Production of radioisotopes for medical applications

Thierry.stora@cern.ch

Did you say ? (topics to be covered)

Production

of medical

radioisotopes

Detailled structure of the course

PART 1 - General topics

- Introduction – potassium
- Medical use of radioisotopes:
  - Imaging, diagnostics
  - Treatment
  - Physical and biological properties
- Production:
  - Reactions
  - Targetry
  - Radiochemistry
  - Radioprotection

PART 2 – Adv. concepts

- Advanced accelerator concepts:
  - Neutron production at cyclotrons
  - ADS Myrrha
  - ESS
  - Harvesting at FRIB
- Radioactive Ion Beams:
  - Purification by mass separation
  - Hadron therapy with PET isotopes

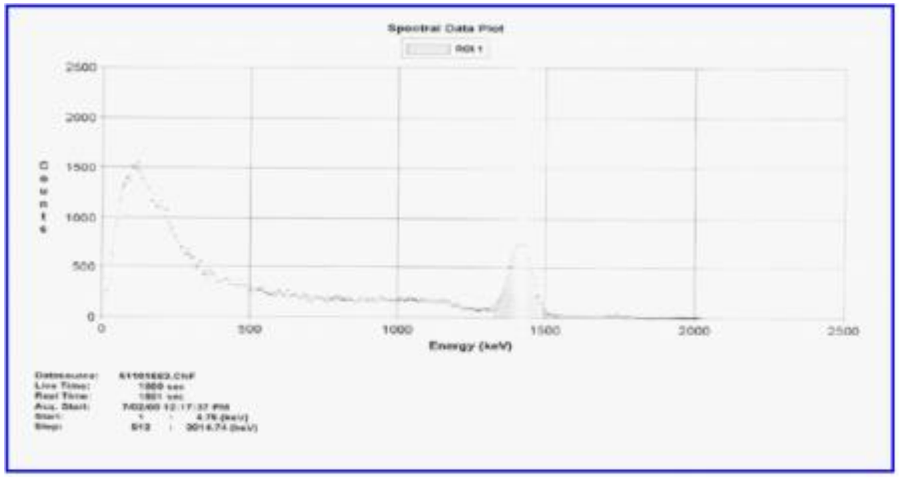
Radioisotopes in biological organisms

Daily, we “internalize” radiomarkers with rather well defined protocols

evian
Natural Spring Water

Country	France
Source	Évian-les-Bains
Type	still
pH	7.2
Calcium (Ca)	80
Chloride (Cl^-)	6.8
Bicarbonate (HCO_3)	360
Magnesium (Mg)	26
Nitrate (NO_3)	3.7
Potassium (K)	1
Silica (SiO_2)	15
Sodium (Na)	6.5
Sulfates (SO)	12.6
Website	http://www.evian.com

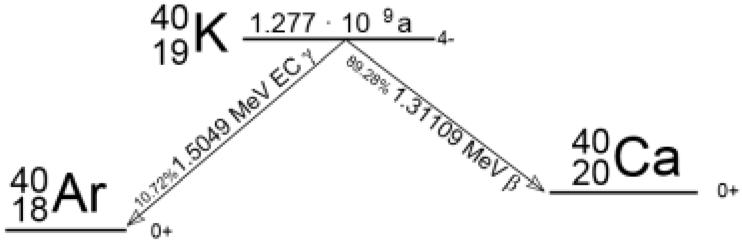
All values in milligrams per liter (mg/l)



M Goma et al

^{40}K, a radioisotope “bio” for imaging and treatment ?

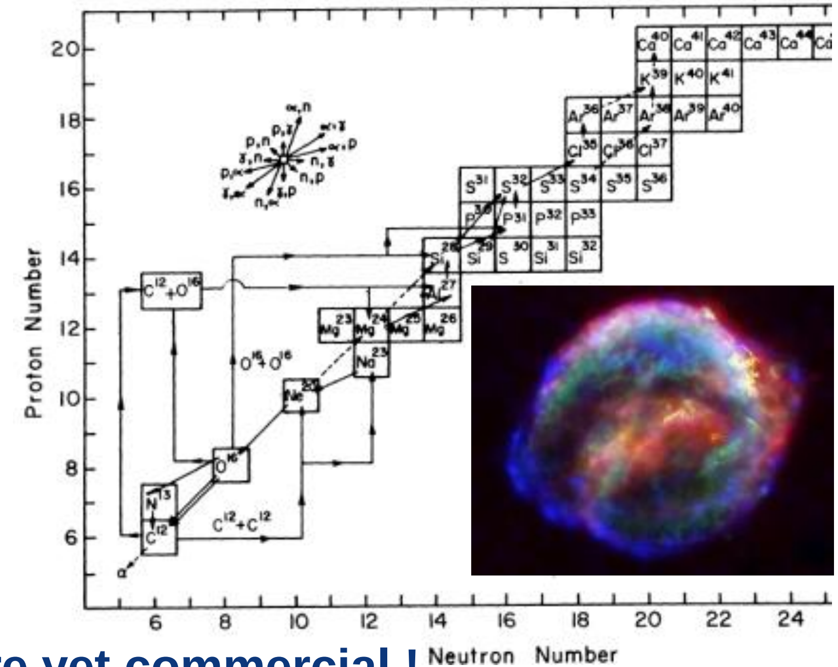
There is ~0.01% natural ^{40}K on Earth
Our whole body natural activity
is of ca 4 kBq (0.2 mSv/year)



<u>Method of production</u> :

Neutron capture s-process
in stars ^{39}K(n,γ)^{40}K

Nucleosynthesis in supernovae explosion
12C+16O→X, etc



But none of these production sites are yet commercial !

S. Woosley, Astrophys j

Medical use of radioisotopes

The early days

Published:
May 12th 1921
© The New York Times

The New York Times.

"All the News That's Fit to Print."

THE WEATHER

MME. CURIE PLANS TO END ALL CANCERS

Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.

Courtesy prof O. Ratib

Probably a few GBq open source of $^{223/224}$Radium there

And today

Xofigo has been approved by the FDA (Food Drug Administration) and in Europe for castration resistant prostate cancer with metastasis

1921

How is this image done?

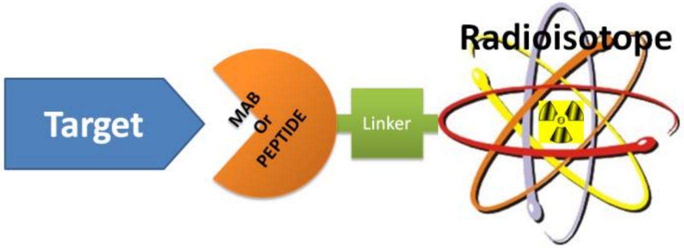
2015

Courtesy prof O. Ratib

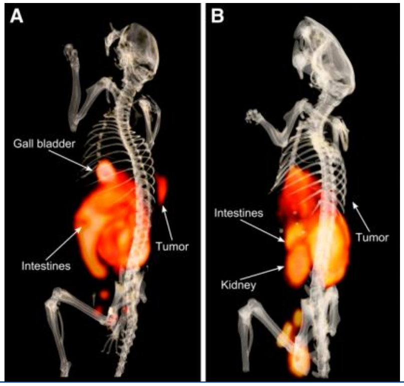
Functional or molecular imaging

Injection of a bioligand

Targeting desired tissue

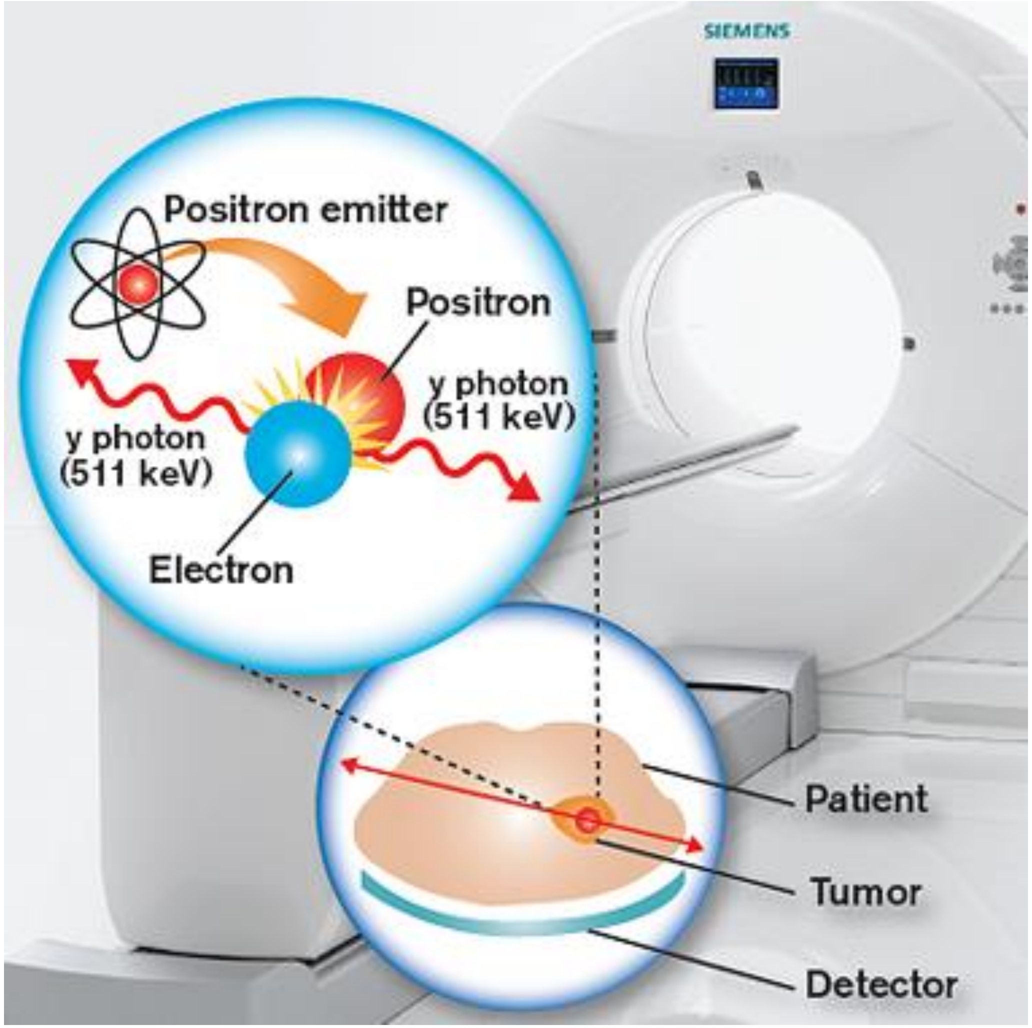


Imaging by emission of radiation
Through radioactive decay
(γ photons
511keV photon from β^+e^- anhilation)



I. Dijkgraaf et al., JNM 53, 947 (2012)

PET scan imaging



List of some PET isotopes

Nuclide	Half-life (min)	Decay mode	Maximum energy (MeV)	Mean energy (MeV)	Max. range (mm)	Max. SA (theoretical) (Ci/μmol)[a]
C-11	20.4	100% β^+	0.96	0.386	4.1	9 220
N-13	9.98	100% β^+	1.19	0.492	5.4	18 900
O-15	2.03	100% β^+	1.7	0.735	8.0	91 730
F-18	109.8	97% β^+	0.69	0.250	2.4	1 710
Cu-62	9.74	99.7% β^+	2.93	1.314	14.3	19 310
Ga-68	68.0	89% β^+	1.9	0.829	9.0	2 766
Br-75	96.0	75.5% β^+	1.74	0.750	8.2	1 960
Rb-82	1.25	95.5% β^+	3.36	1.5	16.5	150 400
I-122	3.62	75.8% β^+	3.12	1.4	15.3	51 950
I-124	6019.2	23.3% β^+	2.13	0.8	10.2	31

SPECT : ^{99m}Tc is the principal radioisotope


nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | Fo

Archive > Volume 504 > Issue 7479 > News Feature > Article

NATURE | NEWS FEATURE

Radioisotopes: The medical testing crisis

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

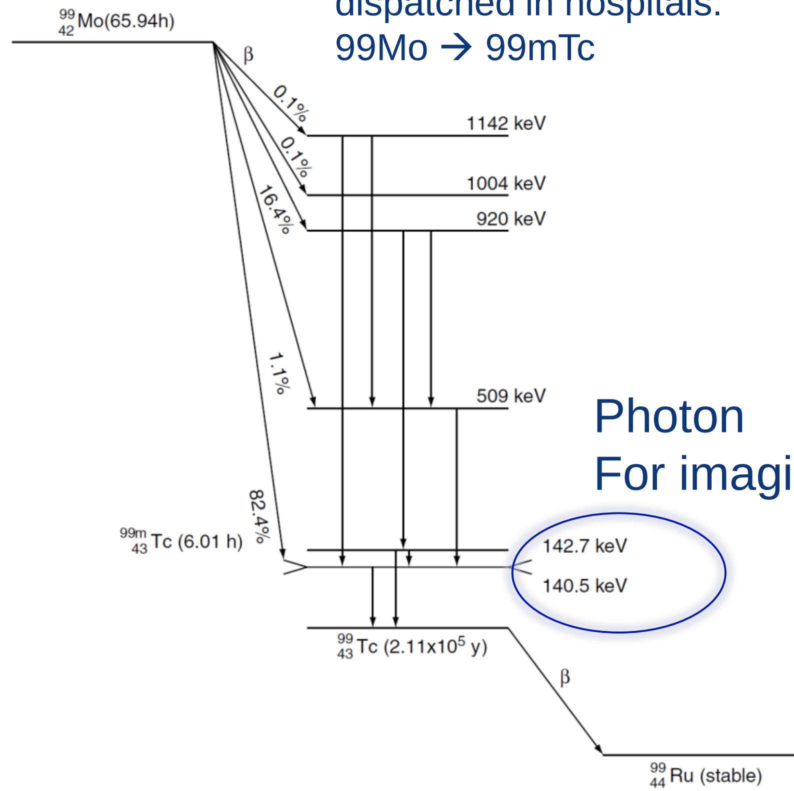
^{99}Technecium supply shortage

(10’000 scintigraphy protocols /Mi US residents/year)

a

ap.

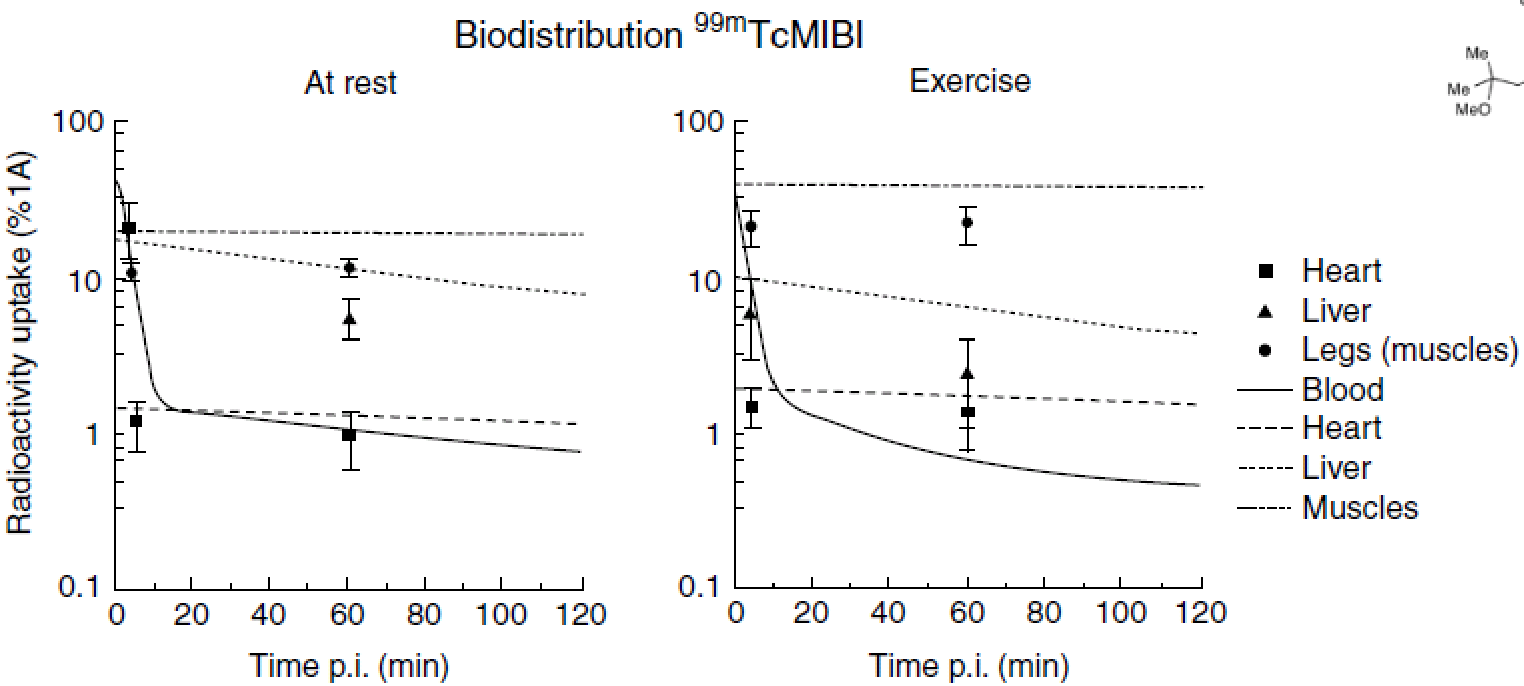
So called generators can be dispatched in hospitals: 99Mo → 99mTc

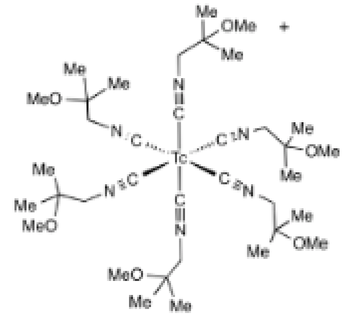


Photon For imaging

Pharmacokinetics vs isotope $T_{1/2}$

- ^{99m}Tc MIBI myocardial perfusion ($T_{1/2}$ = 6h)



