COMPACT AND EFFICIENT ACCELERATORS FOR RADIOISOTOPE PRODUCTION

Concepción Oliver

CIEMAT, Madrid, Spain

concepcion.oliver@ciemat.es

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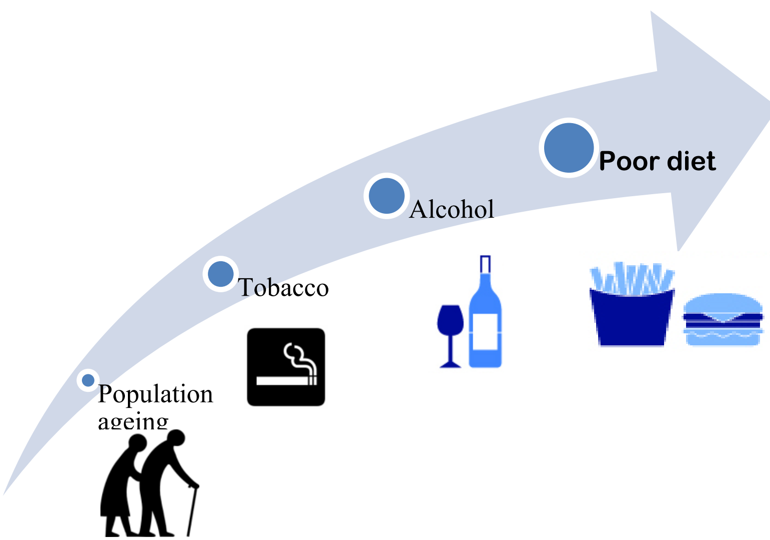
Key facts in medicine

CVD 1st
Cancer 2nd
leading death cause

17.5 million deaths due to CVD
8.8 million deaths due to cancer
(2015)

CVD

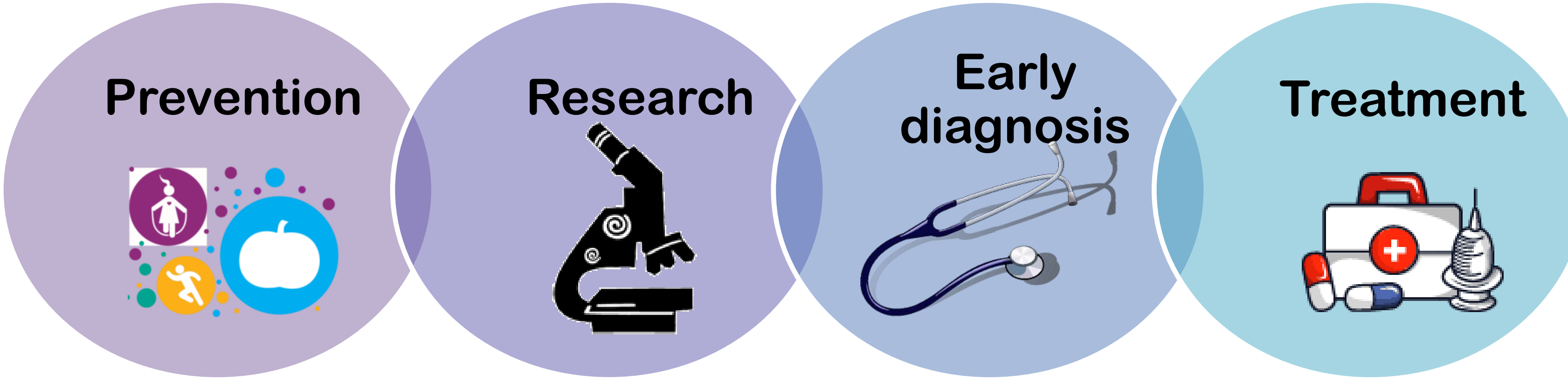
Cancer



70%
Increase of new CVD & cancers in next 2 decades

World Health Organization, http://www.who.int

What can we do?



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Economic cost (2010):

Cancer: US$1.16 trillion

Dementia: US$ 604 billion

CVD: US$683 billion

<30% Access to diagnosis and treatment in low-income countries (90% in high in-come countries)

70-75%

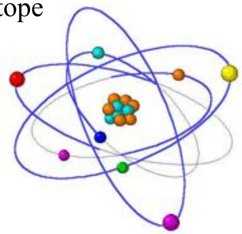
CVD and Cancer Deaths in low and middle in-come countries

World Health Organization, http://www.who.int

It is important to expand the use of such techniques (to reduce the cost) to make them more available to the general population ← **Radioisotopes**

Radioisotopes in Nuclear medicine

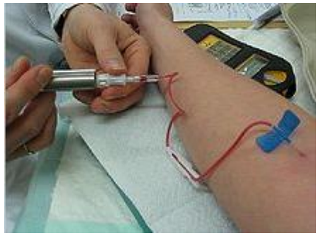
Radioisotope



Radiopharmacy

Radiopharmaceutical

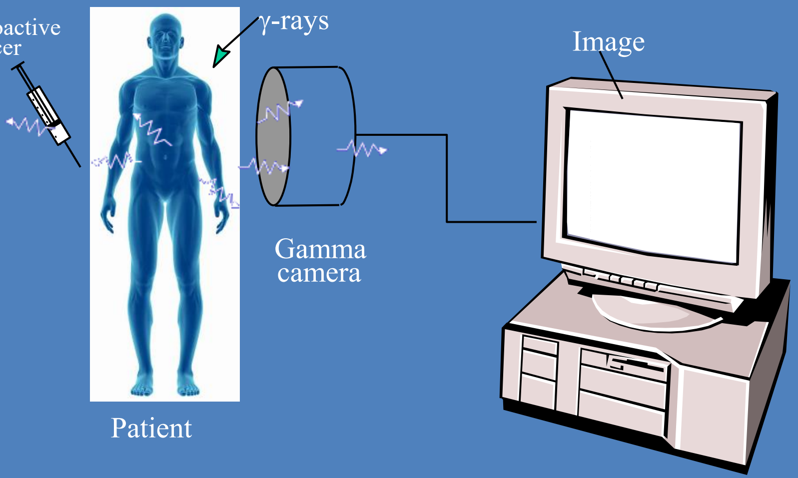
A ^{11}C labeled radiopharmaceutical



Localized in some organs or tumors

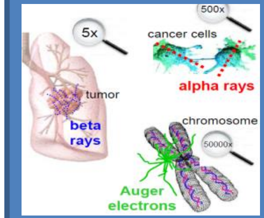
Imaging

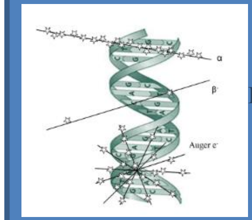
- Gamma radiation (Energy 100-300 keV)
- It provides physiological information
- Useful tool for the diagnosis, treatment planning and follow-up of different diseases.
- Short-life process
- Minimum dose to patient



