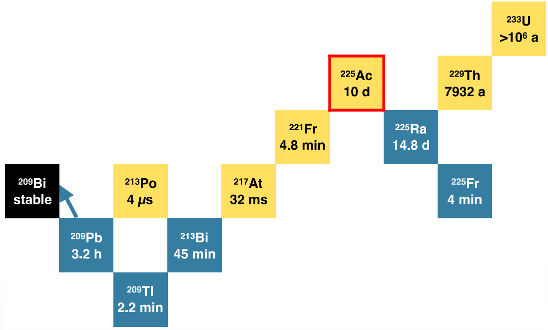


Private facilities have taken up market demand. Now the governments' cyclotrons are mainly directed to research and development of new radiopharmaceuticals

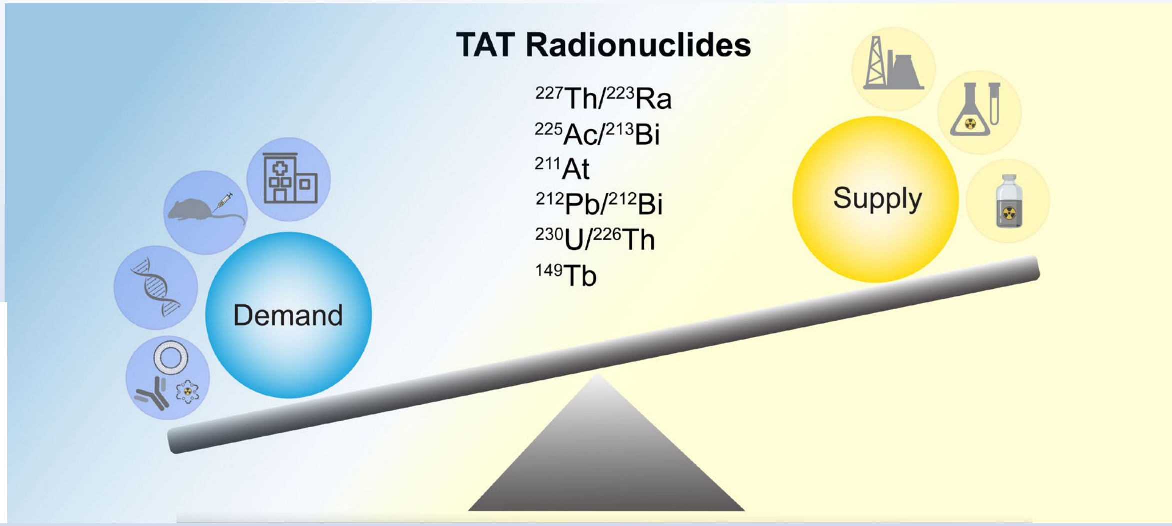
Production characteristics

- The facilities are investing in modern equipment and approaches looking to improve the development of new radiopharmaceuticals in Brazil. With this objective, many facilities maintain research agreements with universities with a focus on training new professionals.
    - There are 4 cyclotrons located inside the university's campuses
- The nuclear medicine in Brazil is expanding, the perspective is the increase the number of nuclear medicine centers and more investments in the development of new radiopharmaceuticals
- The same for cyclotrons, the perspective is to increase the number of new cyclotrons aiming to serve the most distant regions
- To improve the aspects of the regulation with the same speed with the field changes

Where are the needs ? Example of Targeted Alpha Therapy



JNM
The Journal of Nuclear Medicine



Production and supply of alpha particles emitting radionuclides for Targeted Alpha Therapy (TAT).

Valery Radchenko, Alfred Morgenstern, Amirreza Jalilian, Caterina Ramogida, Cathy S Cutler, Charlotte Duchemin, Cornelia Hoehr, Ferrid Haddad, Frank Bruchertseifer, Haavar Gausemel, Hua Yang, Joao Alberto Osso, Kohshin Washiyama, Kenneth Czerwinski, Kristen Leufgen, Marek Pruszynski, Olga Valzdorf, Patrick Causey, Paul Schaffer, Randy Perron, Maxim Samsonov, D. Scott Wilbur, Thierry Stora and Yawen Li

Journal of Nuclear Medicine July 2021, jnumed.120.261016; DOI: https://doi.org/10.2967/jnumed.120.261016

US Department of Energy (DOE) Accelerator Facilities

BNL BLIP

- 200 MeV, 165 μA p+ beam
- Ac-225, Ti-44, Se-72, Be-7, Y-86, Rb-83, Zn-65
- New hot cells under development for processing of alpha emitting isotopes
- 19 MeV cyclotron for Ac-225
- Ops coordinated with RHIC