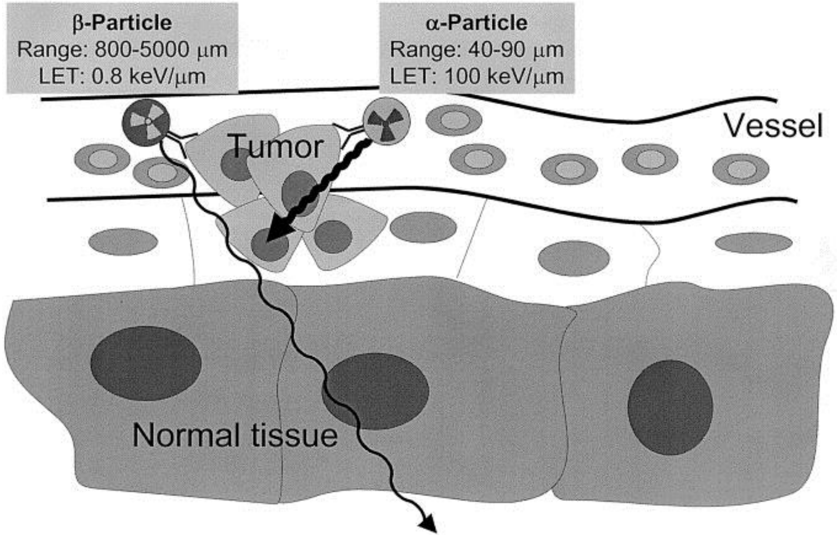


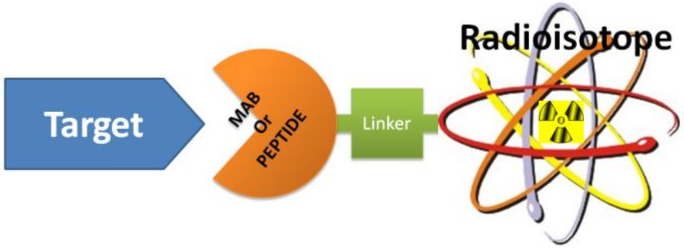
^{99m}Tc MIBI

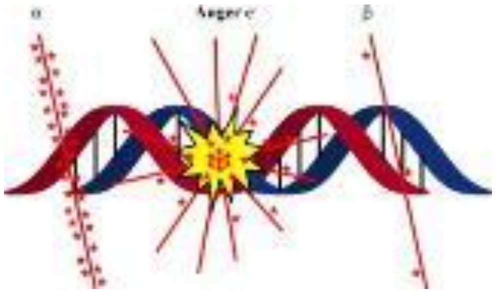
M. Konijnenberg,
99mTc sestamibi 2012

Targeted internal therapy

This is moving and localising several isotope sources close to the tissue to be treated





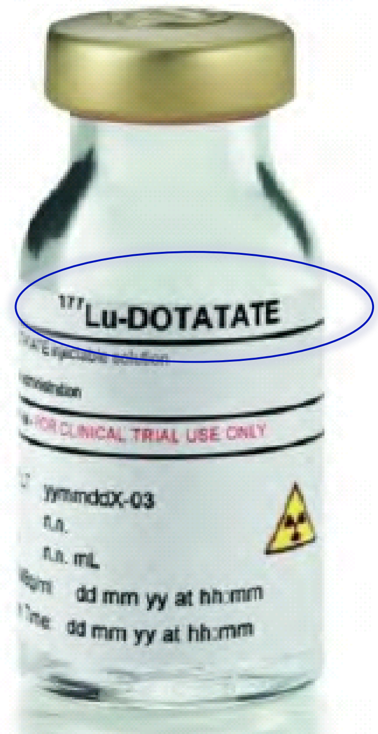


Already seen for imaging (slide # ?)

Targeted internal therapy

Lutathera®

- Phase II results in progressive midgut carcinoid showed Progression-Free Survival of more than 44 months compared to the reported 14.6 months of Novartis' Sandostatin® LAR
- Lutathera® was shown to increase overall survival by between 3.5 and 6 years in comparison to current treatments, including chemotherapy.
- It was also shown to significantly improve quality of life



Courtesy Prof. Ratib

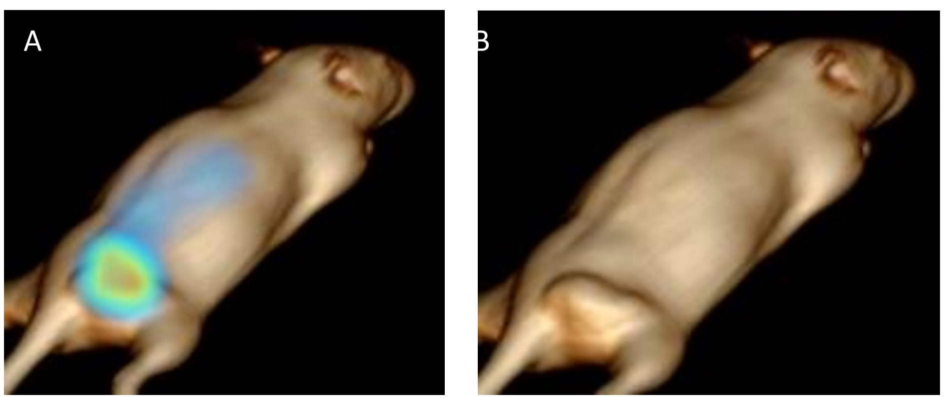
Theranostic pairs

It combines a pair of isotopes, one for imaging and the other for therapy

Ideally with the same bioconjugate

And even more ideally, with 2 radioisotopes of the same chemical element

This leads to an ideal protocol for personnalized medicine :
the radiopharmaceutics dose can be adjusted
and the efficacy of the treatment followed.

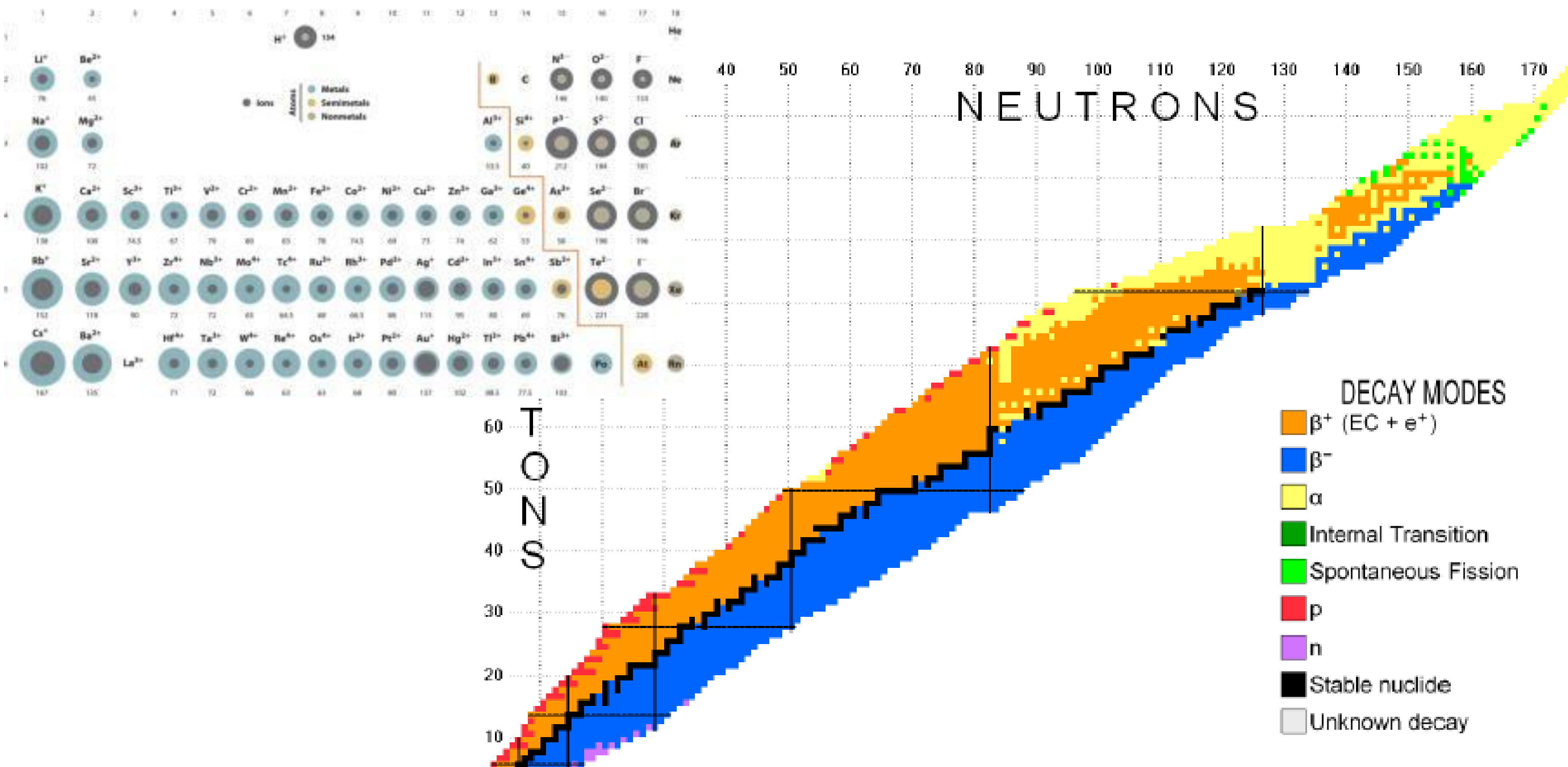


C 177Lu-DOTA-RM6 radiopeptide targetting grafted “PC3” prostate cancer cells in mice

F. Bucchegger et al.

Production of medical radioisotopes

Which radioisotopes do we need ?

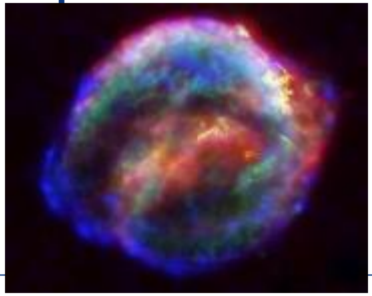


While there are a few “blockbusters” (^{99m}Tc, ^{18}F)
and some other emerging (^{177}Lu, ^{223}Ra)
There is room/need for even **better suited new radioisotopes along with their production**

What accelerator to produce which isotopes ?

- (p,n), (p,2p), (p,α), (p,X), (p,αn), etc… p^+ A/q=1
- (d,n), (d,p), etc… d^+ A/q=2
- (^{3}He,n), (^{3}He,α), etc… $^3He^{++}$ A/q=1.5
- (α,n), (α,2n), (α,p), etc… α^{++} A/q=2
- (^{7}Li,Xn), etc … Li^{++} Li^{+++} A/q=3.5, 2.33
- (n,γ), (n,2n), (n,p), etc… n^0 A/q=0

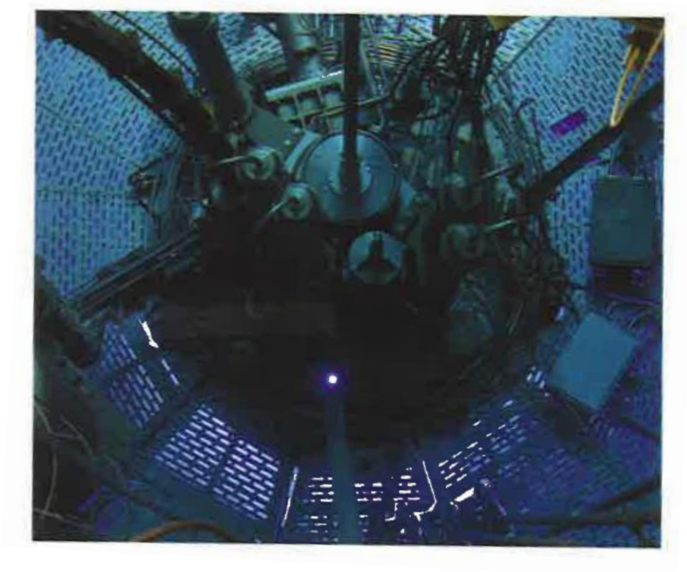
- And we need accelerators, facilities, concepts better suited than explosive supernovae



Classical medical isotope production methods

The most common methods :

At medical cyclotrons (p/d/α,X) 9-70MeV



At nuclear reactors (n,X)

More prospective : compact Linacs,
Heavy ion cyclotrons, high energy p drivers

Regulation of radiopharmaceuticals : Swiss example

swissmedic

Fabrication du radionucléide :

Les **<u>réactions nucléaires employées</u>**…la **<u>demi-vie</u>**, le type et l'énergie du **<u>rayonnement</u>** ainsi que les **<u>effets perturbateurs engendrés par les impuretés</u>**.

Nucléides obtenus par bombardement de cibles : matériau cible et enveloppe de la cible :
- composition, forme chimique, pureté chimique, état physique et additifs chimiques éventuels, susceptibles d'influer sur le produit
- méthode d'irradiation, environnement physique et chimique (support de la cible)
- rendement

Nucléides produits par fission :
Il convient d'indiquer l'ensemble de la chaîne de nucléides, de la matière première initiale (impuretés comprises) jusqu'aux nucléides filles stables correspondants, y compris la demi-vie, le type et l'énergie du rayonnement. Les effets perturbateurs provoqués par les impuretés ou la matière première doivent être discutés.

Traitement du radionucléide :
- description détaillée de l'isolation (séparation de la cible) et de l'enrichissement du radionucléide souhaité ; rendement.

Propriétés physiques du radionucléide :
Il faut indiquer en détail la demi-vie, le type et l'énergie du rayonnement ainsi que l'évolution dans le temps à compter de la fabrication du radionucléide et jusqu'à la date d'expiration du médicament ainsi que les aspects importants pour l'élimination.

Contrôle du produit fini :
- identité des nucléides
- pureté des nucléides
- pureté radiochimique
- pureté chimique
- activité spécifique

Ident. QM : ZL000_00_003f_WL / V01 / bg, stb, cas / zro / 01.04.2015

Regulation of radiopharmaceuticals : Swiss example

Fabrication :
Used nuclear reaction - isotope half life
Radiation type and energy
Pertubation induced by impurities

Nuclides produced by target irradiation
Target material, target envelop
Composition, chemical form, purity, physical state,
Chemical additives, capable to impact the end product
Irradiation method, physical and chemical environment
Target support
Yield

Nuclide treatment
- Description of isolation (separation from the target), nuclide concentration, yield.

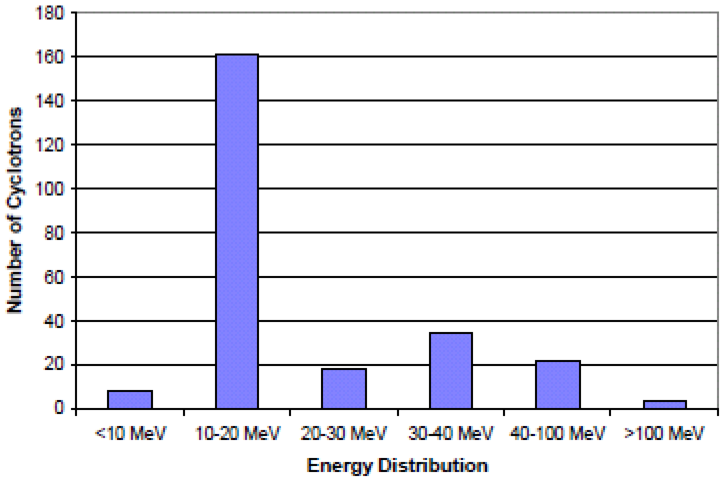
Physical properties of nuclides
In detail : half life, type and energy of radiation, evolution over time from the fabrication to the date of peremption of the drug, important aspects for disposal

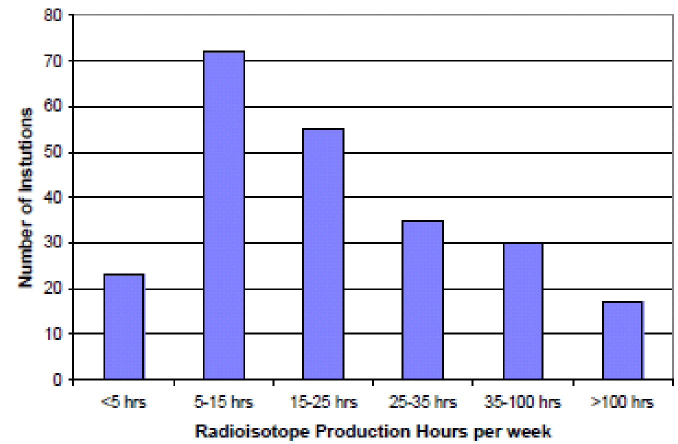
Nuclides from fission
Full nuclide reaction chain, initial material (including impurities), daughter nuclides, half lifes, radiation type and energy
Pertubation from impurities

End product control
- identité des nucléides
- Nuclide identity
- Purity of nuclides
- Radiochemical purity
- Chemical purity
- Specific activity

Ident. QM : ZL000_00_003f_WL / V01 / bg, stb, cas / zro / 01.04.2015

Cyclotrons: distribution in the world





Typical 1-20kW power

IAEA-DCRP/2006

Increasing T1/2

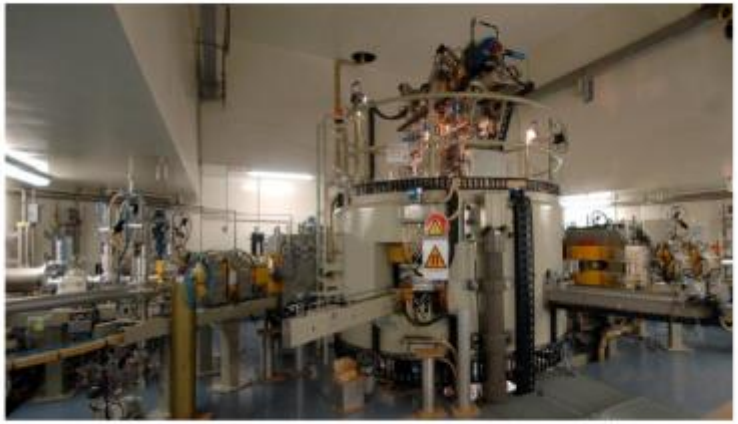
T. Sounalet, ARRONAX

One example : cyclotron in France
For FDG (^{18}F PET isotopes, $T_{1/2}$ = 2 hours)

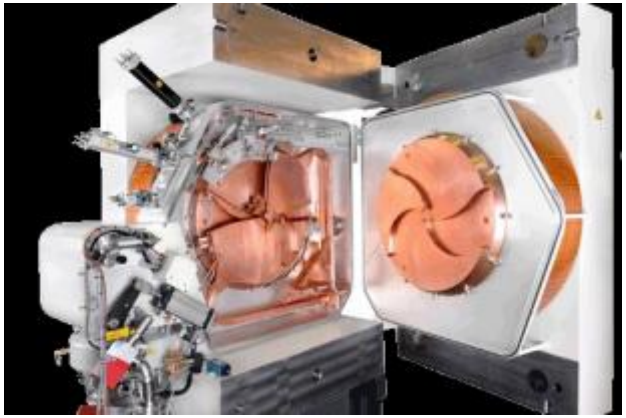
Notion of distance between production center, end-user, and istope $T_{1/2}$