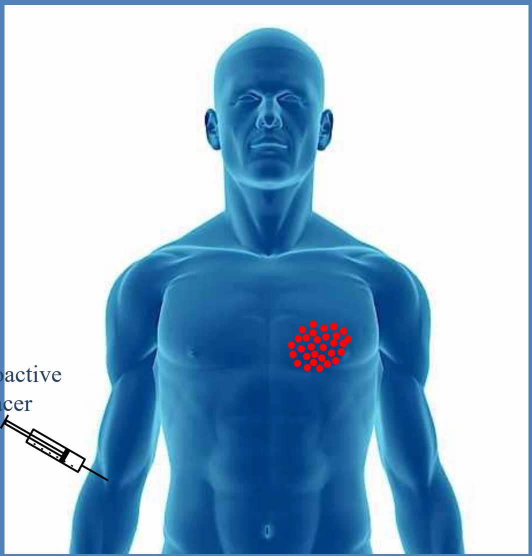
Therapy

- High ionizing particles: alpha, beta, Auger electrons
- High dose



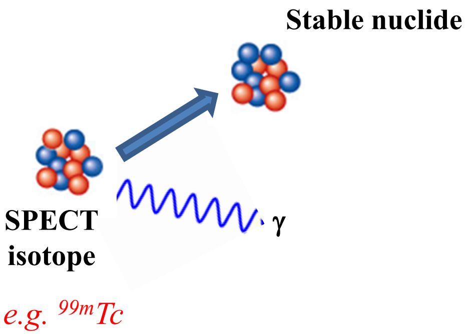


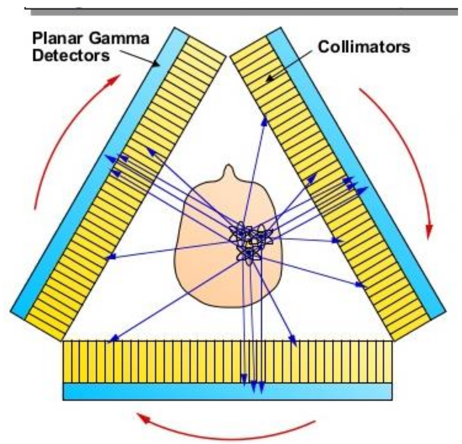
From Thesis H- Thisgaard



Two imaging procedures:

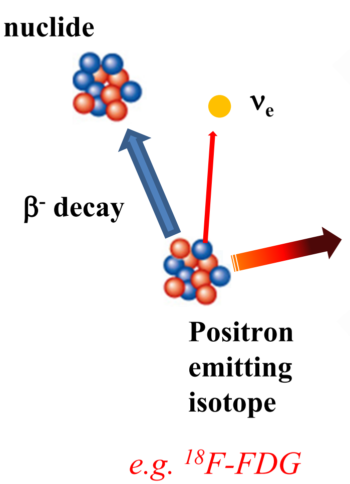
SPECT:
Single Photon Emission Computed Tomography

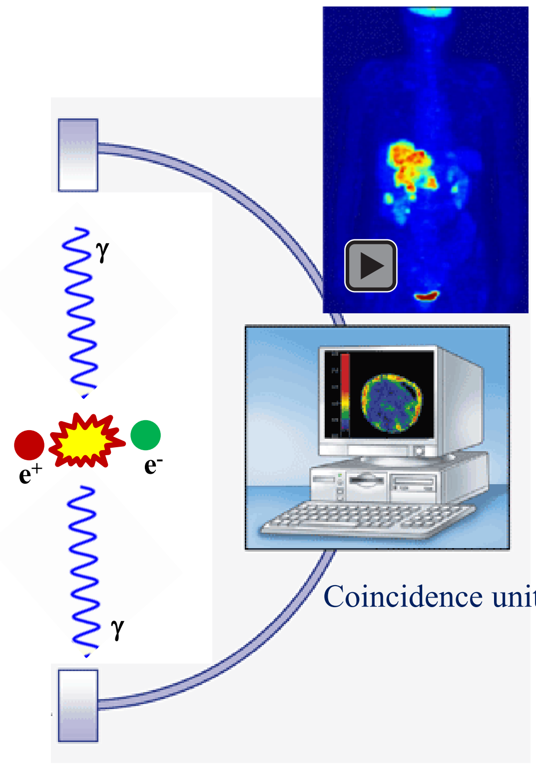


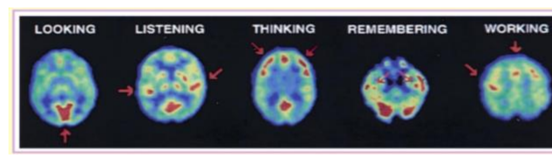


Discovery NM630 GE SPECT camera

PET:
Positron Emission Tomography







Phelps, PNAS, 2000, 97, 9226

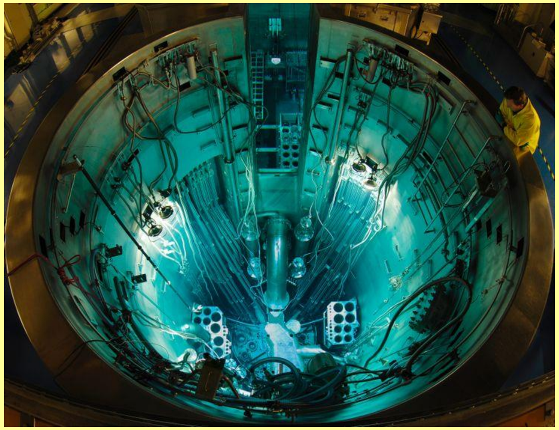
Higher resolution but expensive technique