LANL IPF

- 100 MeV, 300 μA p+ beam
- Ac-225, Am-241, Al-26, As-73, NA-22, Zr-88, Y-88
- Ops parasitic with LANSCE
- New processing capability (joint NNSA/DOE IP)

ANL LEAF

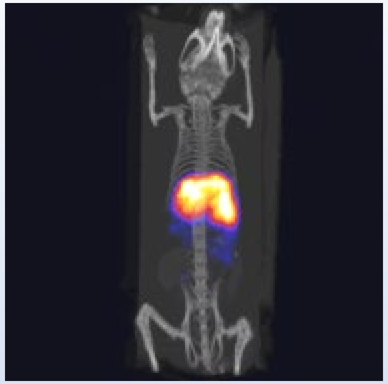
- 20-55 MeV electron machine
- Cu-67: theragnostic radioisotope: therapy and diagnostic capabilities in a single isotope.
- Sc-47 and Ac-225 production is under development.

Newly refurbished hot cells for alpha-processing

Outstanding hands-on training in smaller facilities

Safe radioisotope processing during the COVID-19 pandemic

Drawing of the new a-Target Processing Facility to be located next to IPF



Diagnostic demonstration of Cu-67 in living mice, in collaboration with University of Alabama-Birmingham

Hot cell processing of Cu-67

Facility for Rare Isotope Beams (FRIB) - USA

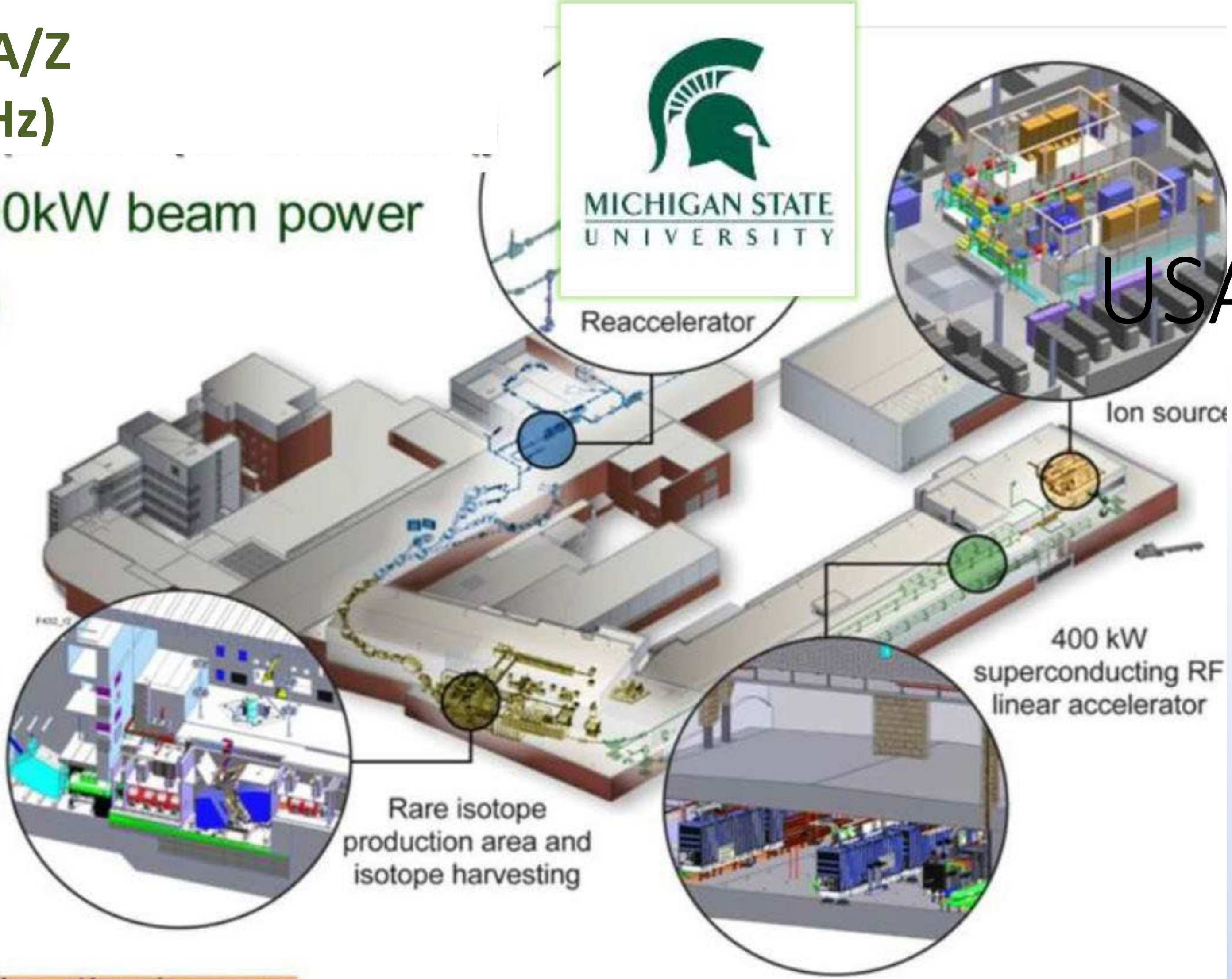
- 200 AMeV, verity A/Z
  SC RF (80- 322 MHz)
- Key Feature is 400kW beam power
  ($5x10^{13}$ $^{238}U/s$)