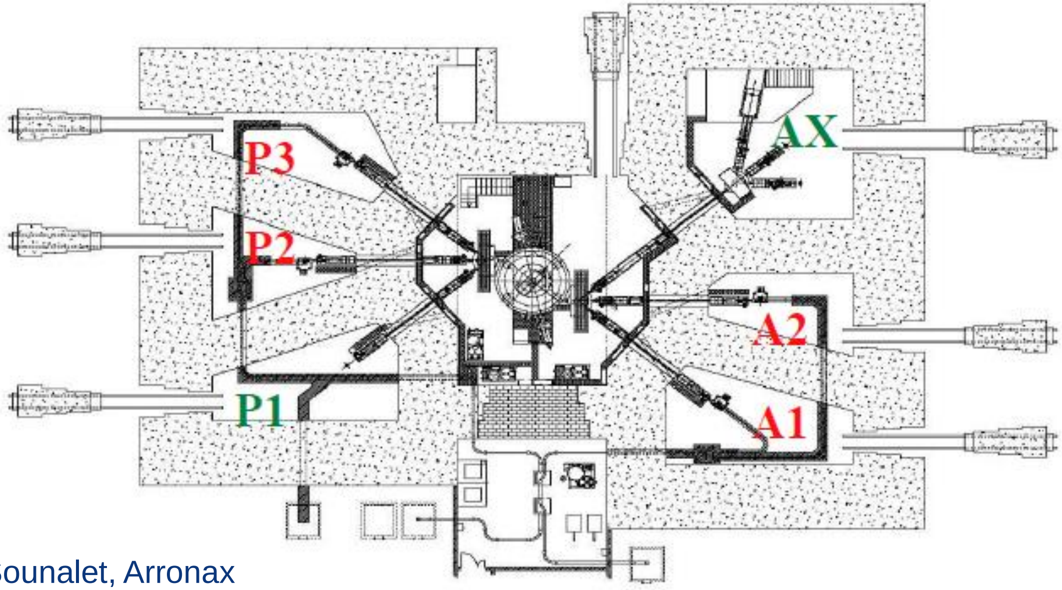
70 MeV p,d,α 35kW vs ~10 MeV p 1kW cyclotrons

IBA cyclotron at ARRONAX



PET trace series of General Electrics



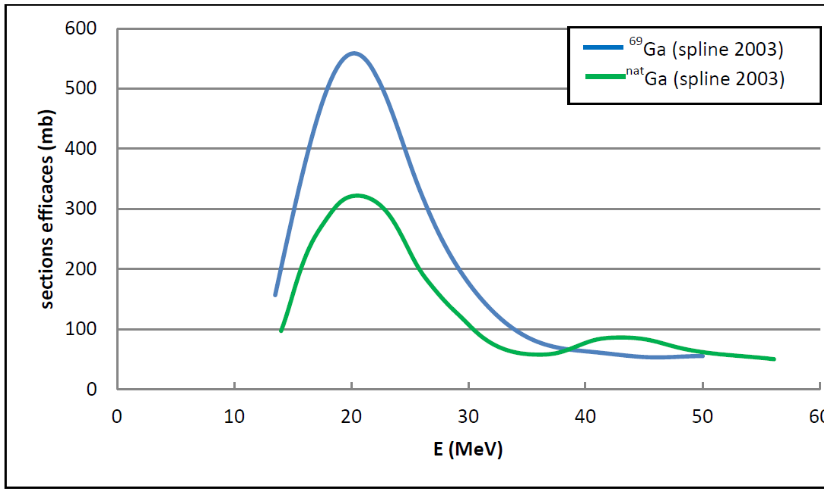


T. Sounalet, Arronax

M. Jensen, RISO

What machine to produce a given medical isotope ?

1st information to consider : excitation function
This is the cross section vs energy of incident particle



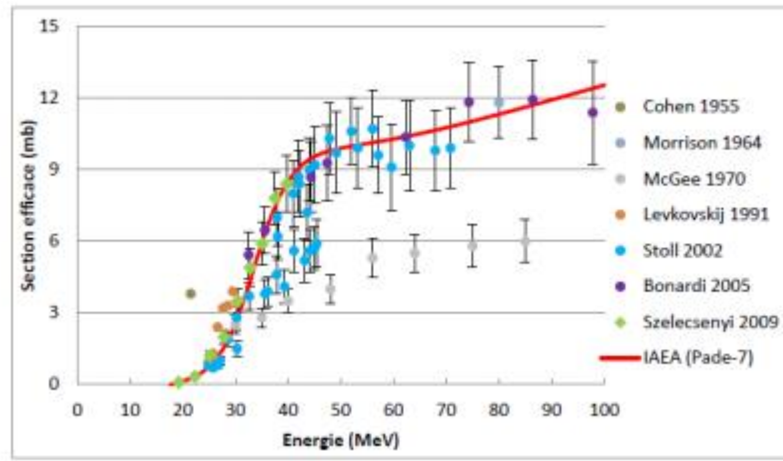


Figure 1.6- Sections efficaces de production $^{68}Zn(p,2p)^{67}Cu$

$^{69}Ga(p,2n)^{68}Ge$ ou $^{nat}Ga(p,x)^{68}Ge$

With protons

mais son coût est très élevé : 5.6 euros par mg (soit 56000 euros pour 10 g de gallium enrichi en 69) par opposition au gallium naturel qui revient à 284 euros pour 10 g de gallium avec une pureté (99.999%). Il faudra faire à un moment le choix du gallium utilisé et trouver le meilleur compromis entre le prix de revient de la cible et le rendement de production du ^{68}Ge. Il faut aussi faire intervenir comme élément de choix de la présence d'impuretés additionnelles non voulues provenant du ^{71}Ga dans le cas d'une cible en ^{nat}Ga.

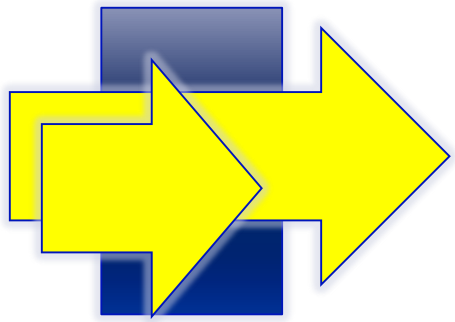
From excitation function to production rate

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

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

R [Bq] = Iλ**/(1-**λ**) = I** for 5 $T_{1/2}$ (λ=0.606/$T_{1/2}$) **saturation activity**

Incident particle
Beam intensity

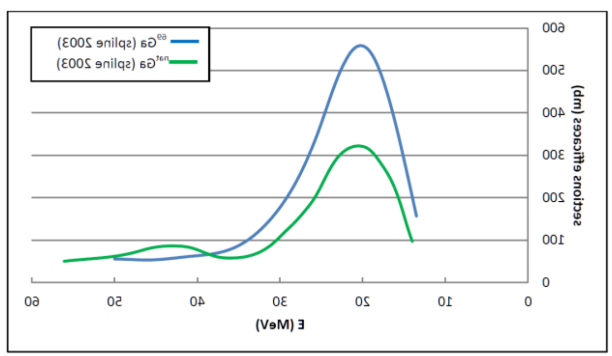


Bragg peak possibly
in a dump

Target thickness

An individual dose

For imaging is ~100`s MBq
For treatment ~ 1 GBq



Optimization vs production and contamination

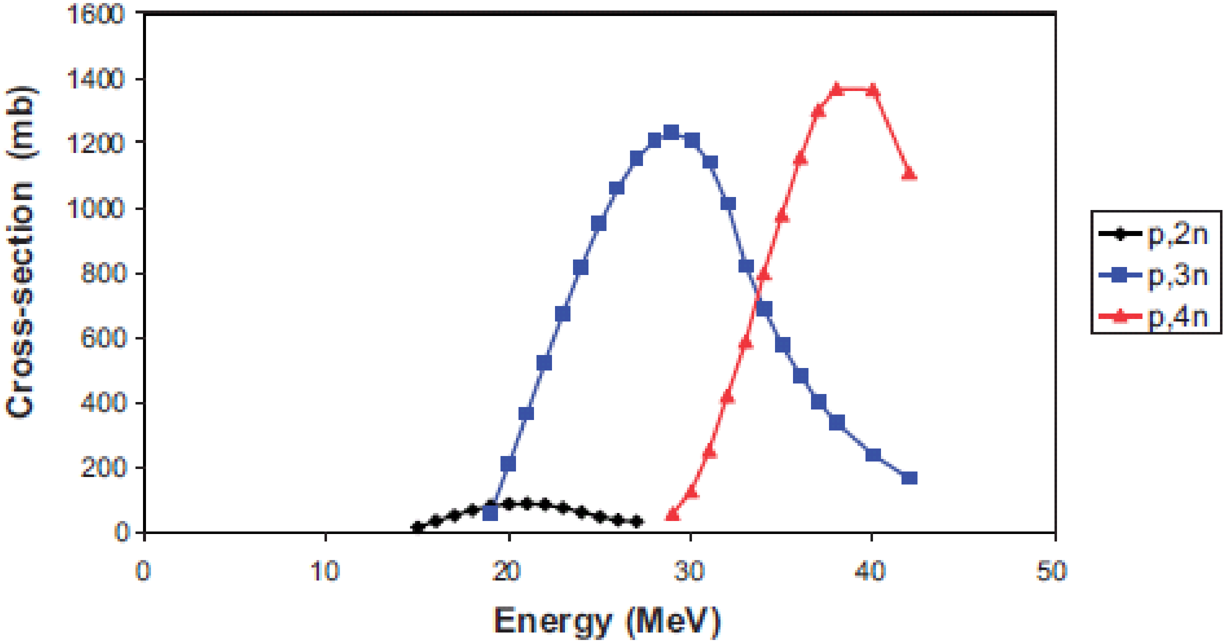


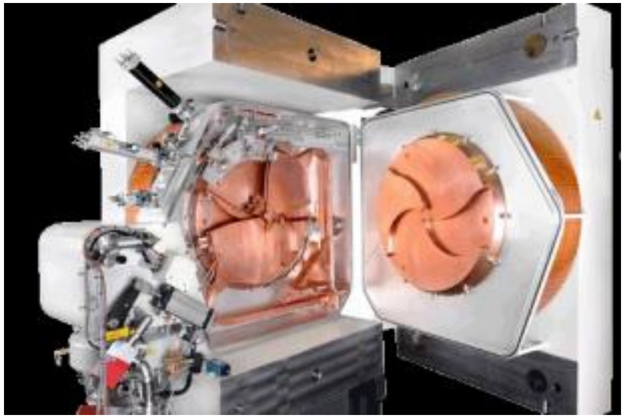
FIG. 5.21. Cross-section versus energy plot for the ^{203}Tl(p, 2n)^{202}Pb, ^{203}Tl(p, 3n)^{201}Pb and ^{203}Tl(p, 4n)^{200}Pb nuclear reactions.

General nuclear data: http://www.nndc.bnl.gov/
Cross sections neutrons: ENDF : http://www.nndc.bnl.gov/exfor/endf00.jsp
Cross sections p,d,α, etc : 0-200MeV TALYS/TENDL http://www.talys.eu/tendl-2014/
Multipurpose MC code. Dosimetry, production : Fluka http://www.fluka.org
Tools for nuclear data (decay, shielding, etc): http://www.nucleonica.com/

Linacs vs. cyclotrons

	Principle	Operation	Focusing	Extraction	Beam quality	RF power	Cost	Maintena nce
CYCLOTRON	Cyclic (magnet based)	CW	Weak	Lossy	Average	**Low**	**Low**	Higher
LINAC	Linear (RF based)	Pulsed	**Strong**	**Clean**	**Good**	High	High?	**Lower**

From Linac 4, 20MeV
352 MHz
1 RFQs + 2 DTL tanks
Source W = 45 KeV
L = 12 m
Output W = 20 MeV
Average current = 10 mA
Peak current = 100 mA
Duty cycle = 10 %
2 klystrons @ 352 MHz



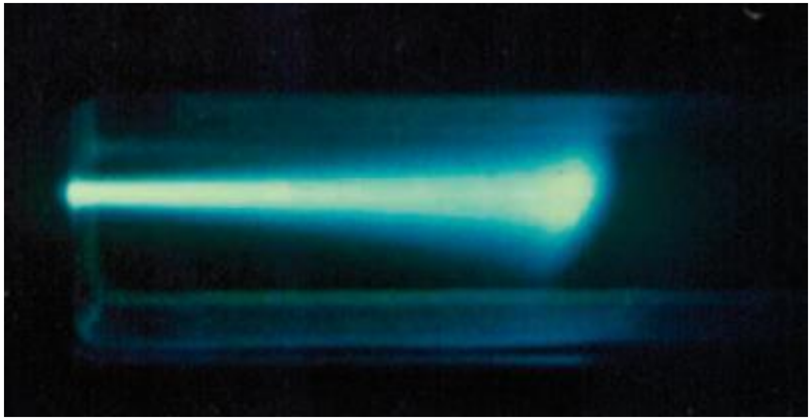
GE PET Tracer

Adapted from M. Vretenar, CERN

Targets (production, not biological !)

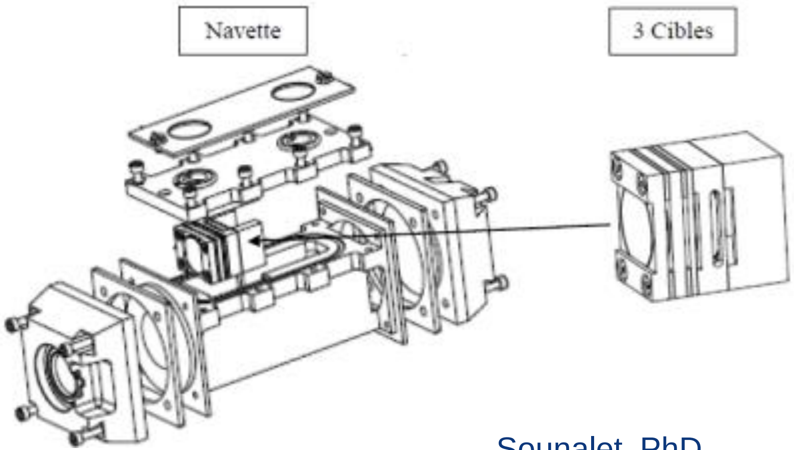
- Main functions of production target:

- nuclei and beam interaction
- confine isotope production
- provide heat dissipation
- perform chemical reactions



Gas target IAEA, trs465

(ie N_2 + trace of O_2 for $^{14}N(p,\alpha)^{11}CO_2$)



Sounalet, PhD

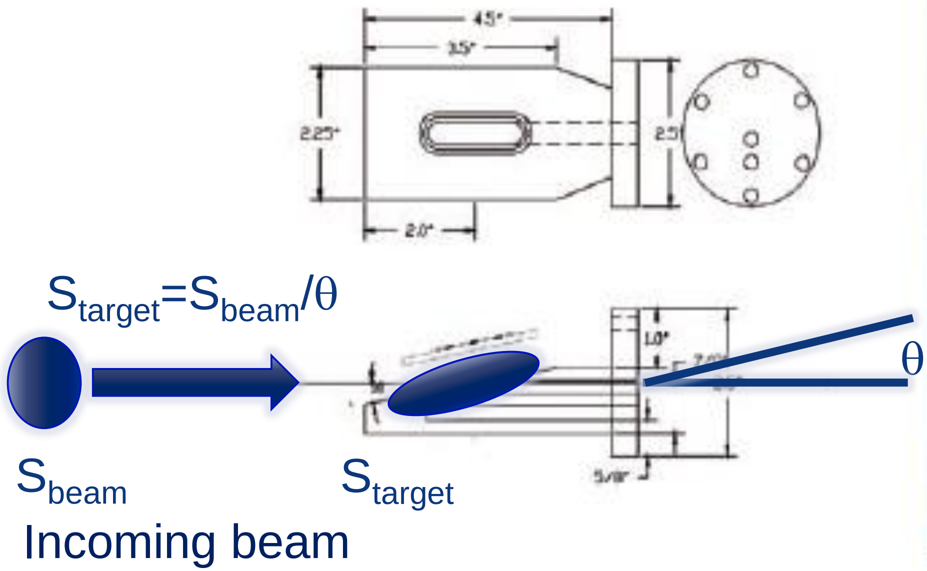
Solid target

(RbCl for ^{82}Sr, Ga_3Ni_2 for $^{68}Ge/Ga$)

Liquid target ($H_2{}^{18}O$ for ^{18}F)

AccSys, IAEA trs465

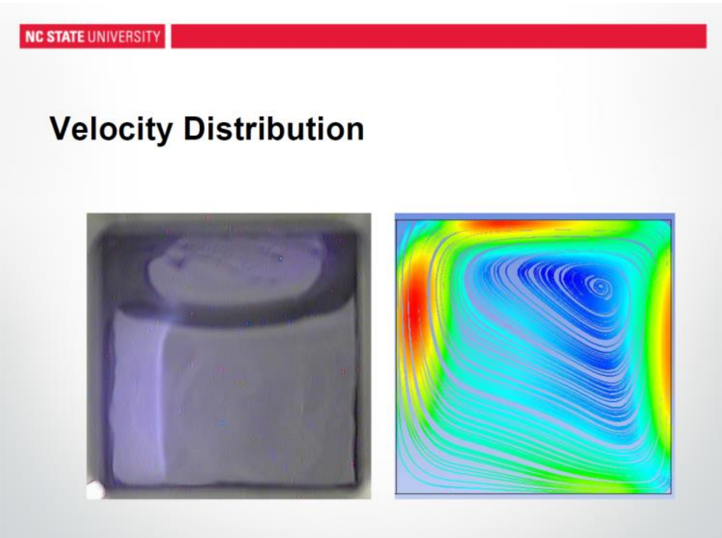
Heat management : tilted target design

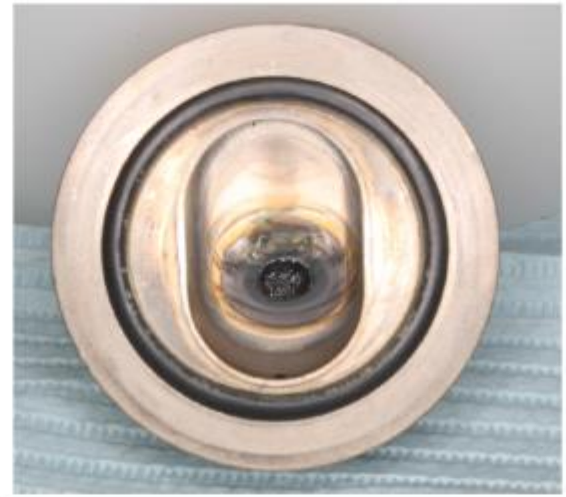


Tilted target to distribute the beam heat deposition
And heat exchange surface area