Siemens PET-CT camera

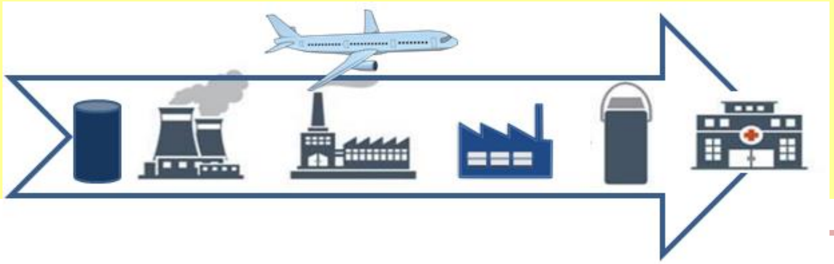
Production

- Artificially produced by research reactors or accelerators
- Sometimes the parent isotope is produced and by the generator concept, the daughter is extracted with an efficient separation technique (e.g. ^{99}Mo/^{99m}Tc)

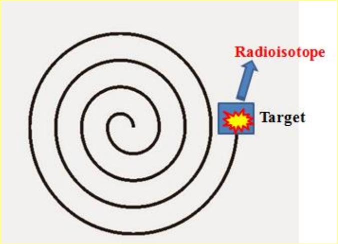
Research reactors



- n-fission or n-capture of HEU targets
- Neutron-rich radioisotopes (^{99m}Tc, ^{131}I, ^{166}Ho, ^{177}Lu)
- High production yield but low specific activity
- Non-proliferation issues: from HEU to LEU targets



Accelerators

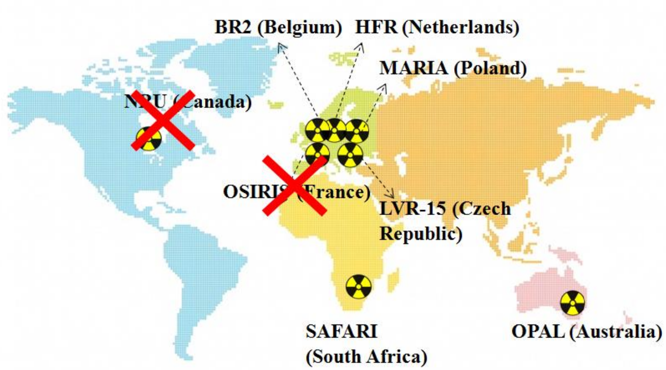


- Target irradiation by accelerated particles in accelerators
- Proton-rich radioisotopes (^{18}F, ^{201}Tl, ^{123}I, ^{67}Ga, ...)
- High specific activity products but low production yield
- Smaller amount of radioactive waste
- Less capital, operating and decommissioning costs
- Easier access than to reactors

Current issues on isotope supply market

Imaging	**SPECT**		^{67}Ga, ^{81m}Kr, **^{99m}Tc**, ^{111}In, ^{123}I, ^{133}Xe, ^{201}Tl, ^{131}I, ^{177}Lu
	PET	Short-life	^{11}C, ^{13}N, ^{15}O, **^{18}F**, ^{68}Ga, ^{82}Rb
		Long-lived	^{44}Sc, ^{64}Cu, ^{76}Br, ^{86}Y, ^{89}Zr, ^{124}I
Therapy		Beta	^{32}P, ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{169}Er, ^{186}Re, 188Re
		Alpha	^{212}Pb, ^{213}Bi, ^{211}At, ^{224}Ra, ^{225}Ac, ^{227Th}, ^{230}U
		Auger	^{51}Cr, ^{75}Sr, ^{77}Sr, ^{125}I

Last decade crisis in reactor-production



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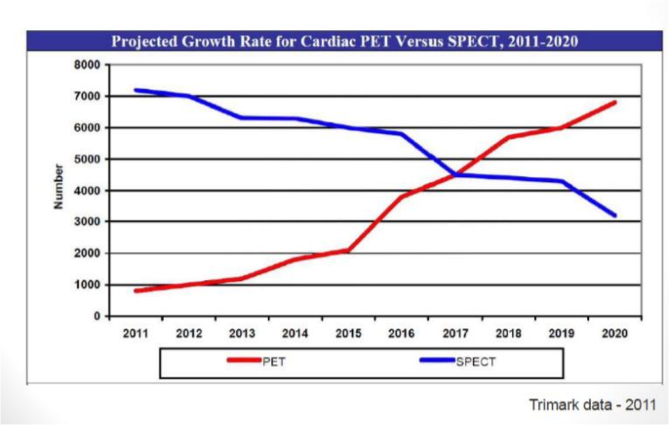
Last decade crisis in reactor-production

Demand for very short half-life PET isotopes



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Last decade crisis in reactor-production

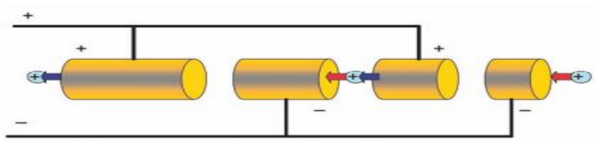
Demand for very short half-life PET isotopes

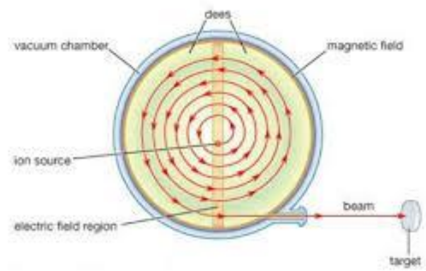
Need of therapeutic isotope availability

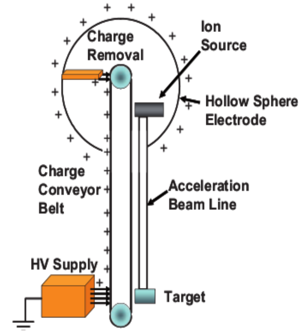
Accelerators

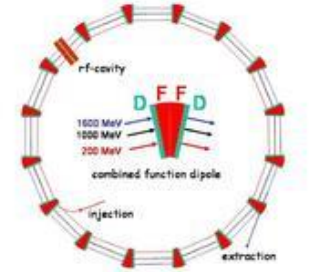
Accelerators

We need accelerators for radioisotope production … But which one??