Apr. 2021:
all 46 CMs
212 MeV/u

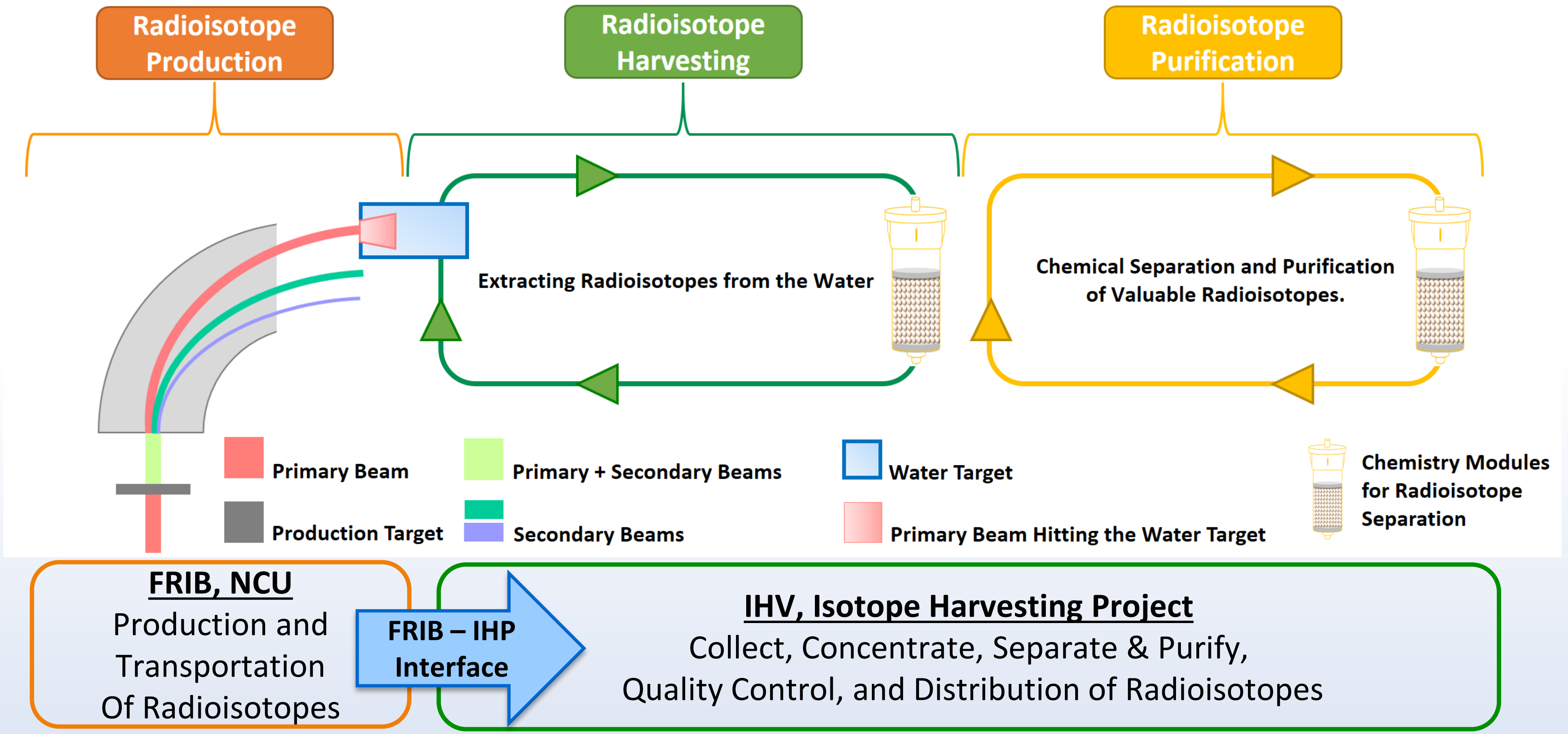
Separation of isotopes "In-flight"