Heat exchange : by contact/convection $Q=kc \times \Delta T \times S_{target}$
by radiation $Q=kr \times (\Delta T^4) \times S_{target}$

Heat (mis)management and beam delivery aspects

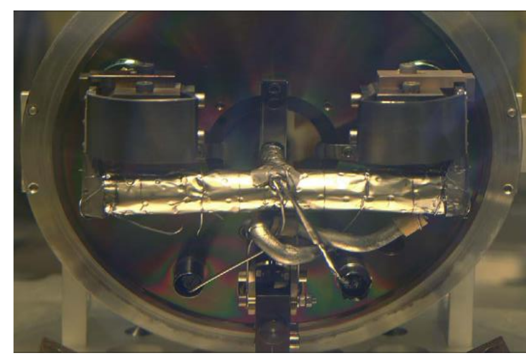




M. Stokely, BTI Targetry

https://youtu.be/p3sjf7ZMPZQ

Pulsed p beam on Tantalum bar
from 1.4GeV Proton Synchrotron Booster
Instant power : > 1GW !
J. Lettry, CERN

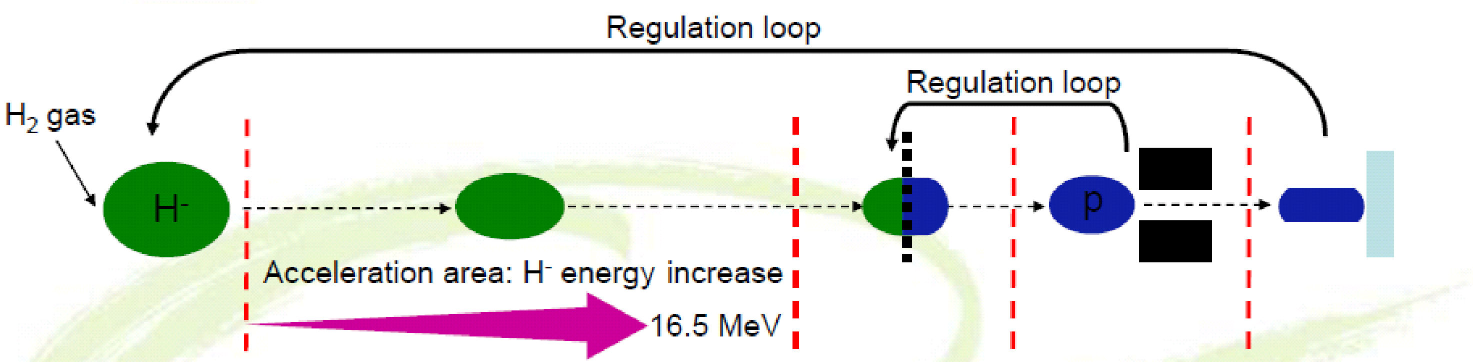


Principle of beam regulation, diagnostics

BRIDGING SCIENCE WITH LIFE

Advanced Accelerator Applications

Proton beam generation principle:



Ion source:

H⁻ generation:

$H_2 \rightarrow H^-$

RF cavities:

H- ions extraction from IS (Puller)

H⁻ ions acceleration

Extraction:

$H^- \rightarrow P$

Beam position

Collimators:

Beam shape

Target:

Beam regulation

Magnetic field (B):

IS plasma generation

H⁻ ions trajectory driver

RF stability (avoid spark avalanche effect)

Vacuum:

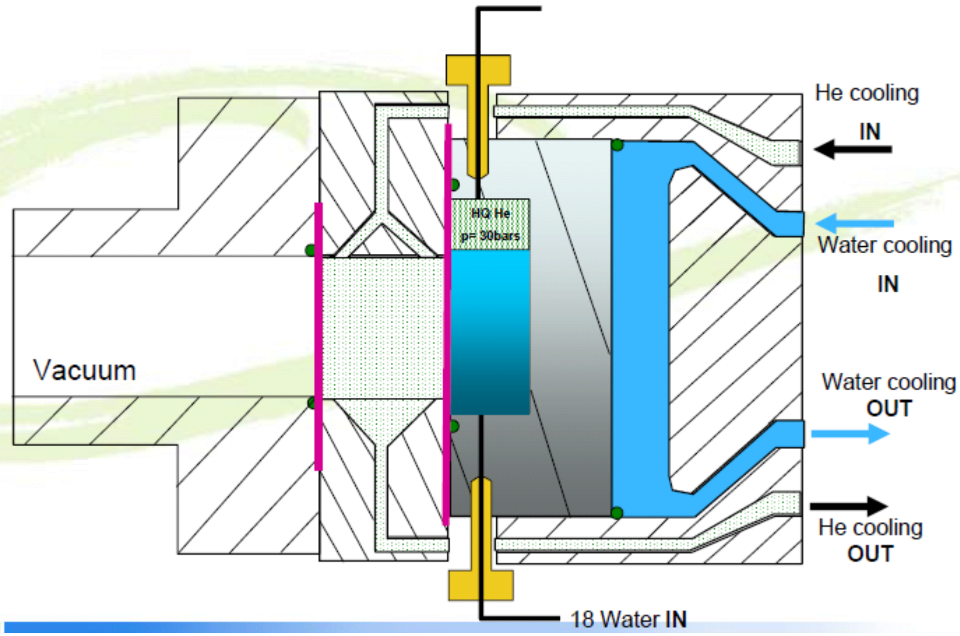
Electrical isolation (40kV)

Reduce interactions: H⁻, P / environement

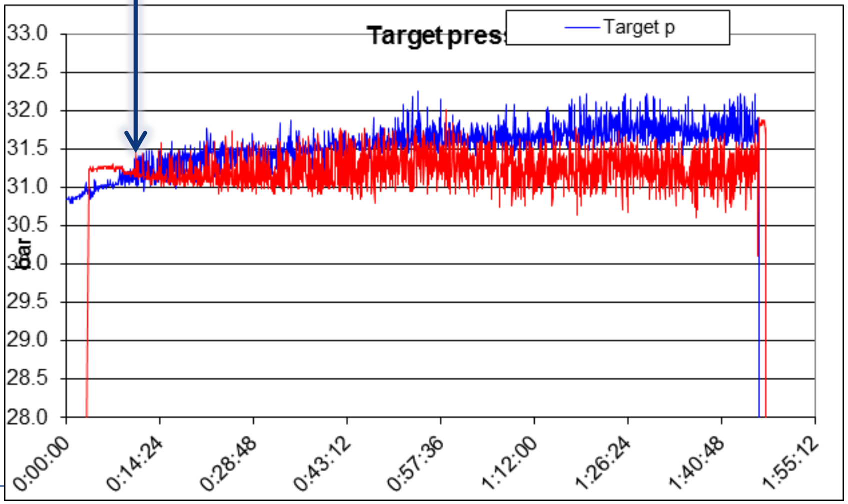
www.adacap.com 4

L. Maciocco, AAA

Target monitoring for mistuning behavior

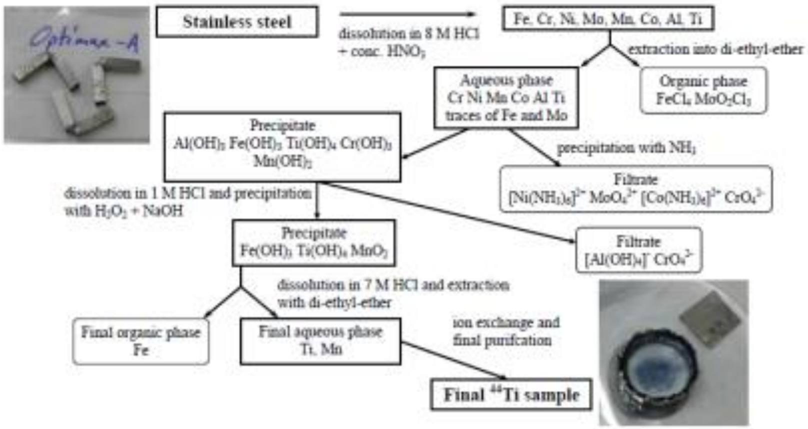


Onset of target boiling as seen
On pressure sensor

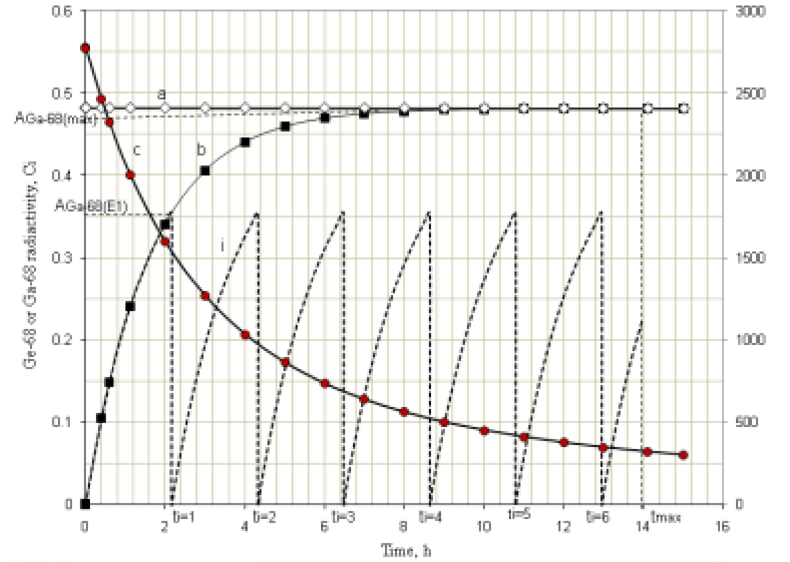


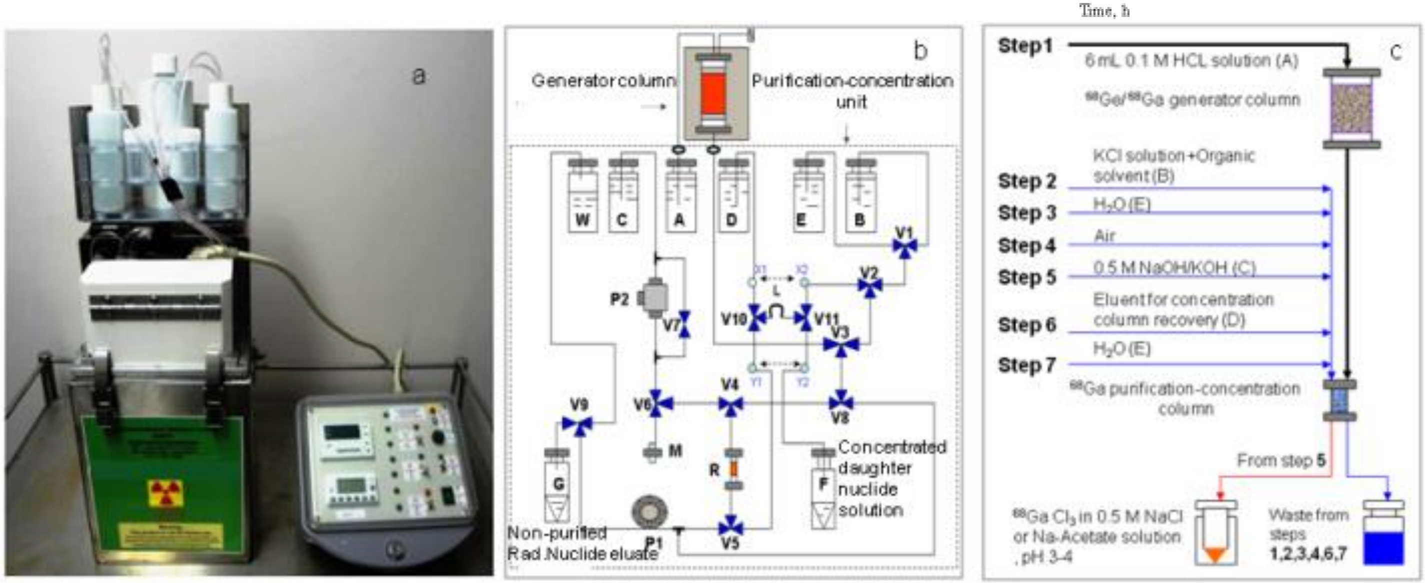
L. Maciocco, AAA

Generators for nuclear pharmacy in hospitals



44Ti/Sc D. Schumann, PSI



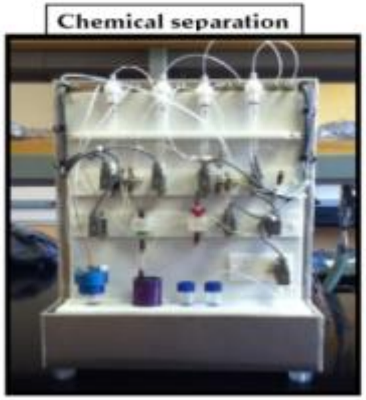


RADIGIS generator from MEDISOTEC, Le *Molecules* **2014**, *19*, 7714

Radiochemistry, transport and use

By the very nature of the activity,
Radioprotection, shielding, compliance (license) with the regulatory bodies will be Influencing/triggering the technical choices

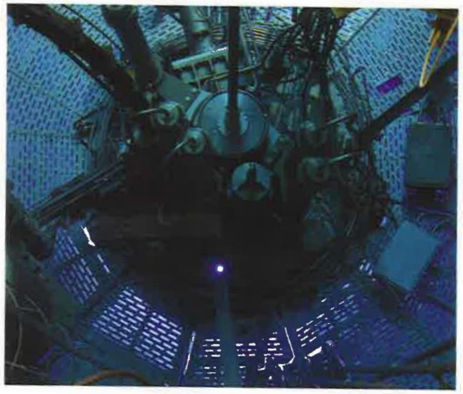
Hot cell for nuclear medicine preparation
Lemer-Pax



Automated chemistry module
P. Schaeffer et al.

AAA

Advanced concepts



Neutron sources

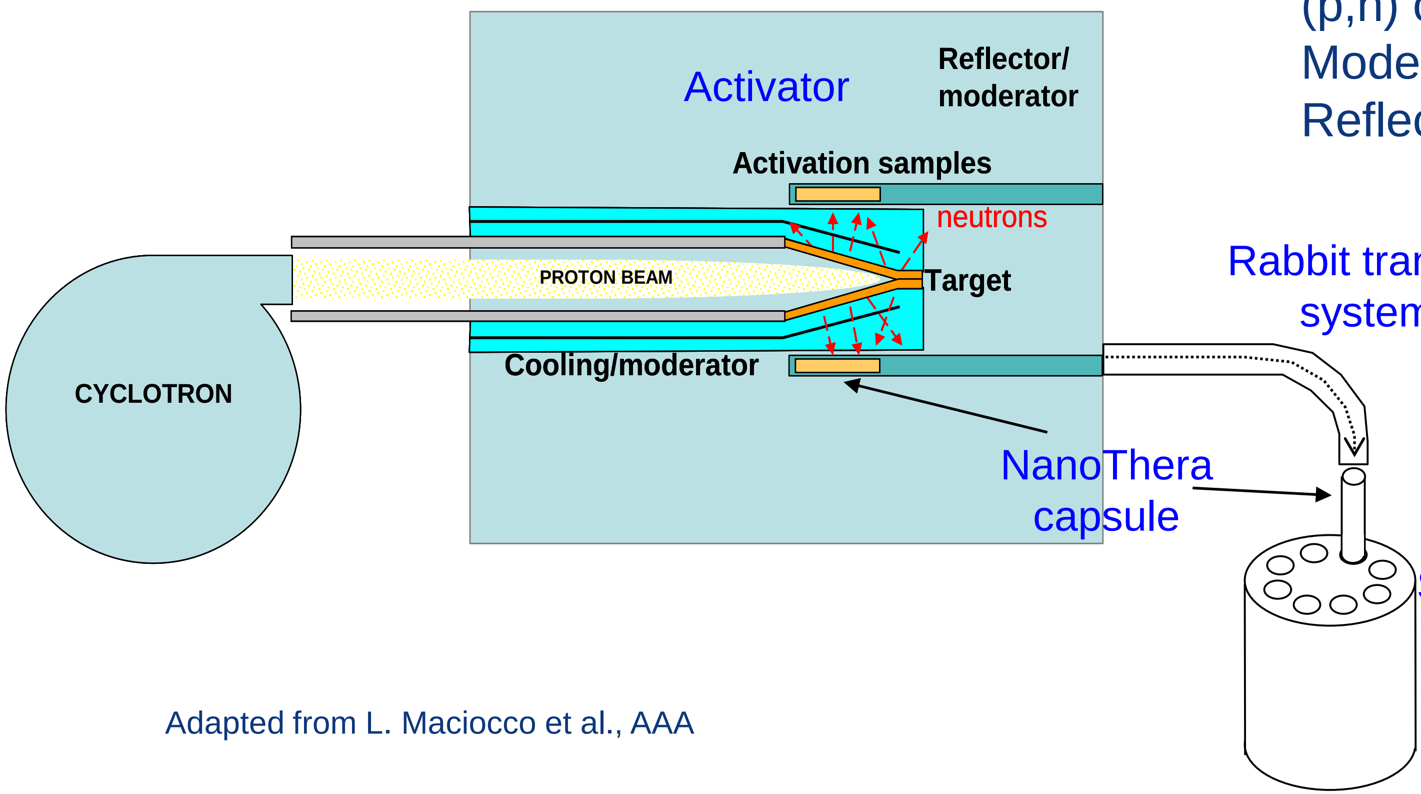
Is (n,γ) more favorable than (d,p)?

the heat load from the beam on the target is decoupled from the target.