Radioisotope production

Production route

- Direct production with ions (p,d) : cyclotrons, linacs, DC, FFAG, ...
- γ-induced reactions (electron machines)
- n- induced reactions (CANS, spallation sources, ...)
- particle-induced U fission

Goal:

- High specific activity → ~E choice
- Maximum production yield→ linear with I

+

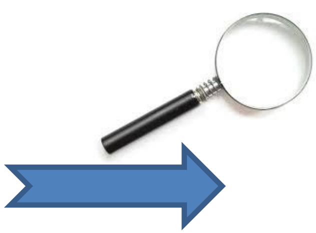
In a medical environment

Localized production:

- Compact machines (footprint, weight, shielding, few infrastructure needs)
- Low acquisition and operation cost
- High reliability operation

On-site production at hospitals:

- Automatic operation, maintenance-free, low radiation to personnel



- Development on compact, low cost accelerator technology but also
- Targetry development
- Target processing to get a radiopharmaceutical fulfilling standard requirements
- Target recycling for a cost-effective production

Review of compact accelerators

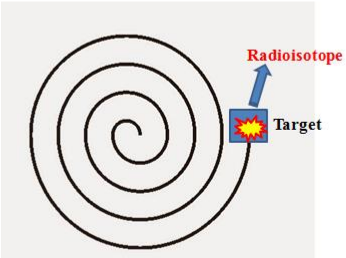
- ❑ CYCLOTRONS
- ❑ ION LINACS
- ❑ ELECTRON LINACS
- ❑ ELECTROSTATIC MACHINES
- ❑ Other proposals: FFAG, LASER, CANS, ...

Just an overview of some representative examples

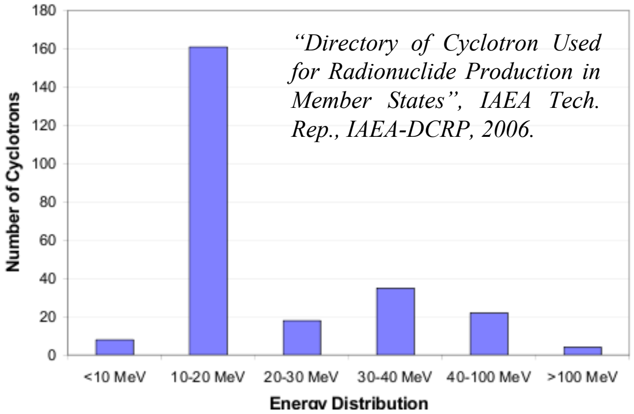
(based on a personal selection)

Cyclotrons

- ❑ Standard solution for radioisotope production
- ❑ Increasing of number of cyclotrons in the last decades
- ❑ Key properties: compactness, low cost and commercially available



CYCLOTRONS FLAVORS
- ✓Positive/negative particles
- ✓Single/multi-particle acceleration
- ✓Internal/external ion source
- ✓Resistive/superconducting magnet
- ✓Self-shielded/vault



"Directory of Cyclotron Used for Radionuclide Production in Member States", IAEA Tech. Rep., IAEA-DCRP, 2006.

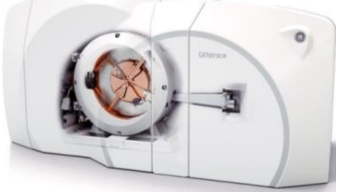
Low Energy cyclotrons	Medium Energy cyclotrons	High energy cyclotrons
Energies < 15 MeV Short-lived PET isotope production: ^{18}F, ^{11}C, ^{13}N, ^{15}O On-site production (hospital)	Energies 15-30 MeV SPECT isotopes: ^{99m}Tc, $^{123\text{-}124}$I, ^{111}In, ^{201}Tl, ^{103}Pd Hospital/local distribution	Energies >30 MeV ^{67}Cu, ^{82}Sr, ^{211}At Research lab/industry

Low energy cyclotrons

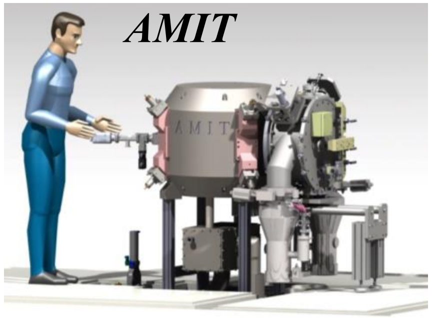
- On-site production (cyclotron in hospital)
- Very compact and low cost solution
- Integrated product:
  accelerator+ targetry+radiochemistry
- Reliability, user-friendly, flexibility, minimum personnel dose

Low energy cyclotrons

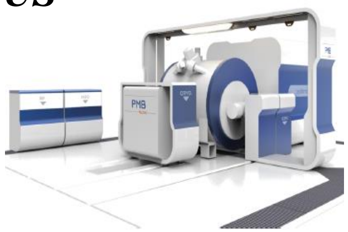
GENtrace



AMIT

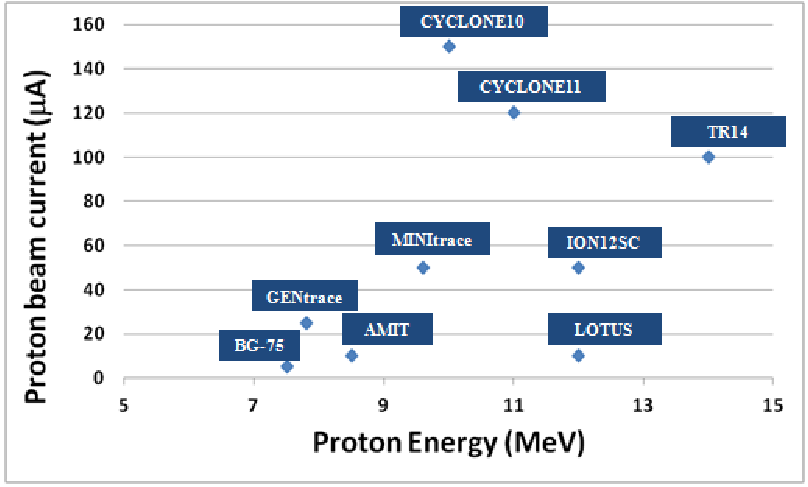


LOTUS

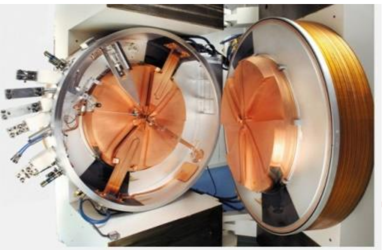


ION12SC

Cyclotron	E_p (MeV)	I_p (µA)	Peak B (T)	Weight (Tons)
LOW ENERGY				
GENtrace, GE	7.8	-	2.2	6.7
MINItrace, GE	9.6	>50	2.2	9.1
Eclipse, Siemens	11	>120	1.9	11
Cyclone10, IBA	10	>150	1.9	12
Cyclone11, IBA	11	120	1.9	13
TR14, ACSI	14	>100	2.1	23
BG-75, ABT	7.5	5	1.8	3.2
AMIT, CIEMAT	8.5	>10	4	3
ION12SC, Ionetix	12	~10	4.5	2
LOTUS, SigmaPhi-PMB-CEA	12	50	2.3	-