Suited for all elements and short half-lives

Fast, stopped, and reaccelerated radioactive beams



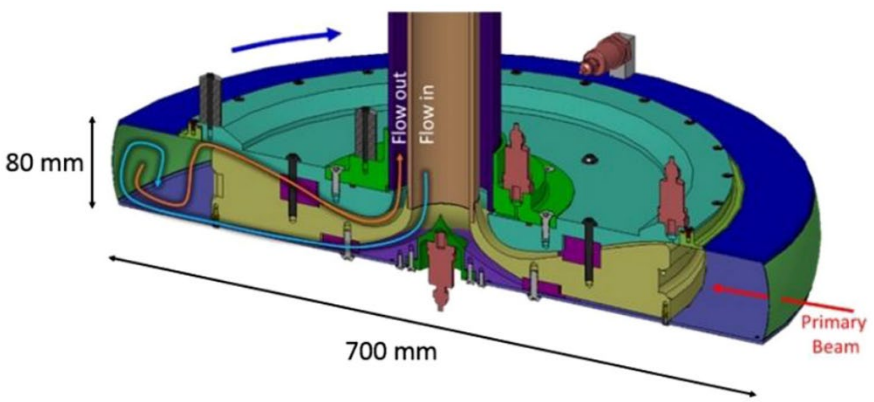
02 IHP OVERVIEW



High Level Requirements

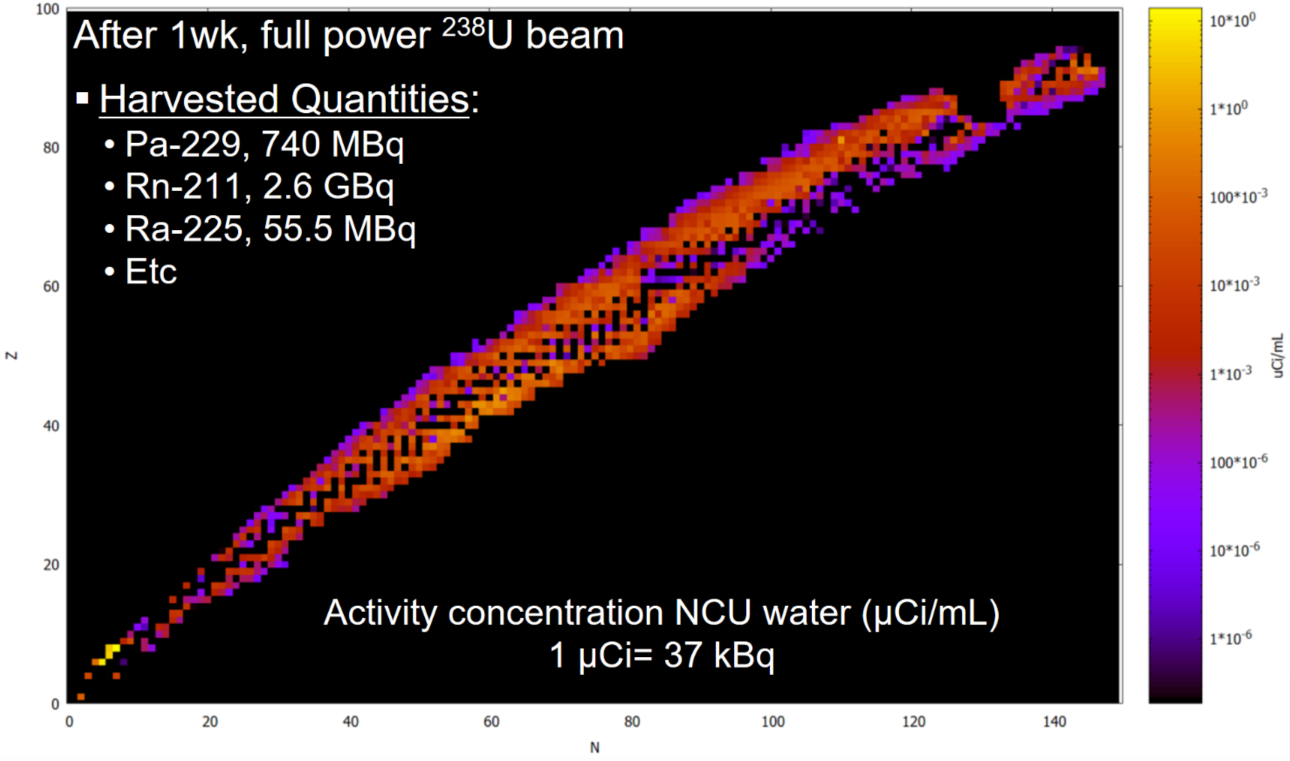
- ➢Radioactive gas and water transportation: Piping and facility modifications
- ➢Radioactive handling equipment and shielding: Radiation shielding, radiation monitoring, QA/ QC, controls