Production of neutrons from proton beams of cyclotron

- Concept deriving from the Neutron-driven element transmuter (based on the Adiabatic Resonance Crossing concept) proposed by C. Rubbia in 1995-1998 (TARC experiment-CERN)

Some ideas
(p,n) on 7Li or 10Be target
Moderator : H2O, parafin
Reflector : iron, graphite



Adapted from L. Maciocco et al., AAA

The THERANEAN activator

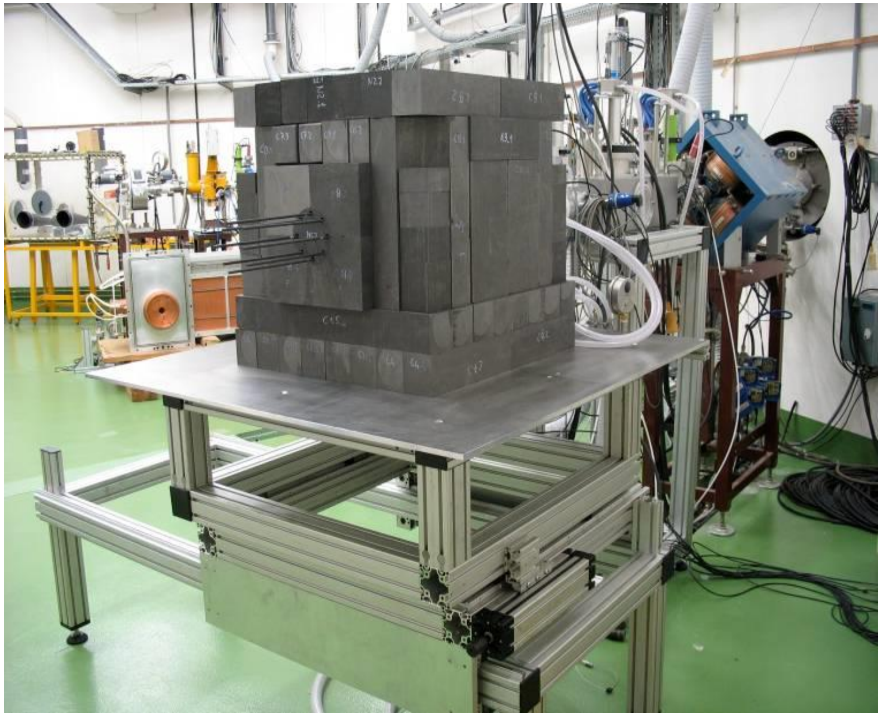
- Concept deriving from the Neutron-driven element transmuter (based on the Adiabatic Resonance Crossing concept) proposed by C. Rubbia in 1995-1998 (TARC experiment-CERN)

- First prototype (INBARCA activator, 2 kW) built and tested in 2005-2008 in JRC-IHCP cyclotron (40 MeV, 50 μA), Ispra (Italy)

- THERANEAN activator (70 MeV, 350 μA) designed for industrial production of therapeutic activities of β^--emitting radioisotopes (optimised for ^{166}Ho)
  - ✓ Proton target (25 kW) designed through coupled Monte Carlo (power deposition) - CFD (thermal hydraulics) - FE structural numerical simulation
  - ✓ Compact neutron activator (neutron moderation/confinement), designed through extensive Monte Carlo simulation using both MCNPX and FLUKA codes
  - ✓ Final activator assembly (supplied with 16 activation channels with remote loading, for a total production capacity of 64 capsules) designed for routine production and installed in P1 bunker in ARRONAX

L. Maciocco et al., AAA

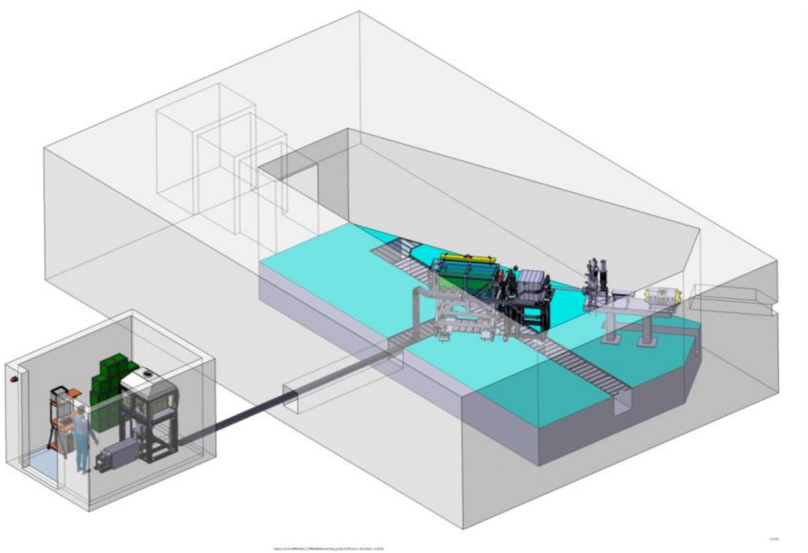
INBARCA activator at JRC Ispra (40 MeV, 50 uA)

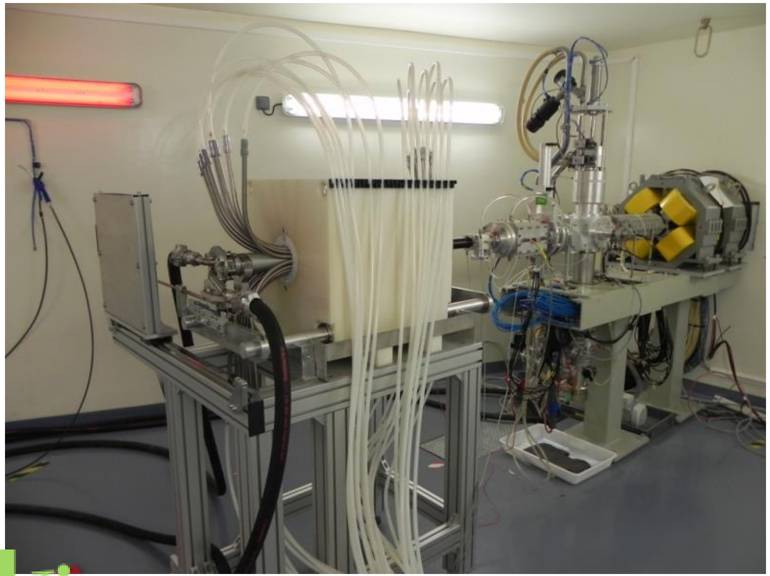


L. Maciocco, AAA

The TheraneaM neutron activator

- Capable of producing more than 50 doses per batch of Ho-166 microparticles for brachytherapy
- Energy: **70 MeV**
- Max experimental proton beam current: **375 µA**
- Experimentally validated in May 2014





L. Maciocco, AAA

Comparison of numerical and experimental results

- Maximum total neutron flux in activation channels at 350 μA: 2×10^{12} n/cm^2/s
- Maximum saturation yields per sample mass and unit current [MBq/g/μA]:

Sample	Reaction	INBARCA experimental (36 MeV)	THERANEAN (70 MeV)		
			Experim.	MCNPX (ENDF-B VI)	FLUKA
Mo metal foils	$^{98}Mo(n,\gamma)^{99}Mo$	0.9	2.1	1.0	2.0
Ho metal foils	$^{165}Ho(n,\gamma)^{166}Ho$	153	808	505	NA

L. Maciocco, AAA

Comparison of numerical and experimental results

- Maximum total neutron flux in activation channels at 350 μA: 2×10^{12} n/cm²/s
- Maximum saturation yields per sample mass and unit current [MBq/g/μA]:

Sample	Reaction	INBARCA experimental (36 MeV)	THERANEAN (70 MeV)		
			Experim.	MCNPX (ENDF-B VI)	FLUKA
Mo metal foils	$^{98}Mo(n,\gamma)^{99}Mo$	0.9	2.1	1.0	2.0
Ho metal foils	$^{165}Ho(n,\gamma)^{166}Ho$	153	808	505	NA

Higher energy together with optimised neutronic design results in a yield improvement of a factor 5/μA for ^{166}Ho with respect to the INBARCA prototype
Improvement factor for ^{99}Mo limited to factor 2.3 (higher energy cross-section)

L. Maciocco, AAA

Ho-therapeutic particles activation capabilities

- Activity for a 6h run and irradiation time to obtain ^{166}Ho therapeutic specific activities at EOB+12h (per g of particles, at 350 μA)

Sample	Application	6h-Yield (after 6h irr. and 12h decay) [GBq/g]	A_{thera} [GBq/g]	Irrad time for A_{thera} [h]
Theranean Ho oxide sub-micro particles suspensions	**Intra tumoral treatment**	**19**	**3.5 [a]**	**1**
Microparticles Ho-PLLA, 30 μm, 17 %wt Ho content [b]	**Intra arterial injection for liver cancer treatment**	**7.8**	**1-25[c]**	**1-24**

a) Based on INBARCA animal tests results (50 μl for 1 cm tumour)

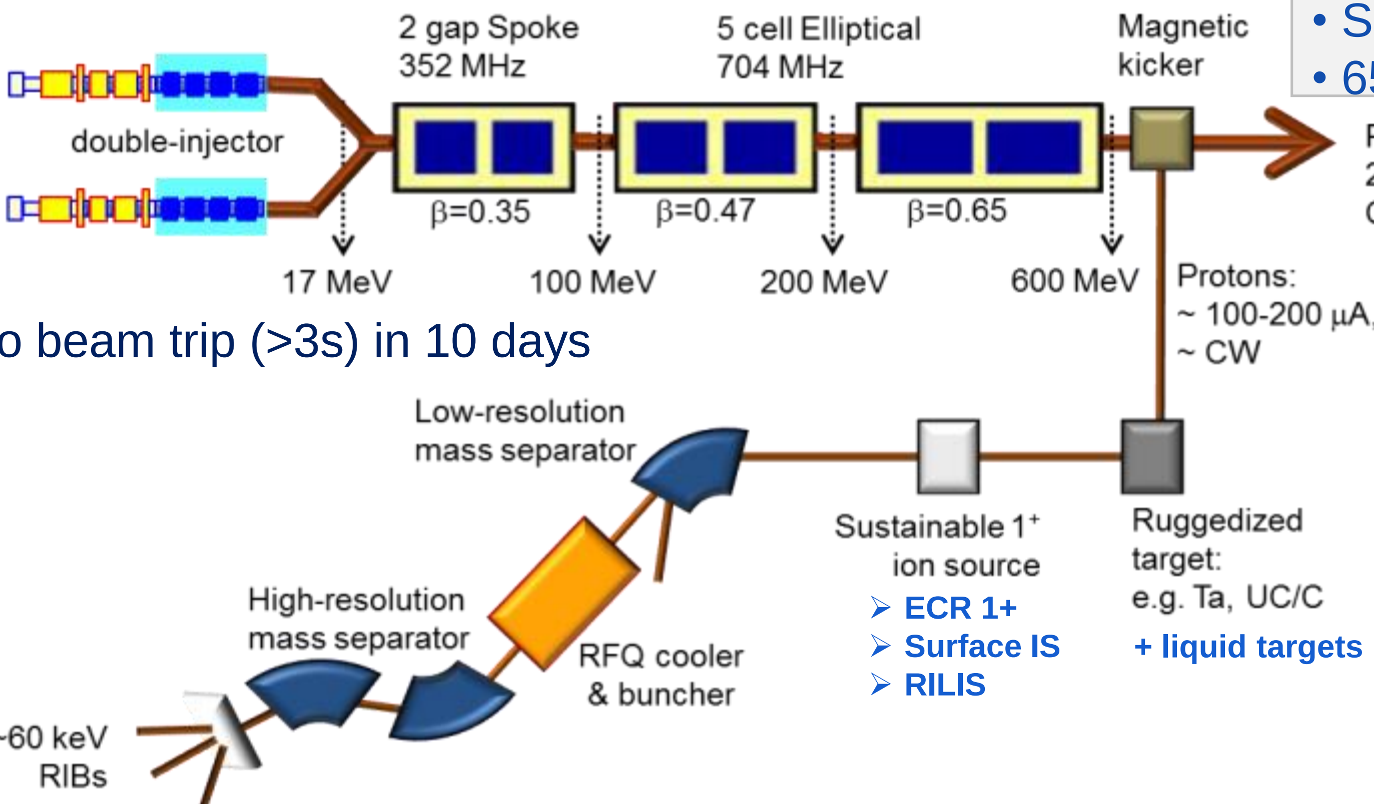
b) Based on INBARCA activation results (particles supplied by University Medical Centre-Utrecht)

c) Depending on liver weight and effective dose, data from Smits, Nijsen et al., J. of Exp. & Clin. Cancer Research, 2010

New large scale facilities for medical isotope production

MYRRHA (ADS) & ISOL@MYRRHA

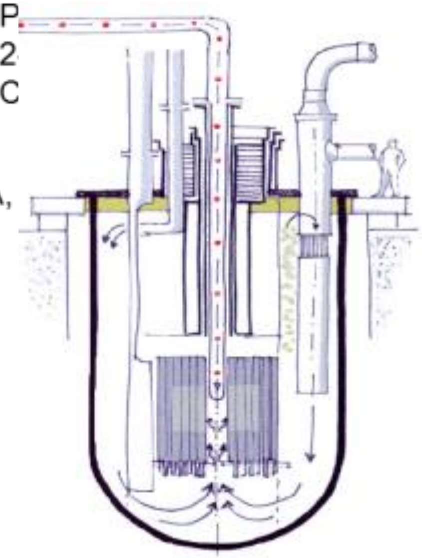
Reactor
- Subcritical/Critical
- 65 to 100 MWth

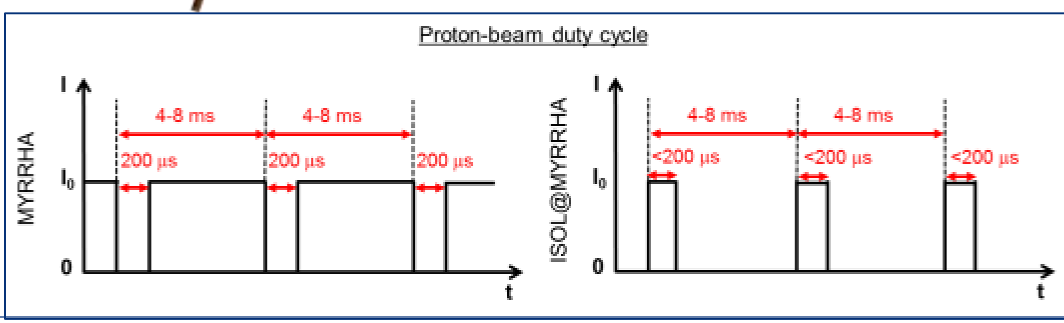


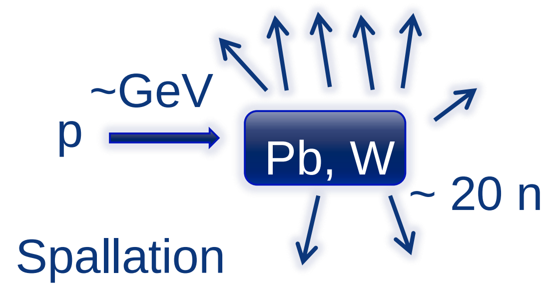
No beam trip (>3s) in 10 days

- ECR 1+
- Surface IS
- RILIS

+ liquid targets



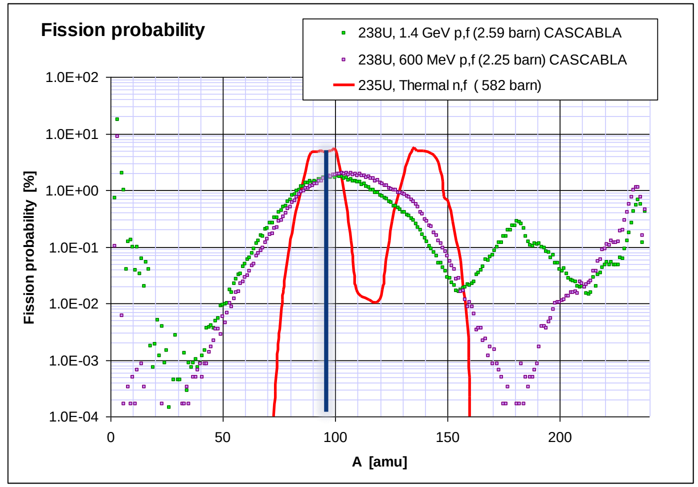


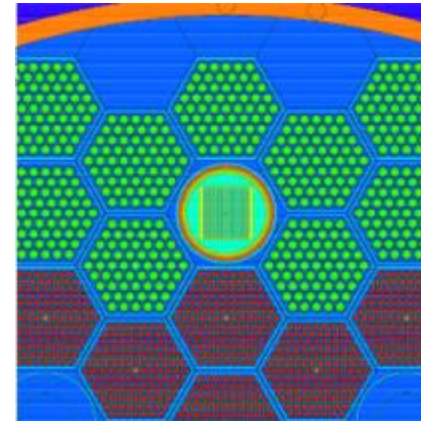


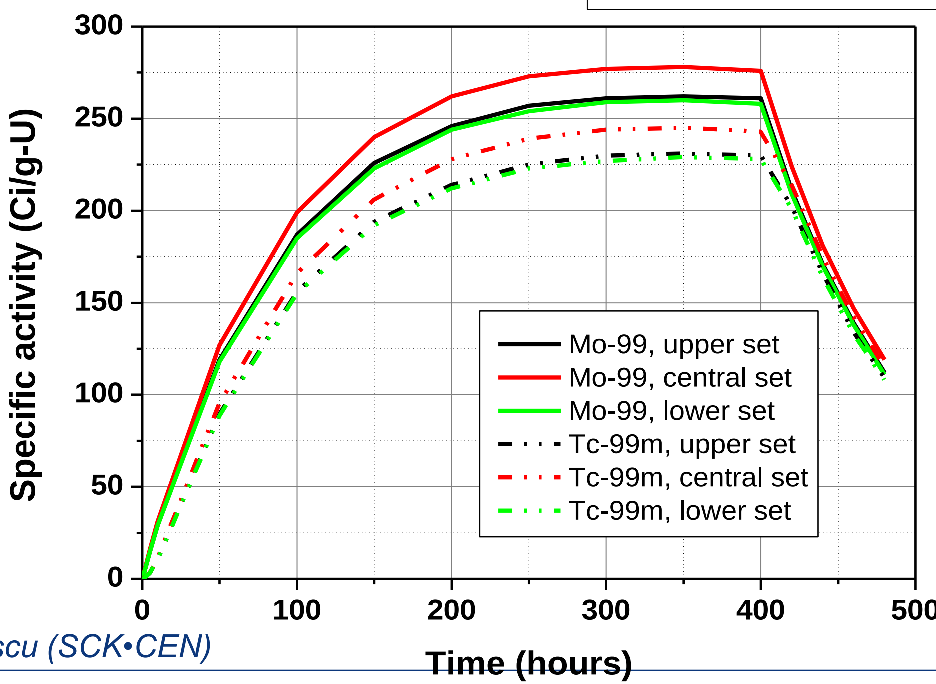
Courtesy L. Popescu (SCK•CEN)