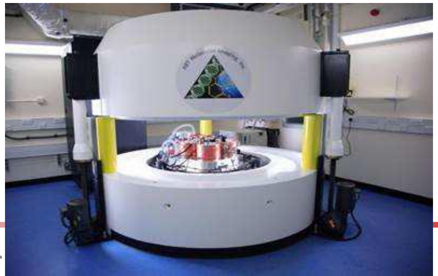


MINItrace

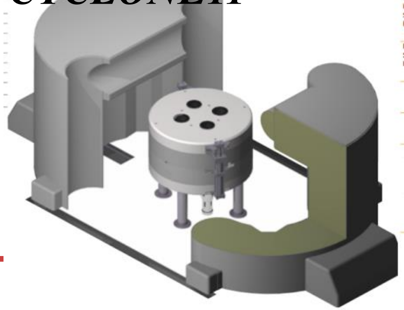


ECLIPSE

BG75



CYCLONE11



Medium energy cyclotrons

- Energies 15-30 MeV
- Relative high current (>300μA)
- Versatile radionuclide production: ^{99m}Tc, $^{123\text{-}124}I$, ^{111}In, ^{201}Tl, ^{68}Ga, ^{103}Pd
- Larger, heavier, expensive machines (w.r.t. PET cyclotrons)
- Local production facility (hospital/industry)
- Main alternative for ^{99m}Tc reactor-production

PETtrace

Cyclotron	E_p (MeV)	I_p (μA)	Peak B (T)	Weight (Tons)
MEDIUM ENERGY				
BEST15, BEST	15	400	-	14 (magnet)
PETrace ,GE	16.5	>100	1.9	22
Cyclone18 IBA	18	150	1.9	25
KIUBE, IBA	18	<300	-	18
TR19, ACSI	19	>300	2.1	22
TR24, ACSI	24	>300	2.1	84
BEST25, BEST	25	400	-	50 (magnet)
Cyclone30,IBA	30	<1500	1.7	50
TR30, ACSI	30	>1000	1.9	56

TR30

KIUBE

BEST15

BEST25

TR19

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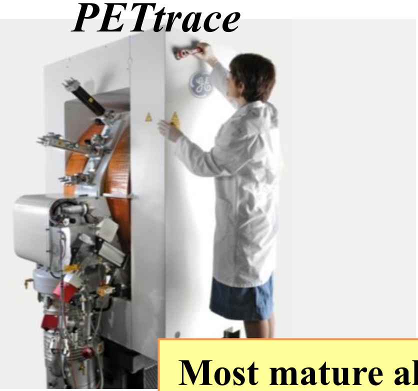

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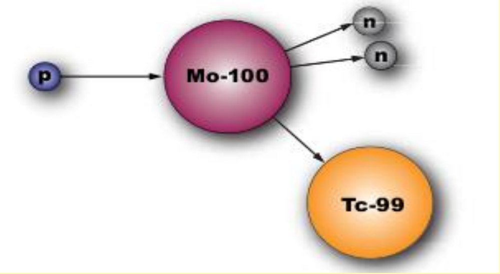
TR19, ACSI	19	>300	2.1	22
TR24, ACSI	24	>300	2.1	84
BEST25, BEST	25	400	-	50 (magnet)

KIU

Most mature alternative to ^{99m}Tc reactor-production:
^{100}Mo(p,2n)^{99m}Tc

- 16-24 MeV proton (optimum 20-24 MeV)
- Enriched ^{100}Mo solid target
- Many progress in the last years
  - development of suitable targetry
  - radiochemistry of target
  - target recycling
- product quality fully adequate for clinical use

→ short-term solution for ^{99m}Tc local distribution



F. Benard *et al, J Nucl. Med.*, 55(6), 1017-1022, 2014
O. Lebeda et al., Nucl. Med. Biol., vol. 39, p. 1286–1291, 2012
S. V. Selivanova et al., J. Nucl. Med. Vol. 56, p. 1600-1608, 2015

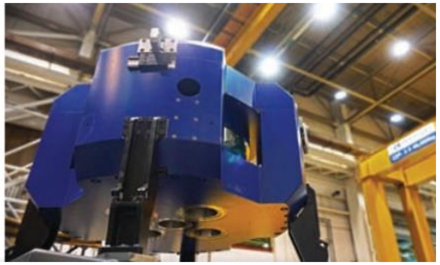
High energy cyclotrons

- High current production (~1 mA)
- Production: ^{82}Sr, ^{68}Ge, ^{67}Cu, ^{211}At, ^{47}Sc, ^{52}Fe, ^{55}Co and ^{76}Br, some therapeutic radionuclides
- Centralised production facility combined with a high potential for research
- Multi-particle acceleration
- Multiple beam lines
- Solid target capabilities

Still compact?

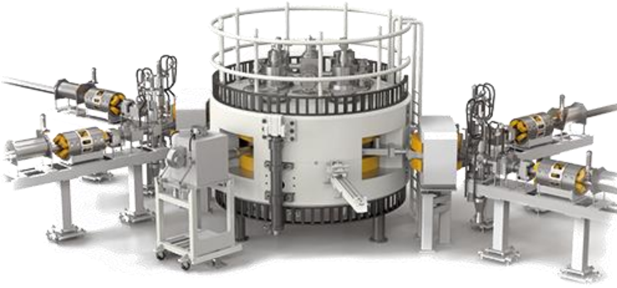
Cyclotron	E_p (MeV)	I_p (µA)	Peak B (T)	Weight (Tons)
MEDIUM ENERGY				
BEST35, BEST	35	1000	-	55 (magnet)
Cyclone70, IBA	70	<750	1.6	145
BEST70, BEST	70	700	1.6	195 (magnet)

BEST35



BEST70

CYCLONE70



Why using linacs for radioisotope production?