02 BEAM DUMP AND RADIOISOTOPE PRODUCTION



*FRIB Beam Dump

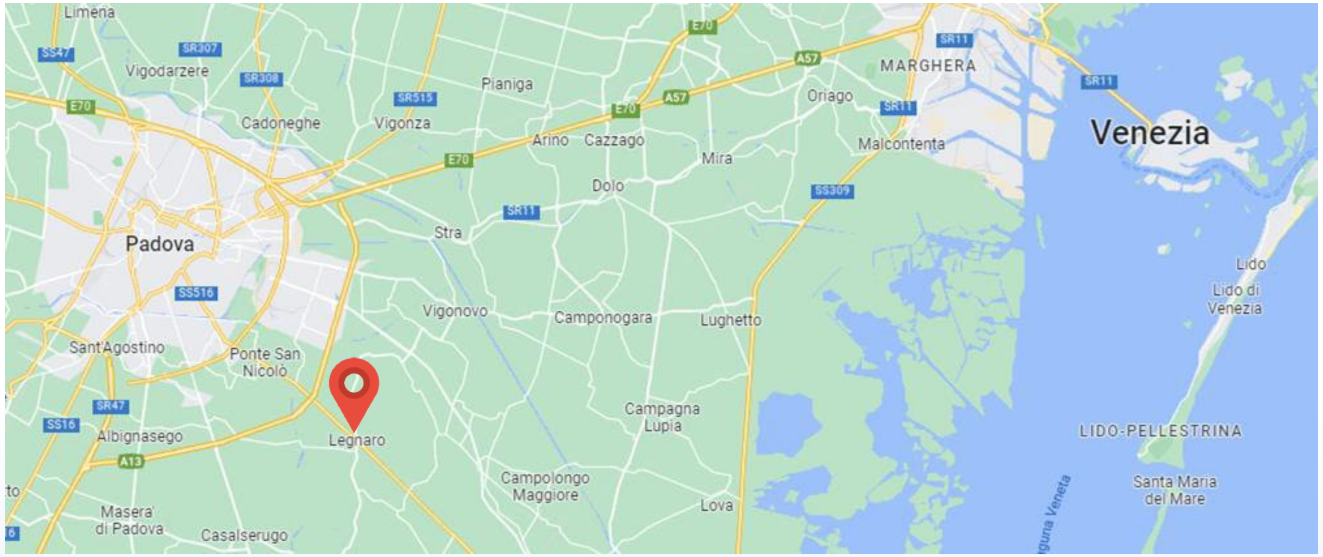
Ti–6Al–4V: low density, high strength, good corrosion resistance, and good fatigue performance
Primary ion beams: From ^{18}O to ^{238}U
Beam power: ~400 kW
Energy: 200MeV/u
Total volume of water: 7000 L



†Beams	^{48}Ca	^{64}Zn	^{78}Kr	^{238}U
†Radioisotopes	$^{47}Ca \rightarrow {}^{47}Sc$	$^{62}Zn \rightarrow {}^{62}Cu$	$^{77}Kr \rightarrow {}^{77}Br$	$^{211}Rn \rightarrow {}^{211}At$
†Production Rates of Mother	370.0 GBq/d	118.3 GBq/d	247.9 GBq/hr	15.9 GBq/d

*M. Avilov, A. Aaron, A. Amroussia, et al.; Thermal, mechanical and fluid flow aspects of the high power beam dump for FRIB; Nucl Instrum Methods Phys Res B; 376 (2016) 24–27.
†E. P. Abel, M. Avilov, V. Ayres, et al.; Isotope Harvesting at FRIB: Additional Opportunities for Scientific Discovery; J Phys G: Nucl Part Phys; 46 100501 (2019) 1 – 33.