Radioisotope (Mo-99) production capability

- Sub-critical @ 73 MW





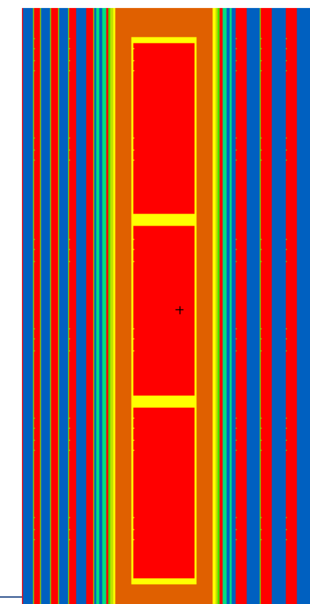


Average specific power

173 W/cm^2

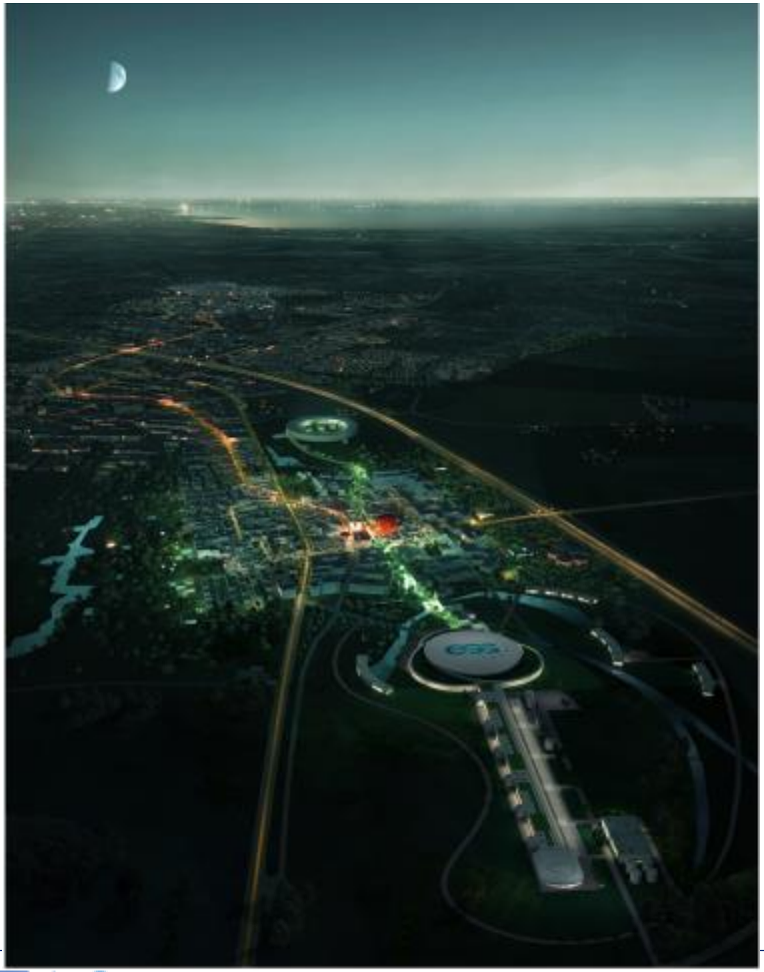
184 W/cm^2

171 W/cm^2



L. Popescu (SCK•CEN)

ESS and radioisotopes



Primary mission:
Neutron scattering studies for material science, biology etc.

When: 2019, complete 2025

Where: Lund, Sweden

Alternative uses:
Workshop on using ESS for basic research, i.e. neutron, neutrino, nuclear, muon and medical physics in 2009.

Courtesy prof Cederkall

ESS and radioisotopes

Accelerator

The ESS accelerator high level requirements are to provide a 2.86 ms long proton pulse at 2 GeV at repetition rate of 14 Hz. This represents 5 MW of average beam power with a 4% duty cycle on target.

62.5 mA, average current

FDSL_2012_10_02

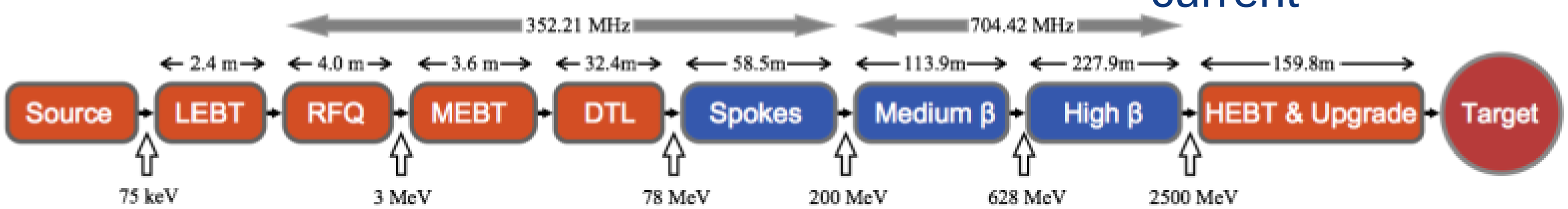


Figure 4.52: Superconducting sectors in the accelerator layout block diagram, coloured blue: spokes, medium-β, and high-β.

Section	Number of modules	Frequency [MHz]	Input energy [MeV]	Cavities per module	Cavities per sector	Module length [m]	Sector length [m]
Spoke	14	352.21	79	2	28	2.9	58.5
Medium-β	15	704.42	201	4	60	5.6	113.8
High-β	30	704.42	623	4	120	6.7	227.9
Total	59				208		400.16

Courtesy prof Cederkall

Table 4.11: Main parameters of the spoke, medium-β and high-β sectors.

ref: ESS TDR

The LANSCE concept and beam skimming (E. Pitcher, T. Shea, ESS)

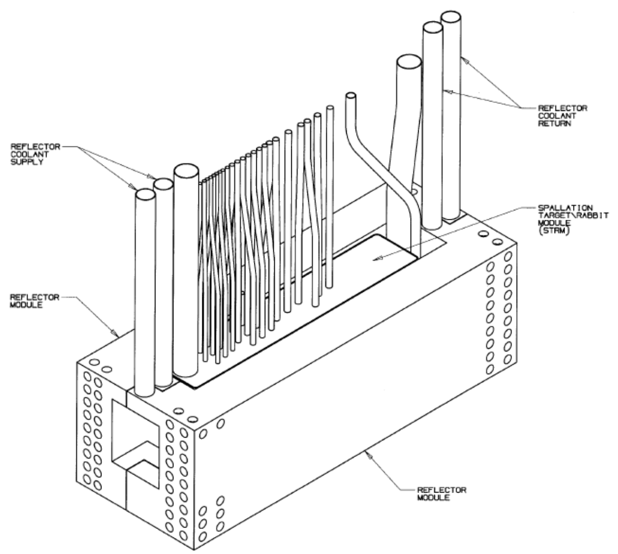
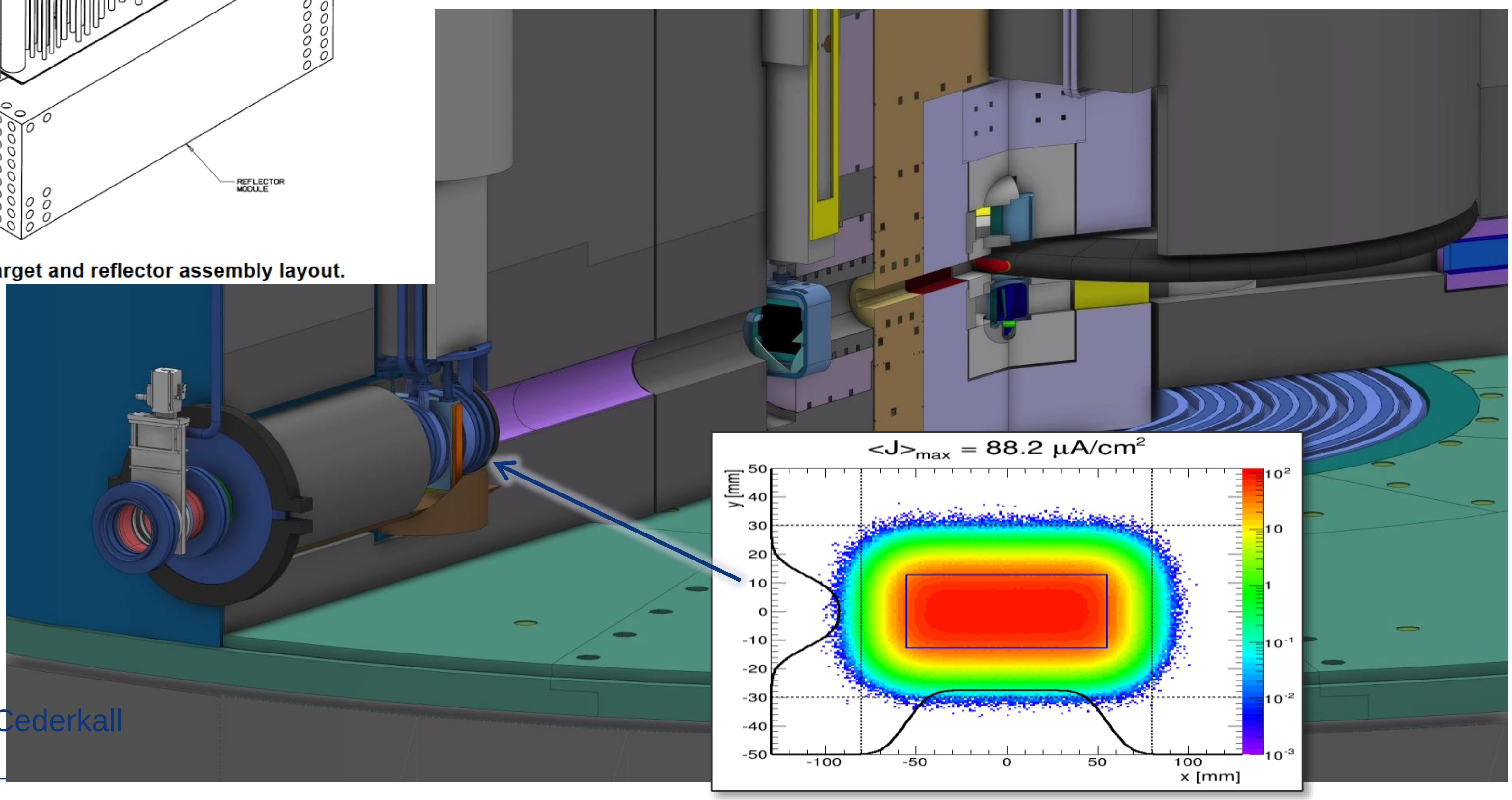


Fig. 3. Target and reflector assembly layout.

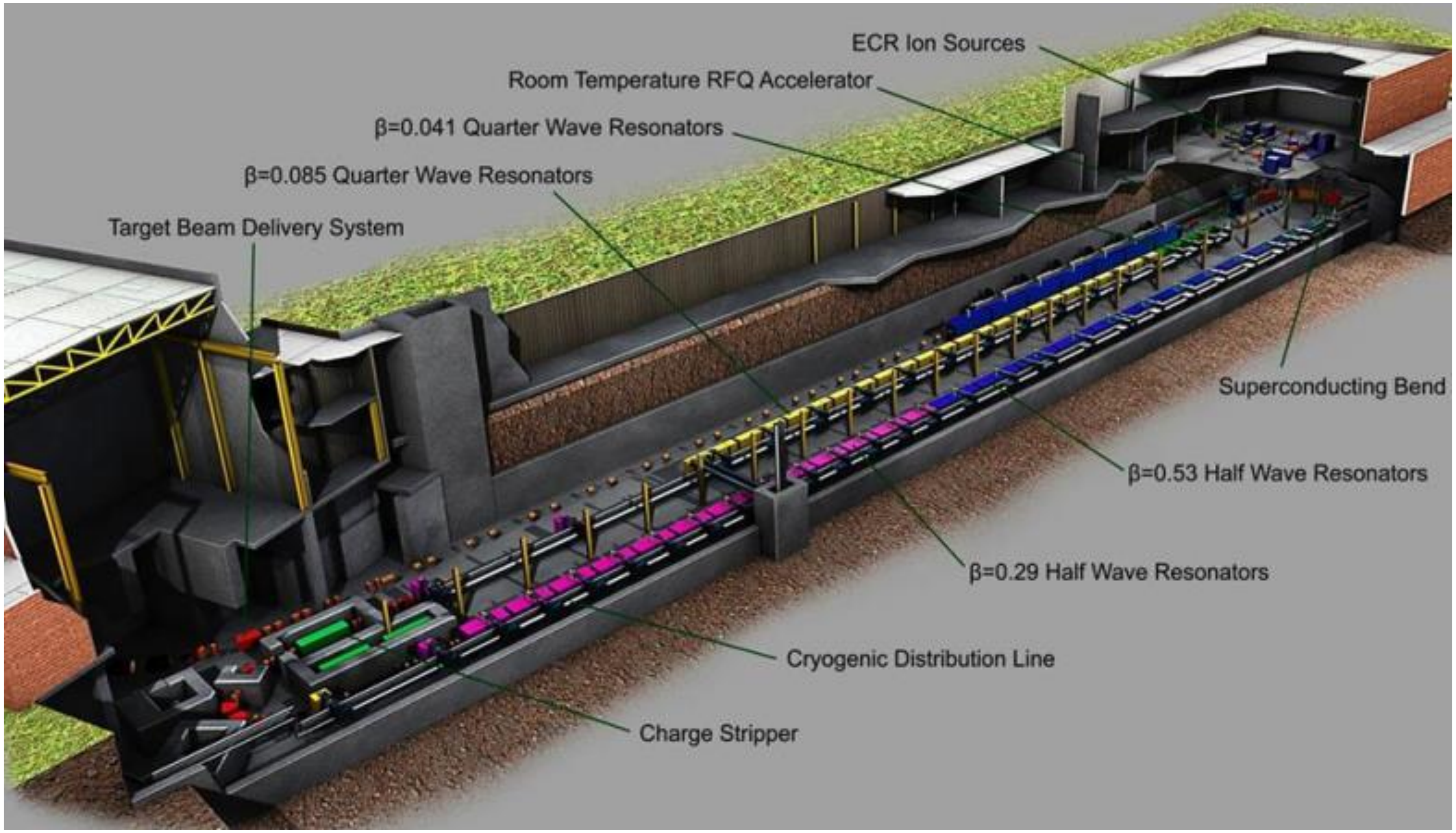
- Isotope production targets placed directly in proton beam path
- Rapid target insertion and removal using "rabbits"
- Isotopes produced via (p,x) reactions placed in front
- Isotopes produced via (n,x) reactions placed in back



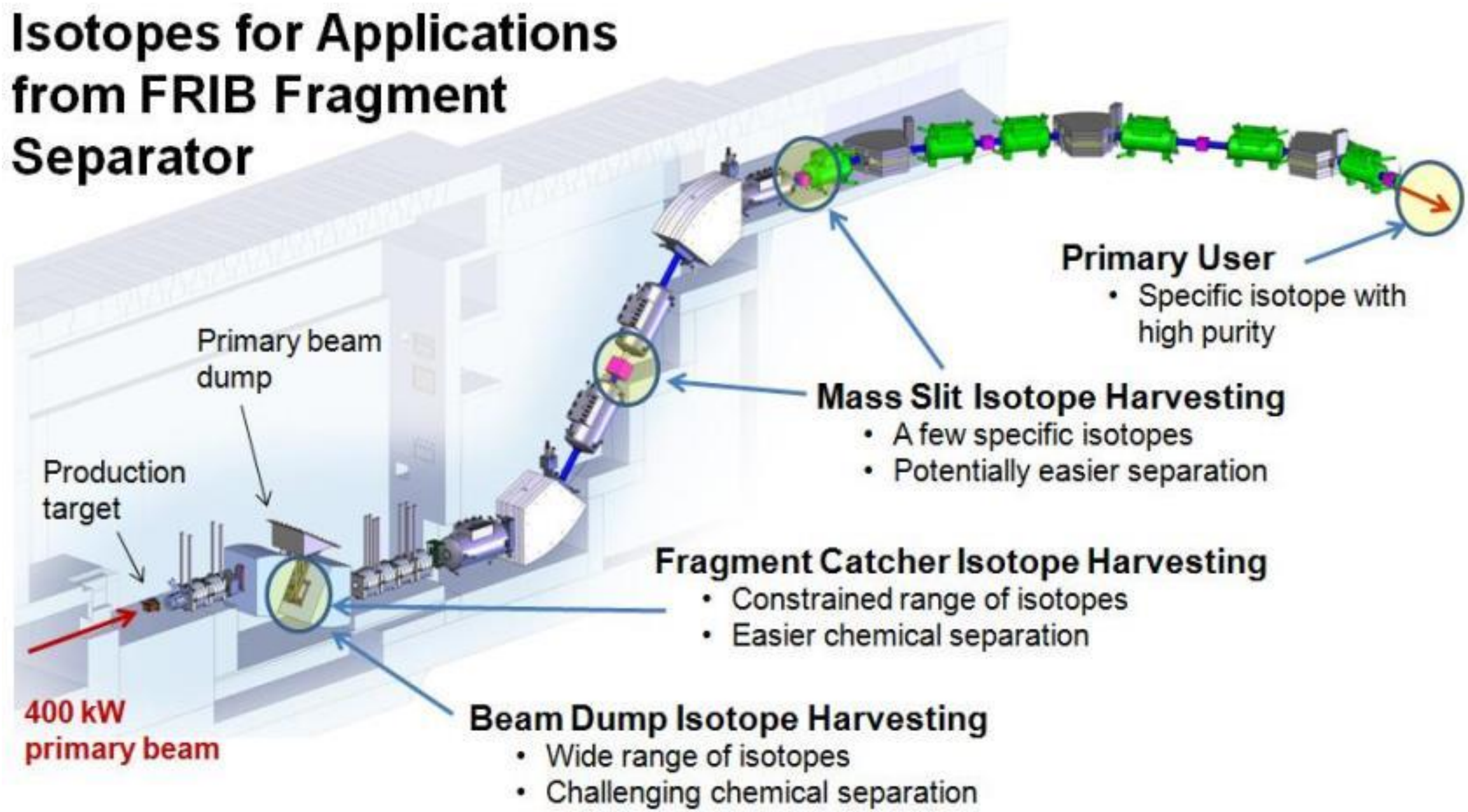
Courtesy prof Cederkall

Radioisotope harvesting in the water beam dump of FRIB

FRIB is a future heavy ion fragmentation facility at MSU, USA
Up to U beams at 200GeV/c, 400kW