- ❑ Strong focusing allowing high current beams
- ❑ Limited radiation levels → reduced shielding
- ❑ High Frequency & Superconducting RF developments → compact, high power efficiency
- ❑ Ease of operation and limited maintenance
- ❑ Use of multipole target stations @ different energies

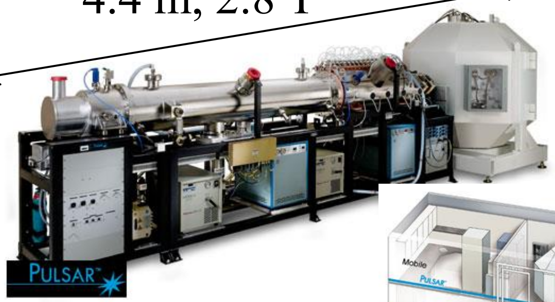
❑ Ion (p,d, alpha) linacs

❑ Electron linacs

Ion linacs for radioisotope production

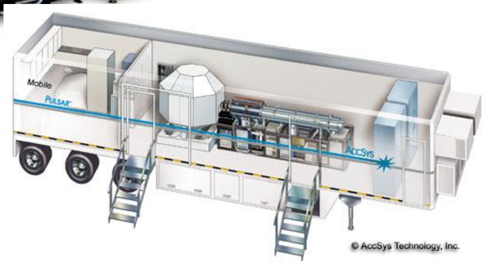
PULSAR®7 linac, by AccSys Technology Inc.

4.4 m, 2.8 T



- 7 MeV, 9 mA, 1% duty cycle p beam
- RFQ+DTL accelerator
- Low energy to reduce footprint, weight and cost
- Production: ^{18}F, ^{111}In, ^{13}N, ^{15}O, 1^{11}In, ^{123}I...
- Mobile PULSAR™ in medical trailers

http://www.accsys.com/pulsar.html



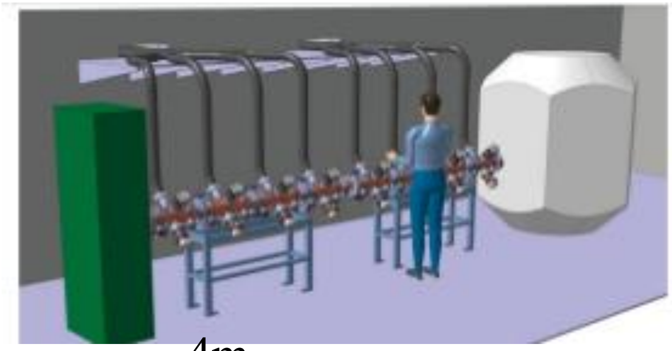
HF-RFQ, by CERN

- ➢ 750 MHz HF –RFQ resulting in short, low cost design
- ➢ Optimized beam dynamics simulations→ limited radiation
- ➢ Designed to minimize power consumption
- ➢ Reliable, limited maintenance
- ➢ PET: 2 RFQ modules, 10 MeV, 20 µA aveg. I, 4% duty cycle
- ➢ SPECT: 2 RFQ +DTL, 18 MeV, 1mA aveg. I, 10% duty cycle

Cern developing 'mini LHC' particle accelerator to treat cancer

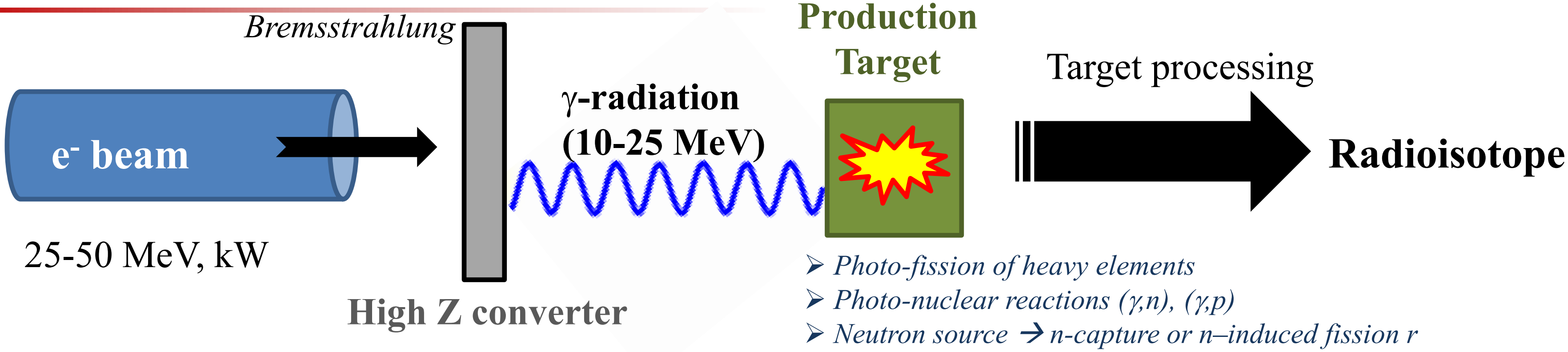
M. Vretenar et al., in Proc. LINAC2016, TH1A06.