INFN-LNL are close to Padova and Venice

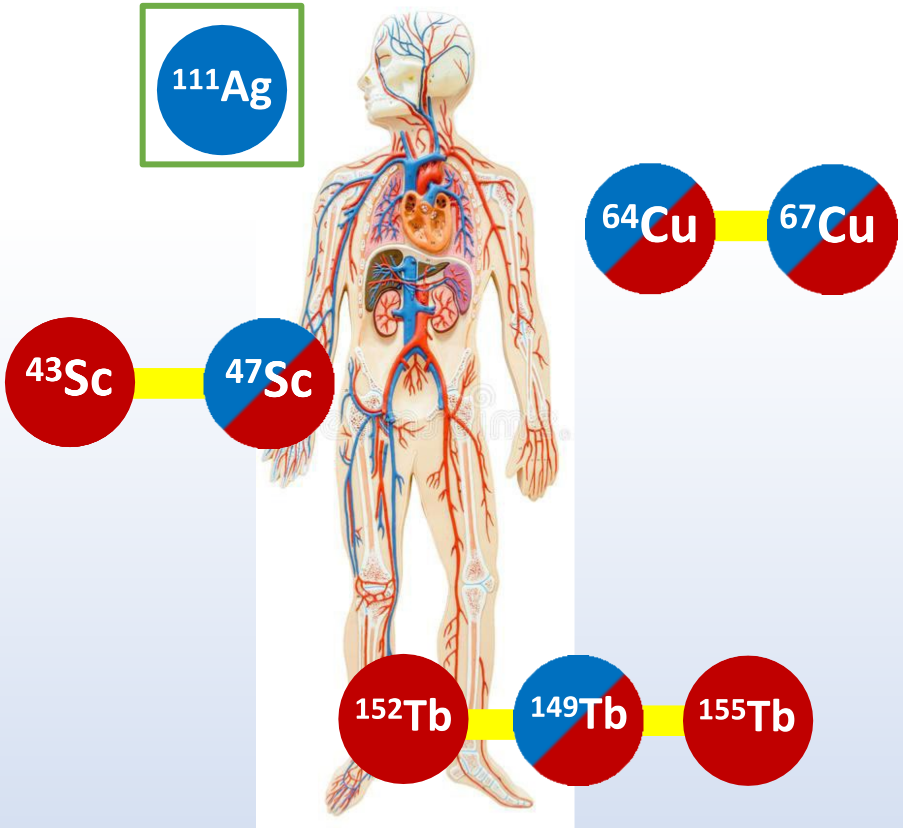


ISOLPHARM

SPES exotic beams for medicine

The ISOLPHARM **ion collection target**

ISOLPHARM allows to produce unconventional medical radionuclides



therapy diagnostics theranostics pairs

^{111}**Ag** production is investigated with two INFN-csn5 projects

(2018-2019)

(2020-2022)

LARAMED research activities & network

Research lines and international projects	Years
Accelerator ^{99m}Tc direct production route through hospital cyclotrons	APOTEMA (2012-2014) TECHNOSP (2015-2017)
"Alternative, non HEU-based, ^{99m}Tc/^{99}Mo supply" IAEA	IAEA CRP (2011-2015)
COpper MEasurement: ^{70}Zn(p,x)^{67}Cu	COME (2016)
Production with Accelerator of ^{47}Sc for Theranostic Applications	PASTA (2017-2018)
"Radiopharmaceuticals Labelled with New Emerging Radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc) IAEA	IAEA CRP (2016-2019)
High Power Target concepts R&D	TERABIO (2016-2019)
High intensity vibrational powder plating (HIVIPP)	E_PLATE (2018-2019)
Multimodal pET/mRi Imaging with Cyclotron-produced $^{52/51}$Mn and stable paramagnetic Mn iSotopes	METRICS (2018-2021)
Research on Emerging Medical radIonuclides from the X-sections: ^{47}Sc e ^{149}Tb, ^{152}Tb e ^{155}Tb (and therapeutic ^{161}Tb)	REMIX (2021-2023)
TOTEM (magneTron sputtering cyclotrOn TargEt Manufacturing)	TOTEM (2021-2022)

National collaboration

- Pavia Univ + INFN Pavia
- LENA Laboratory (PV)
- CNR Milan
- Ferrara Univ. /INFN-Fe
- Padua Univ. /INFN-Pd
- Milan Univ. /INFN Mi
- SC Hospital (VR)
- St. Orsola Hospital (BO)

International collaboration

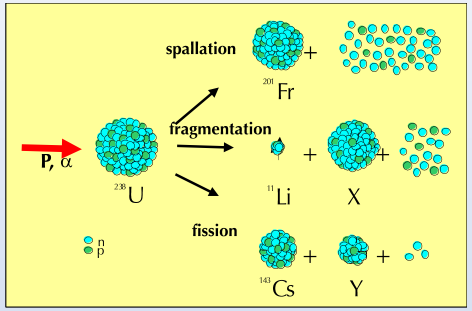
- ARRONAX (Nantes, FRANCE)
- Univ. Winsconsin-MD (USA)
- IAEA

PRISMAP Medical Radionuclides

How to supply “novel” radionuclides with mass separation

PRISMAP proposes to federate a consortium of high energy cyclotrons, research reactors, and isotope mass separation facilities in Europe.