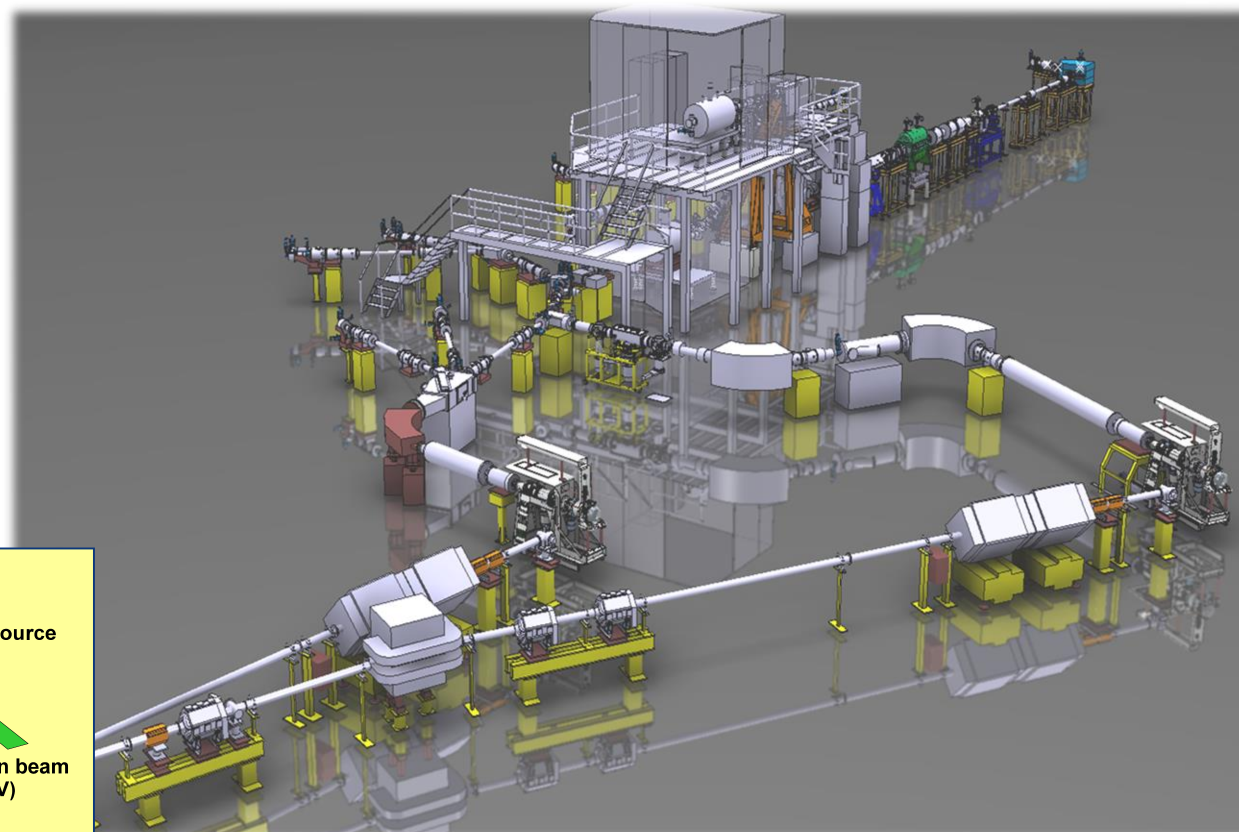


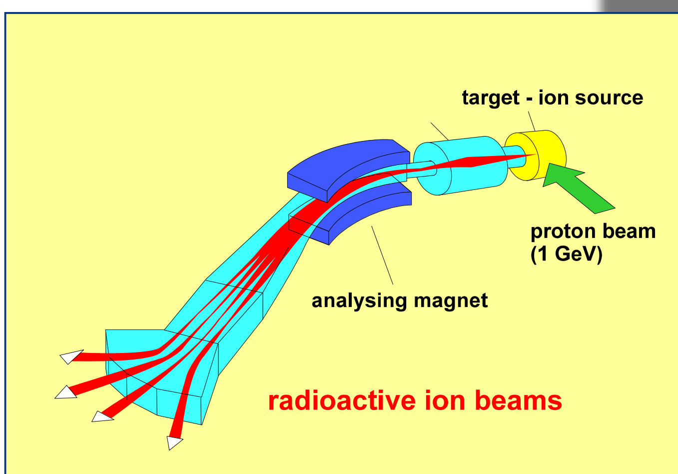
Radioisotope harvesting in the water beam dump of FRIB



Medical radioisotope ion beam purification

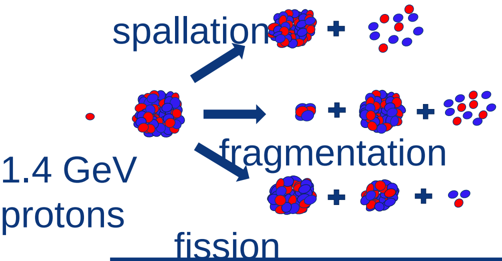
Radioisotope beam formation at ISOLDE, CERN

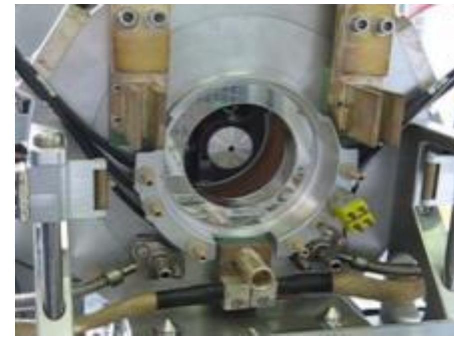


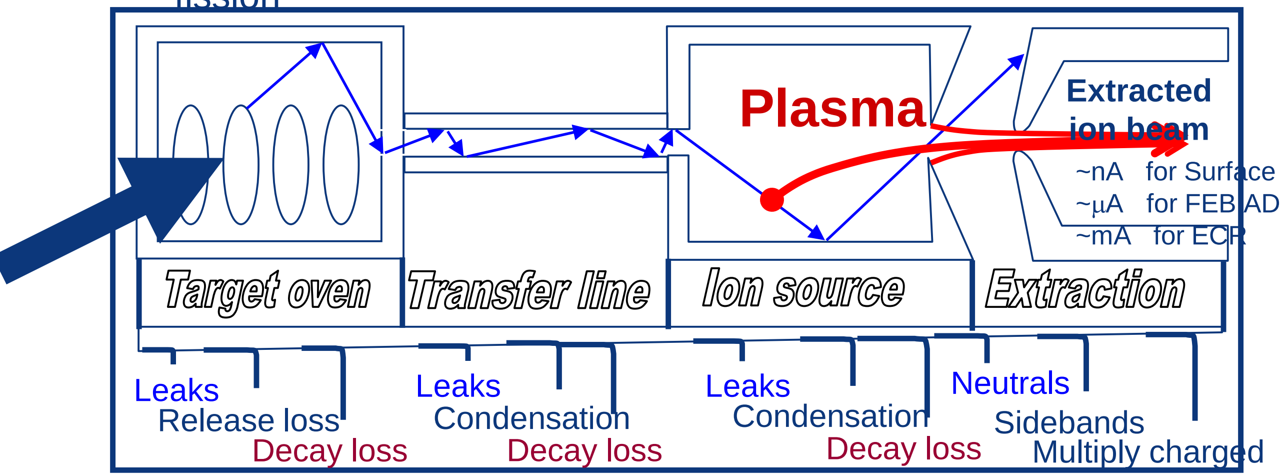


ISOLDE

Principles of radioactive beam production







Primary beam
(MeV/u-GeV/u)

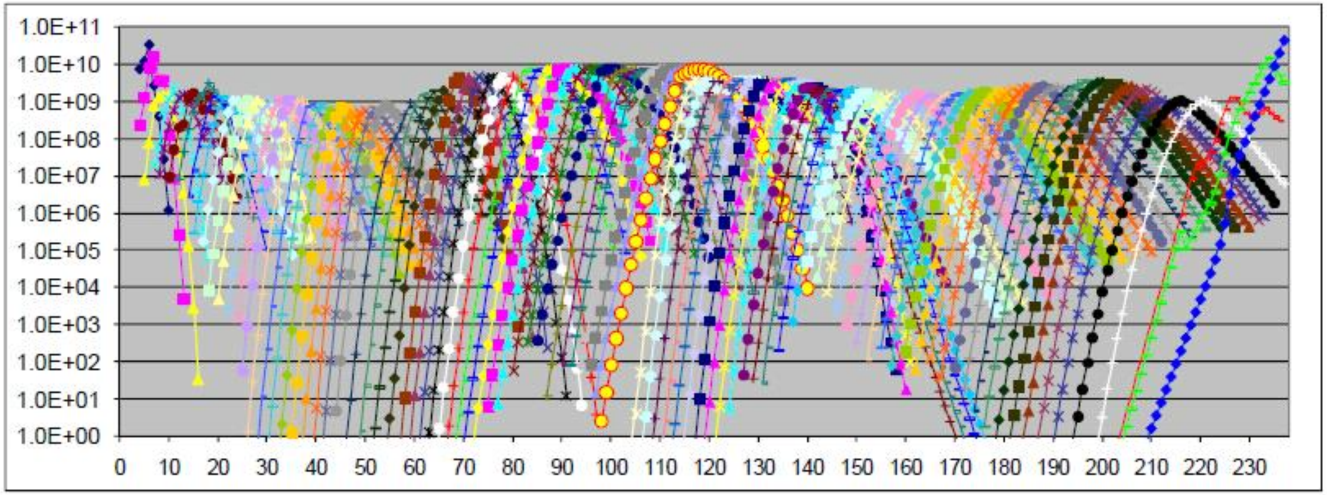
There is an overall efficiency
For these extraction processes

The « ISOL » filter

Isotope mass separation online

1000+ isotopes
(for 73+ elements)
"online"

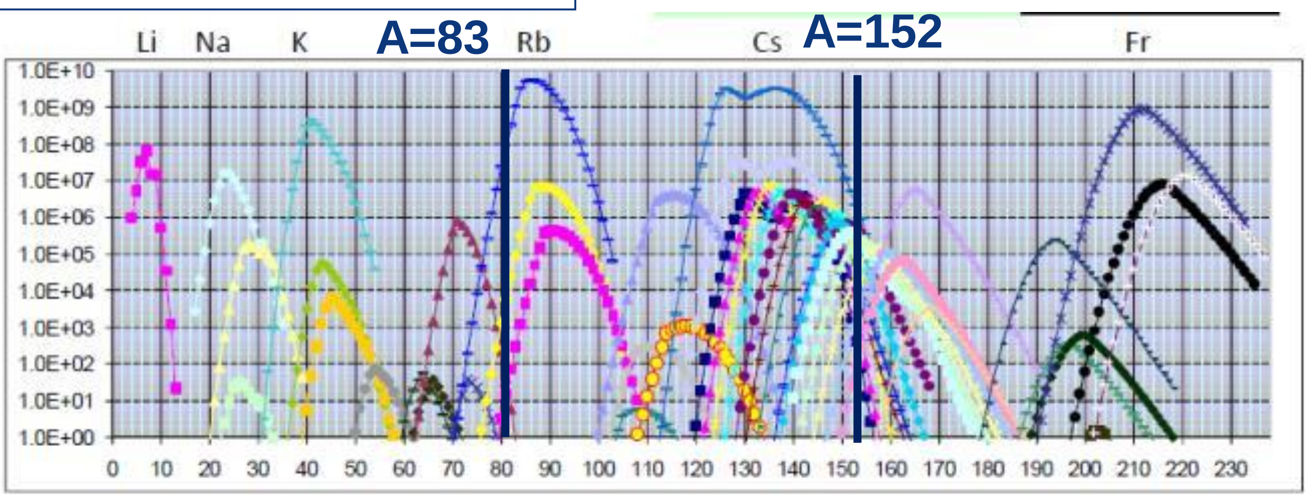
In-target production rate



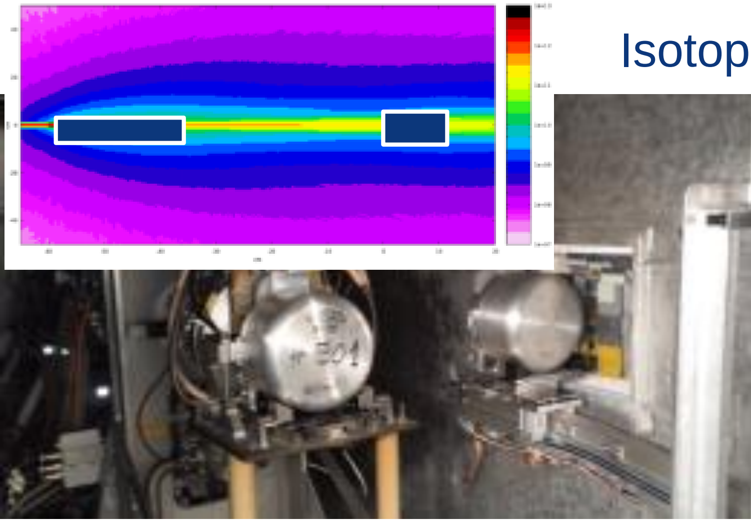
$$I_{[pps]} \sim \Phi_{[pps]} \; \sigma_{[barn]} \; N_{[g/cm2]} \; \varepsilon \; [\%]$$

Intensity
Purity

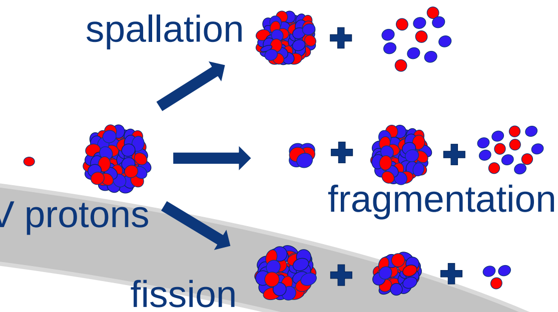
Beam production rate
(Mass separation filter)

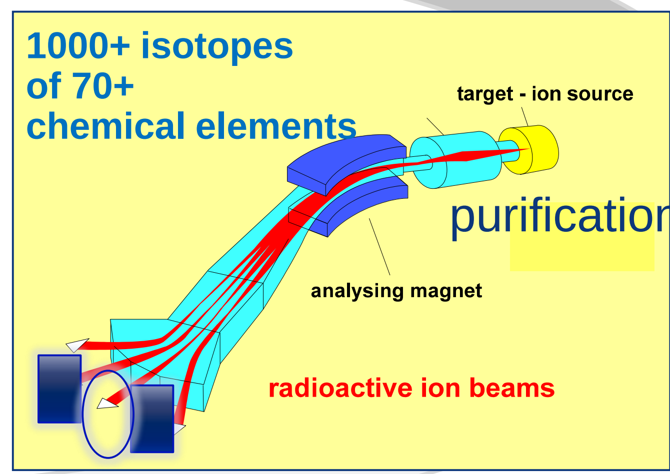


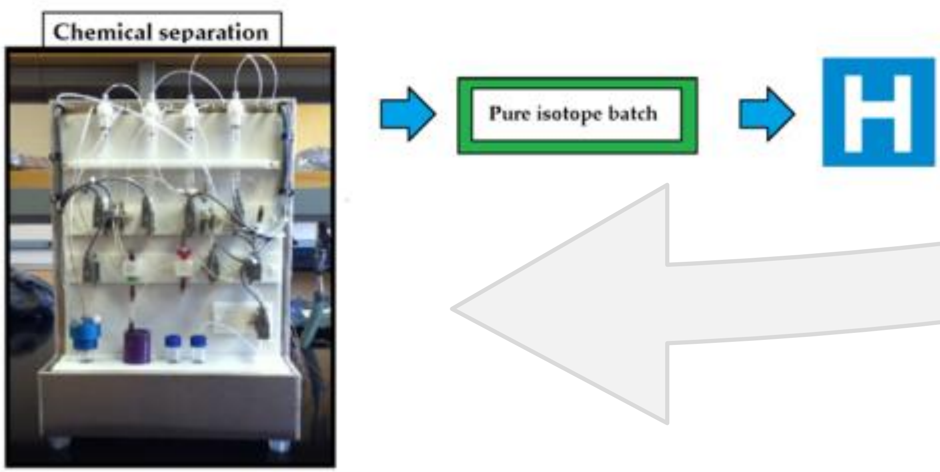
CERN-MEDICIS : Isotope production in the dump and mass separation in the lab



Isotope production



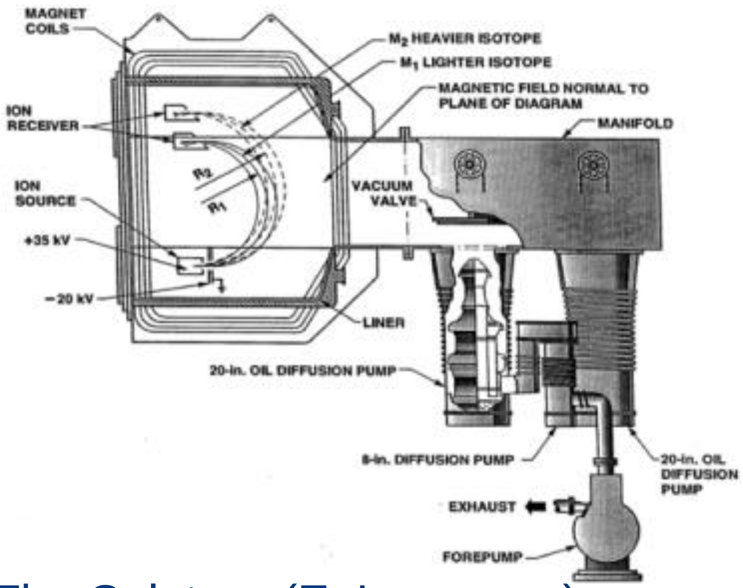




Isotope collection

Isotope mass separation added value

Non carrier added radioisotope fraction (high specific activity)
Efficiencies to be developed
Can this process be applied in large scale ?
A first terrifying use: 235 uranium enrichment of “Little Boy”
And later a much more positive application :
isotope enrichment for medical isotope production



The Calutron (E. Lawrence)