PET production:



4m

Electron linacs



- *Photo-fission of heavy elements*
- *Photo-nuclear reactions (γ,n), (γ,p)*
- *Neutron source → n-capture or n–induced fission r*

Advantages

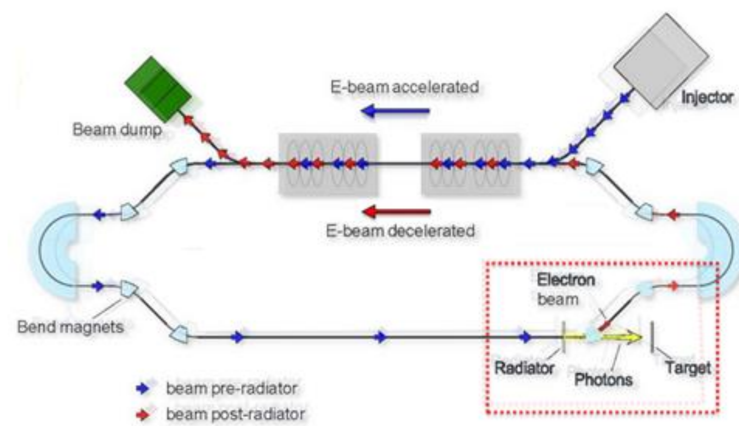
- High current machines
- Reliable, simple and compact (SRF cavities)
- Most cost-effective approach than hadron linacs
- Allows the use of thicker targets
- Fewer undesired isotopes and less radioactive waste

Disadvantages

- Lower cross-sections → need of high power e linacs and thick targets
- Careful design of electron-photon converter
- Activation
- Low Specific activity
- Energy inefficiency → ERL proposal

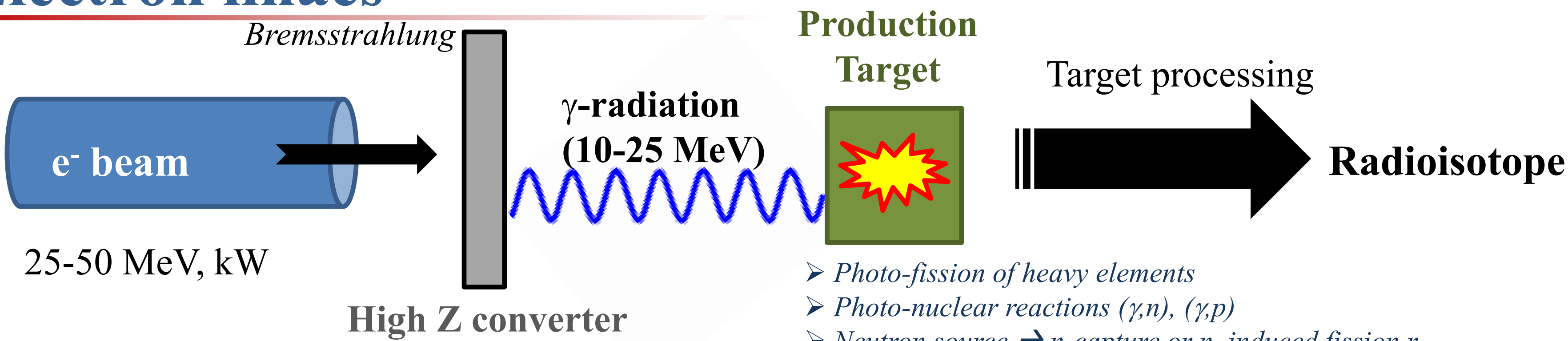
Novel ERL (Energy Recovery Linac) applied to e-linac for radioisotope production:

- ❑ Improvement of overall energy efficiency
- ❑ Reduced power at beam dump → less shielding
- ❑ Efficiency vs compactness



A. Sy *et al.*, "ERL-based technology for efficient production of high-value isotopes", IPAC2017, THPVA144

Electron linacs



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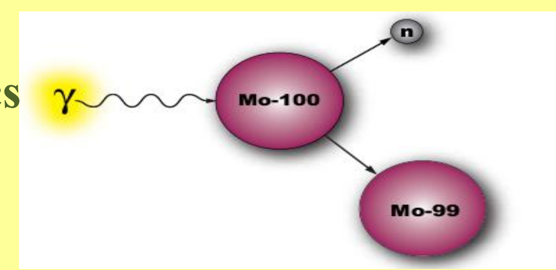
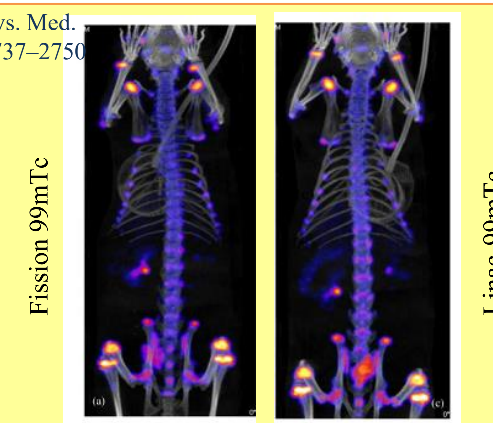
^{99}Mo production with e⁻-linacs



- ✓35 MeV, 40 kW e
- ✓Enriched Mo target
- ✓New 99Mo/99mTc generator for low SA Mo
- ✓Mo target recycling

R. Galea et al, Phys. Med. Biol. 58 (2013) 2737–2750



Electrostatic machines

ONIAC (Siemens)