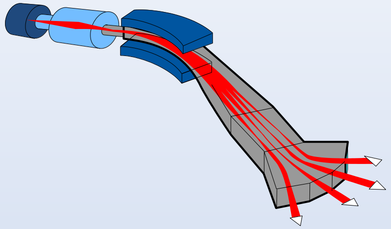
Accelerator



$I_{[pps]} \sim \Phi_{[pps]}\ \sigma_{[barn]}\ N_{[g/cm2]}$ **production rate**

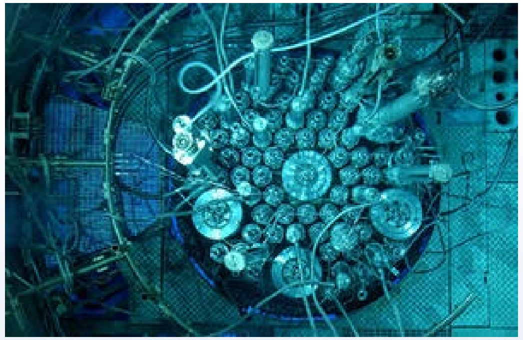
10^{10}pps 100µA (6.10^{14}) 1mbarn 1g/cm^2 for A_{target}=30g/mol

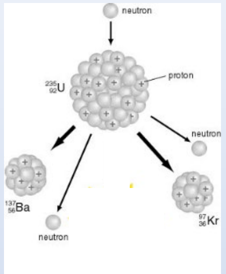
Isotope mass separation



$I_{[pps]} \sim \Phi_{[pps]}\ \sigma_{[barn]}\ N_{[g/cm2]}\ \varepsilon\ [\%]$

Research reactor





$$\frac{dN'}{dt} = nv\sigma_{act} N_T$$

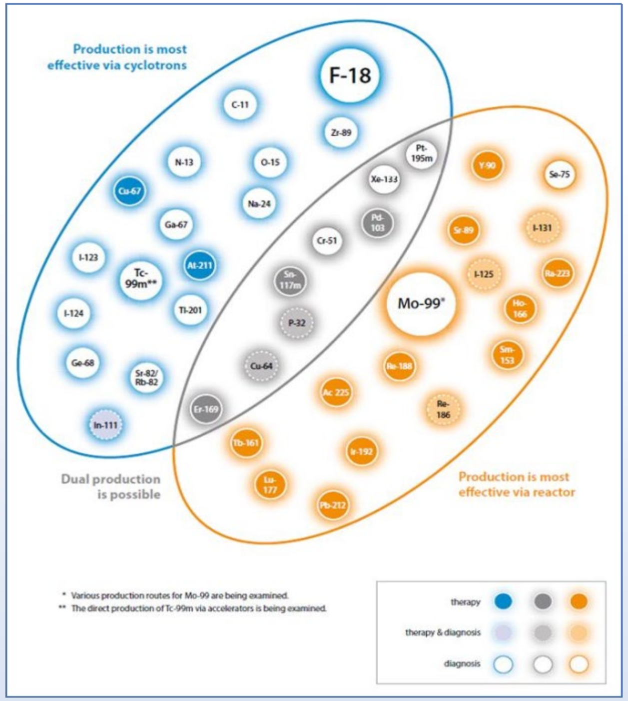
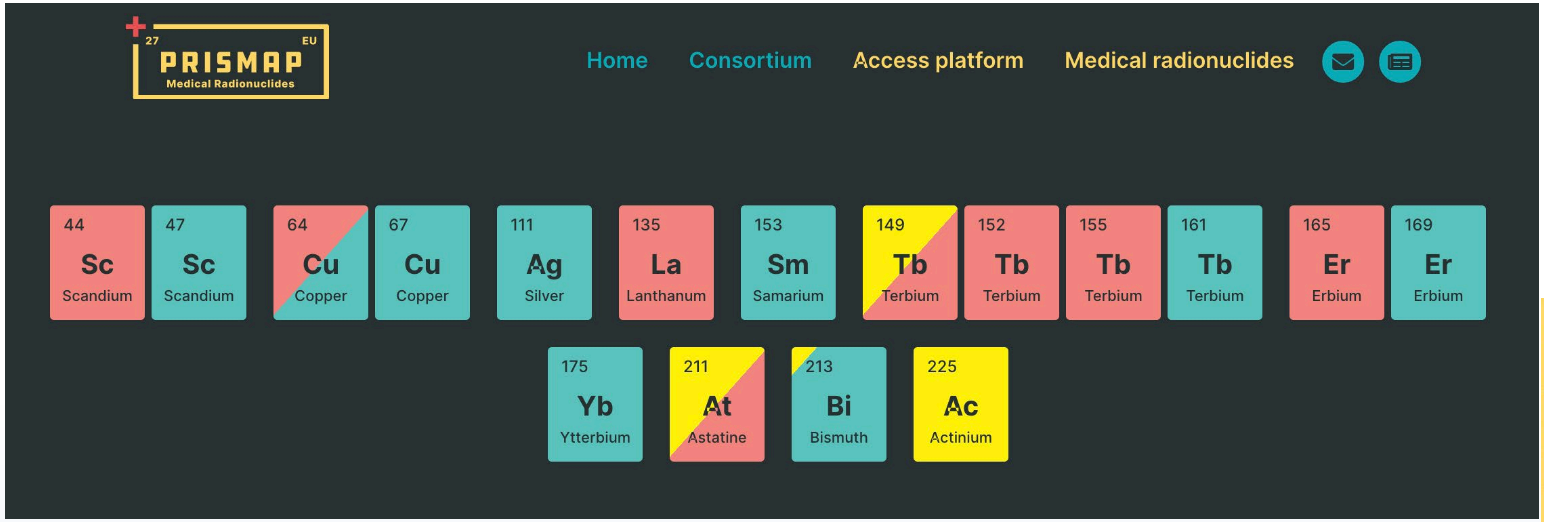


Figure 31 : Main medical radioisotopes production process

European Commission
ENER/17/NUCL/SI2.755660
(2018)

Day-1 radionuclides from PRISMAP



specification sheet for Er-169

Parameter	Specifications
Half-life	9.39 d
Daughter	Stable Tm-169
Branching Ratio/Decay	100% β^-
Production	Er-168(n,γ) Er-169
Purification	Off-line mass separation + 2-step column separation
Chemical Form	In 0.05 M HCl
Specific Activity	n.a.
Radionuclidic Purity	>99%
Radiochemical Purity	n.a.
Chemical Purity	n.a.
Identification	Presence of 109.8 keV gamma line
Appearance	Clear solution
pH	1-2
Activity available	100 MBq
Availability	Few times per year (planning in advance), depends on reactor and MEDICIS schedule
Grade	preclinical, n.c.a.
Other information	Research grade implanted in Al, Zn or NaCl layer on Au foil also possible

Half-life determination of ^{155}Tb from mass-separated samples produced at CERN-MEDICIS

S. M. Collins et al, in preparation

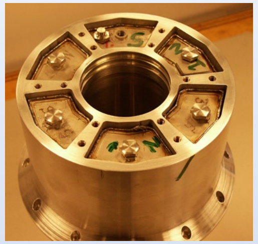
(Some more information at www.prismap.eu)

FLASH Irradiations

- FLASH effect occurs at high irradiation rates (100s Gy/s)
- FLASH radiation damages healthy tissue less, while delivering full damage to the tumour tissue -> increases therapeutic window
- Beam intensity
  - protons ≤ 6×10^{13} pps
  - helium ≤ 10^{13} pps
  - carbon ≤ 10^{10} pps

    → proton, helium dose rate 10^{2} - 10^{4} Gy/s, dependent on field size

    → 90 MeV/A carbon SOBP dose rate up to 200 Gy/min
  - further increase under development (improvement of the source performance and transmission into the cyclotron)
- Development of dose control (diamond detector, N_2 thin dual cap ionization chamber, CW current transformer) and high dose rate dosimetry (Gafchromic Film, Faraday Cup)
- Establish beam parameters, dose delivery and control methods in conformity with ones clinically achievable for FLASH beam irradiations
  - at GPTC and
  - at other facilities.



Conclusions

- Need for medical isotopes is expanding:
  - Small cyclotrons are critically needed in remote areas to increase access
  - Requiring an increased need in training
  - Increased need in workforce development
  - Regulatory burden is increasing
- Novel large facilities coming online:
  - Provide higher energies that can be used to produce novel isotopes through spallation and fission
  - Mass separation providing cleaner isotopes
- New ion beam facilities coming online
- Demand is huge and we are finding ways to fill the gap and increase sustainability