❑ Novel, compact DC electrostatic accelerator for radionuclide production

❑ Features

-Variable energy up to 10 MeV

-Currents up to few mA

-Compact design footprint 2x2 m^2

- Multiple beam lines

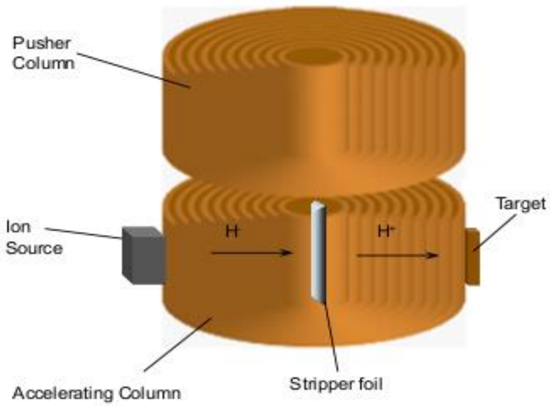
- High energy efficiency

- Low machine radio-activation

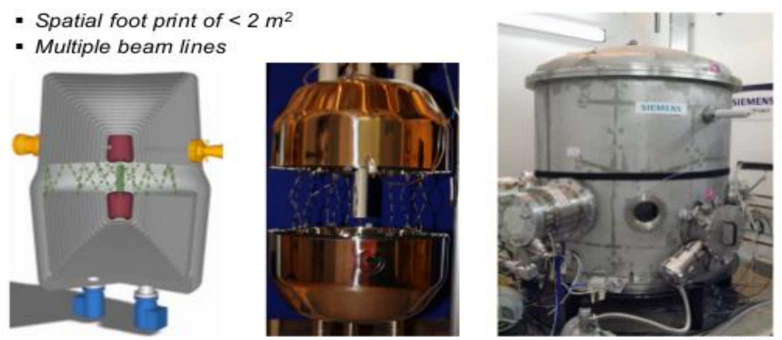
- Robustness

- Low total cost

❑ ONIAC short-lived PET production



Svetlana Gossmann-Levchuk/ Corporate Technologies

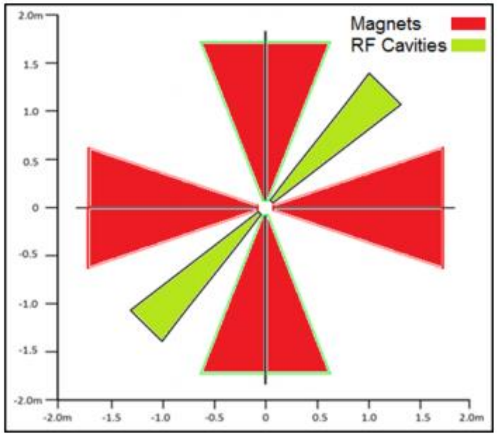


P. Beasley et al., IPAC 2011, TUPS079

Other promising alternatives...

❑ FFAG

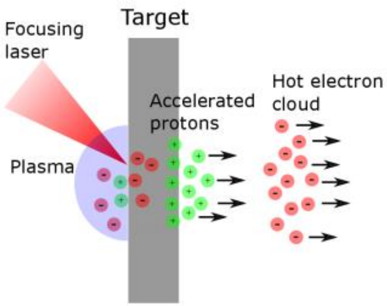
- Novel FFAG application (University of Huddersfield)
- Sector magnet with non-scaling, non-linear field gradients
- Isochronism at 0.3% level, CW operation, 20 mA
- 28 MeV for ^{99m}Tc and other new isotopes
- Compact design (maximum magnet radius 1.7 m)
- Thin internal target placed directly in the machine to improve production efficiency and reduce shielding



D. Bruton,., IPAC2016, TUPOY023
D. Bruton et al., IPAC2017, TUPVA133, this conference

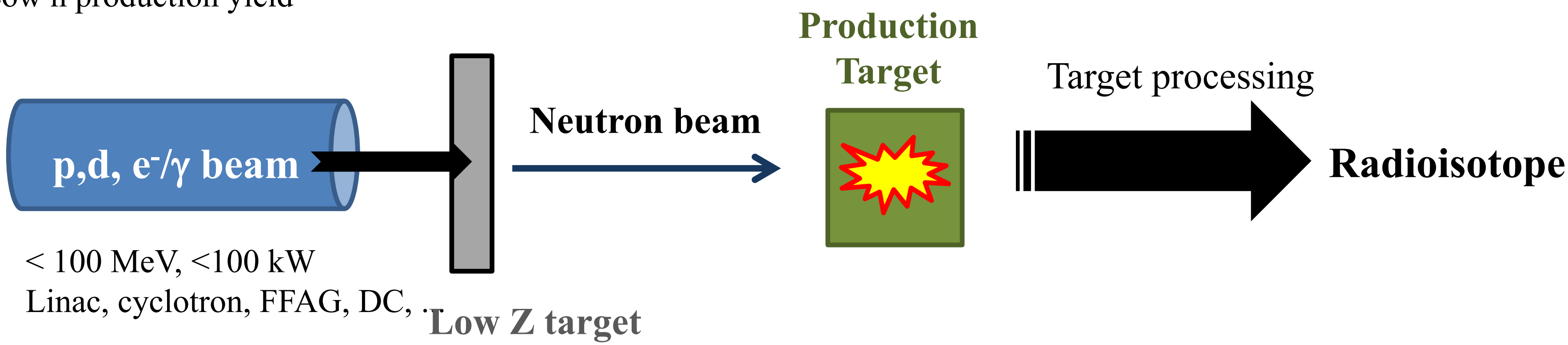
❑ Using lasers

- Use of high-peak power laser for isotope production based on (γ,n) ad (γ,p) reactions
  - Simulation of ^{99}Mo/^{99m}Tc, ^{225}Ra/^{225}Ac, ^{186}Re using high brilliance γ-beam of ELI-NP *W. Luo, Appl. Phy. B, p. 122:8, 2016.*
- Use of MeV p, produced by PetaWatt laser beam interacting with solid targets, for isotope production based on p direct reactions *K.. Ledingham et al., J. Phys. D: Apply. Phys. 37, 2004.*
- Table-top TW laser proposals *M. Seimetz et al., Journal of Instrumentation, vol. 11, 2016.*



Neutron sources

- ❑ Neutrons are widely used for radioisotope production
- ❑ Compact Accelerated-Neutron Sources (CANS) as alternative to spallation sources
- ❑ Use of compact accelerators and target systems with modest shielding (reduced cost)
- ❑ Relatively (compared to spallation sources) inexpensive to build and operate
- ❑ Low n production yield



Multipurpose facilities:

- iThemba in South Africa (25-200 MeV p separated cyclotron)
- KOMAC in Korea (50 MeV cyclotron),
- KURRI-Linac at Kyoto (30 MeV, 6 kW electron linac).
- GRAND (2 mA deuteron, 40 MeV cyclotron) to produce ^{100}Mo(n,2n)^{99}Mo reaction using **fast** (14 MeV) neutrons (C target)
- SHINE D-T generator in a subcritical hybrid system
- LANSAR®, by ACCSYS company, based on p,d linac with a Be target

http://www.accsys.com/lansar.html

Conclusion

Million $ question:

optimum accelerator for Radioisotope Production?

- Availability of accelerators with high performance combined with miniaturized solutions, providing a wide range of accelerator solutions to ensure a reliable radioisotope supply
- Cyclotrons are by far the most mature technology for on-demand production
- Novel compact linacs solutions emerge as an alternative to cyclotrons
- Electron linacs offer a mid-term solution for 99mTc
- Application of "Novel" accelerators to radioisotope production seems promising
- Remember: not only development on accelerator, but (mainly?) in target, radiochemistry, target recycling
- Important: analysis of full solution cost to analyze its viability for cost-effective radioisotope production

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- ❑ Cyclotron … on
- ❑ Novel co…

Thank you !!!

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