MEDICIS-PROMED training network is recruiting 15 PhD students soon

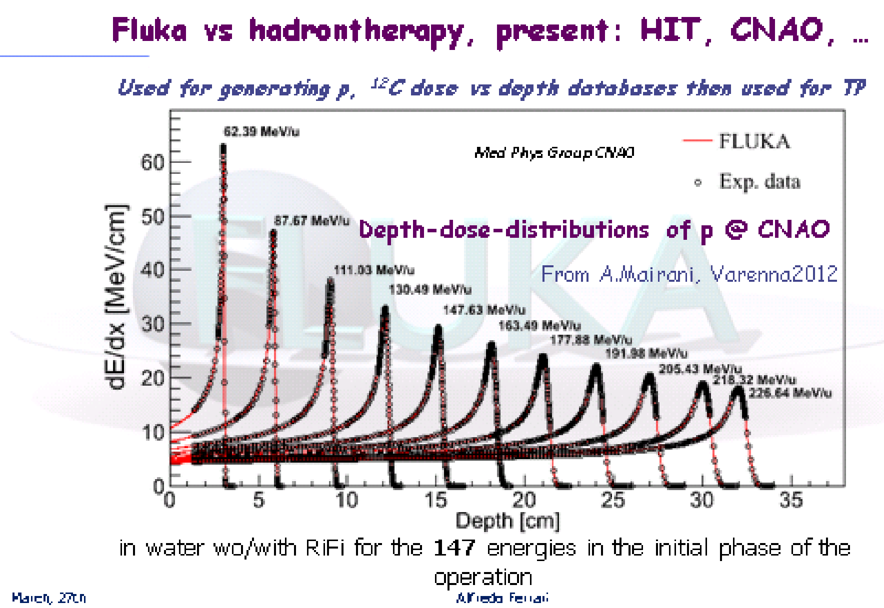
www.cern.ch/medicis-promed

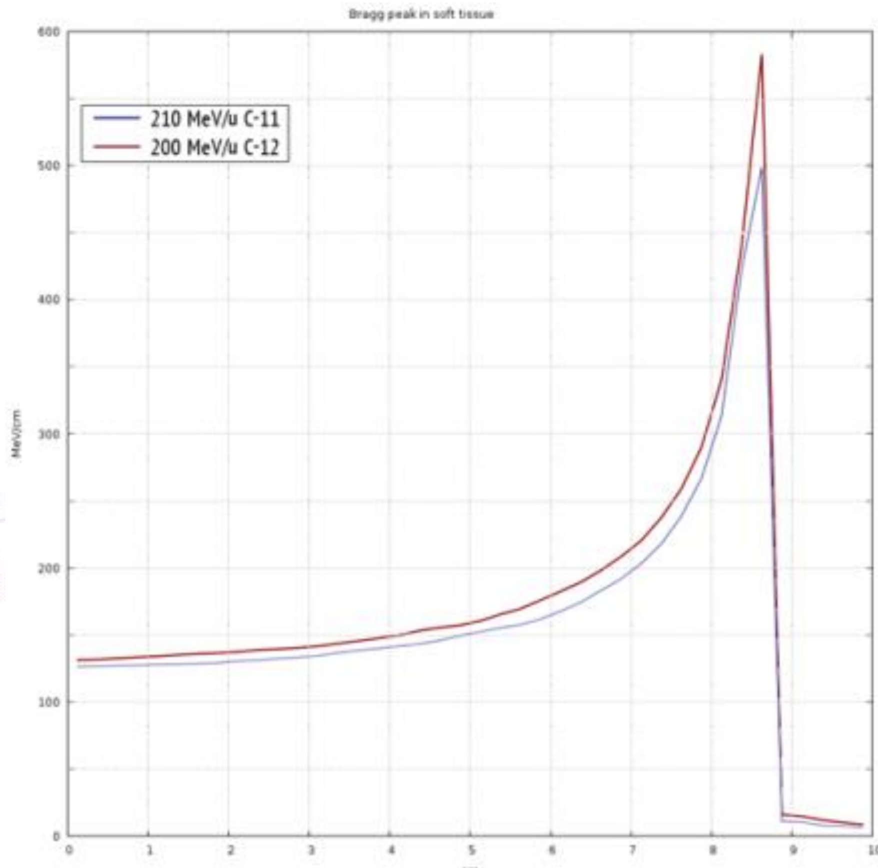
European Organization for Nuclear Research	CERN 1
University of Manchester	Graphene inst. 2
University of Mainz	JOGU 3
Advanced Accelerator Applications	AAA 4
Instituto Superior Técnico	C2TN 5
Centro Nazionale di Adroterapia Oncoologica	CNAO 6
Lemer Pax	PAX 7
University of Leuven	KUL 8

Lausanne University Hospital	CHUV
Geneva University Hospital	HUG
Swiss Fed. Inst. of Tech., Lausanne	EPFL-ISREC
Medaustron	Medaustron
Oxford university consulting	Oxford consult
ARRONAX GIP	ARRONAX
Institut Laue Langevin	ILL

Medical radioisotope ion beam : another option for hadron therapy ?

Treatment with ^{11}C PET isotopes



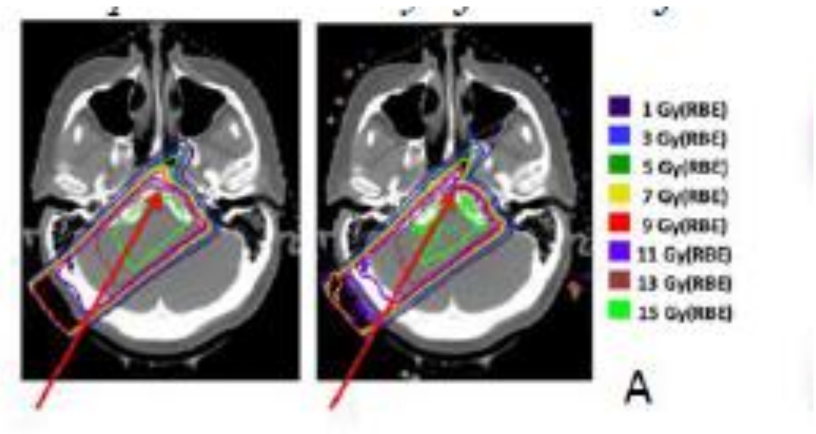


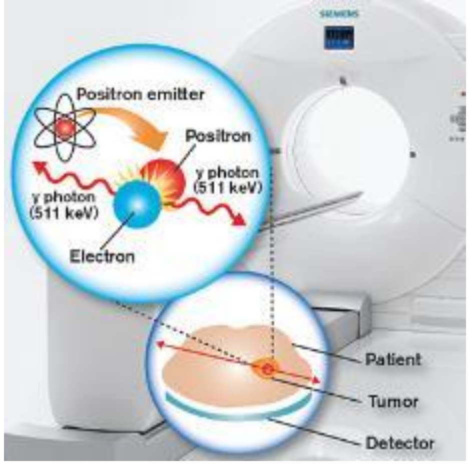
Preliminary Fluka simulations
R. Augusto et al.

^{11}C Beams for combined PET/Hadron therapy

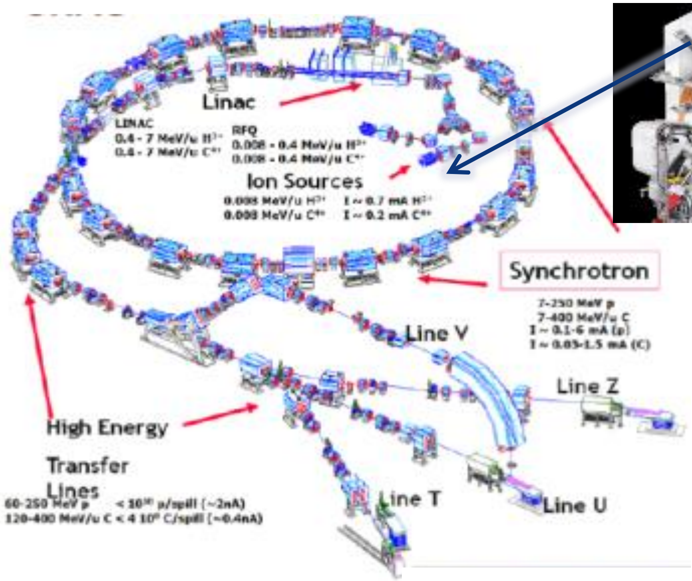
Comparison of in-beam PET with fragment 12C (11C, 15O) and direct 11C use

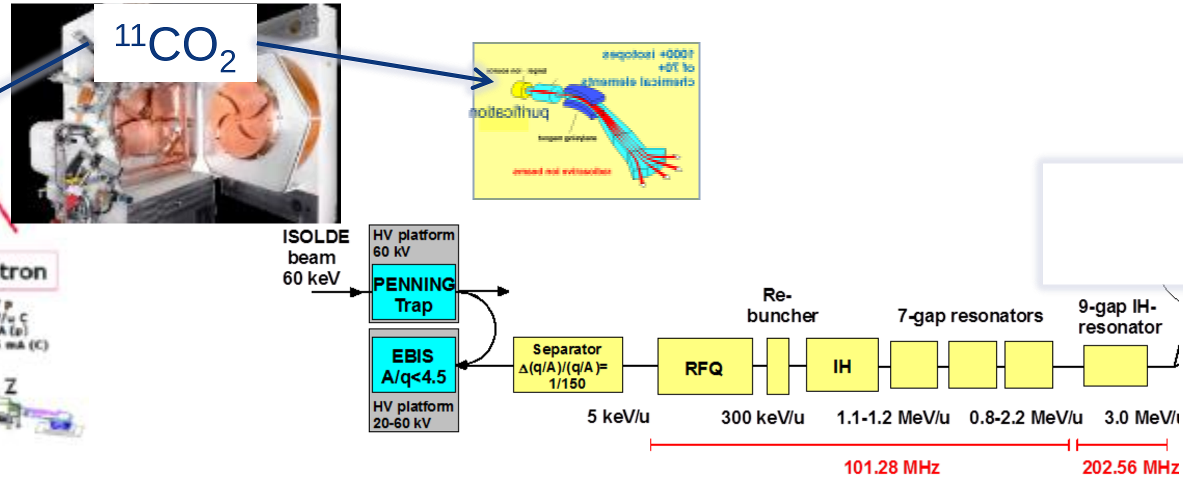
These studies have been performed at HIMAC, NIRS





Possible acceleration schemes : efficiencies matter





"A la Isolde"

Directly in the ECRIS

Method	Cyclotron (protons)		Target	Reaction	Charge breeding strategy (ion sources)	In-target prod. [pps]	Efficiencies: Ion./post-accel./inj+ej.	^{11}C /spills (1Hz)
	E [MeV]	I [μA]						
PET prod (batch)	22	150	N_2 (>1 atm)	$^{14}N(p,\alpha)^{11}C$	ECRIS 0 → n+	$3\ 10^{10}$	5%/30%/20%	$1\ 10^{8}$
REX-ISOLDE ***(ISOL)***	70	1200	NaF-LiF eutect.	$^{19}F(p,2\alpha n)^{11}C$	VADIS +EBIS 1+ → n+	$4\ 10^{11}$	5%/8%/20%	$2.3\ 10^{8}$

- T.M. Mendonca et al., CERN-ACC-2014-0028
  S. Hojo, et al. NIMB 240, 75 (2005).

Conclusion

A medical radioisotope is a radioisotope, with some extra requirements.

A few blockbusters exist, large room for emerging ones.

A large family of different facilities for their production :
From those, compact cyclotrons and linacs for local individual dose production.
Larger infrastructures cover central production before dispatching.
Future large scale facilities are expected to fill some missing gaps.

Beams of radioisotopes will be exploited in the medical field for purification and possibly for hadron therapy

QUESTION ?

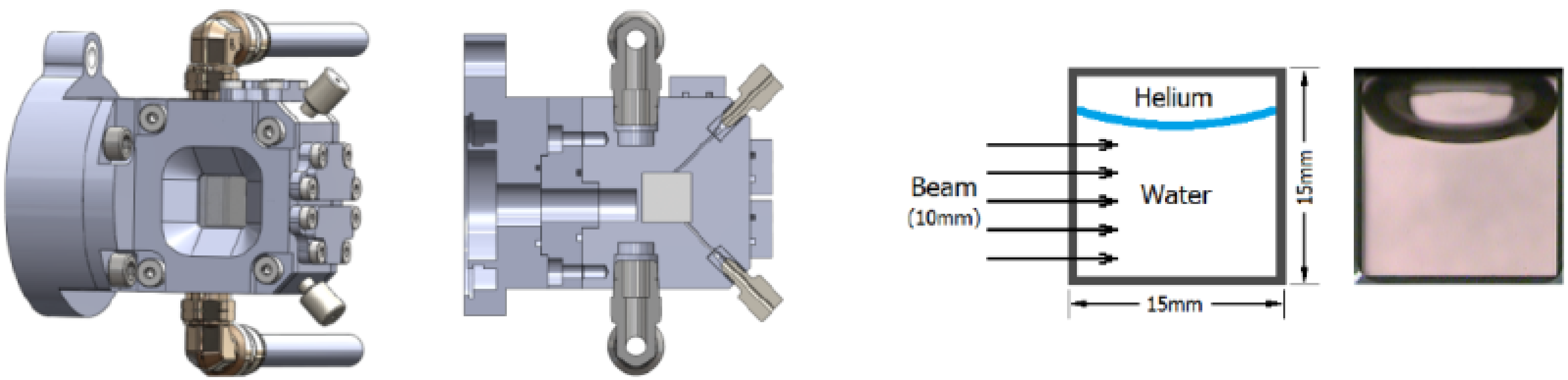
Reserve

WATER TARGET DEMOGRAPHICS

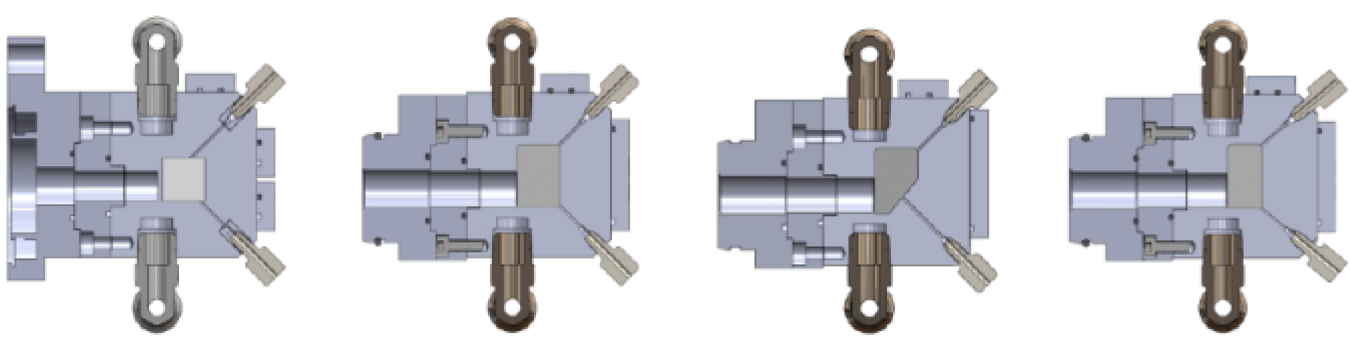
	1998	2015
Maximum Beam Current (μA)	30 - 50	100 - 150
Maximum Beam Power (W)	300 - 600	1300 - 2700
Irradiated Volume (mL)	0.5 - 2.0	2.0 - 4.0
Chamber Material	silver	niobium, tantalum
Helium Window Cooling	> 95%	< 30%

Visualization Targets

- Aluminium body, with two sapphire (Al_2O_3) viewing windows
- Operated on IBA 18/9, with maximum beam powers > 1 kW



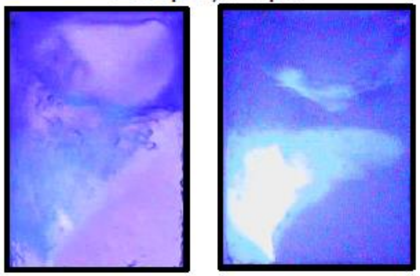
Original Tall Ramp Shallow



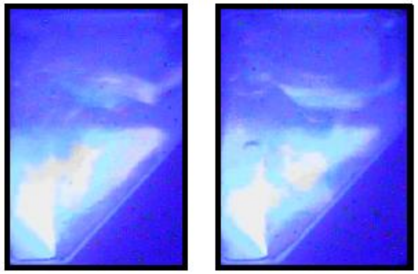
Visualization Conclusions

- Additional chamber height beneficial for vapor accumulation
- Additional chamber depth can accommodate more voiding
- Minimum fill has a threshold to prevent penetration through the overpressure bubble
- **Average power density is the <u>same for all designs</u>: 300 W/mL**

Tall
200psi, 70µA



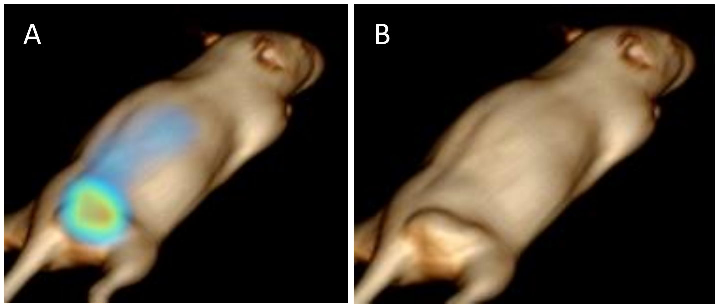
Ramp
200psi, 65µA

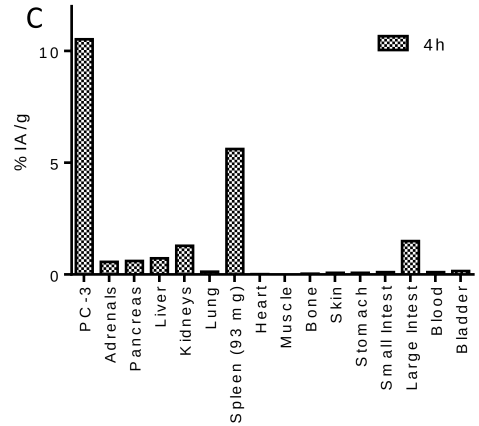


Shallow
200psi, 55µA

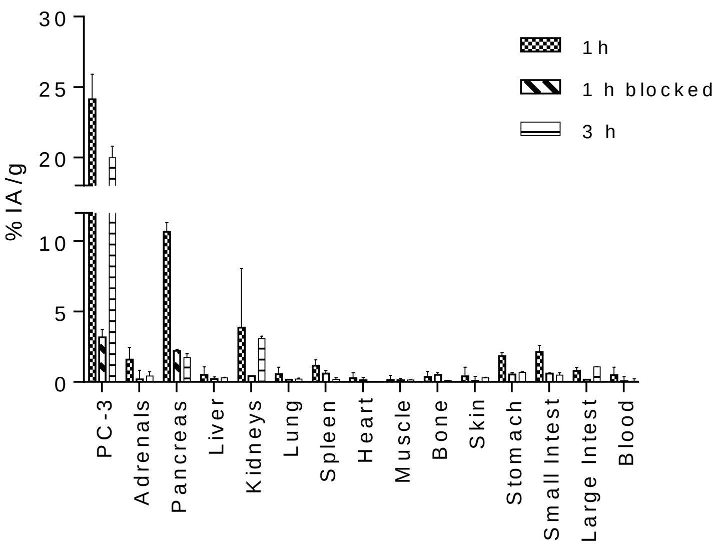
Original
220psi, 65µA

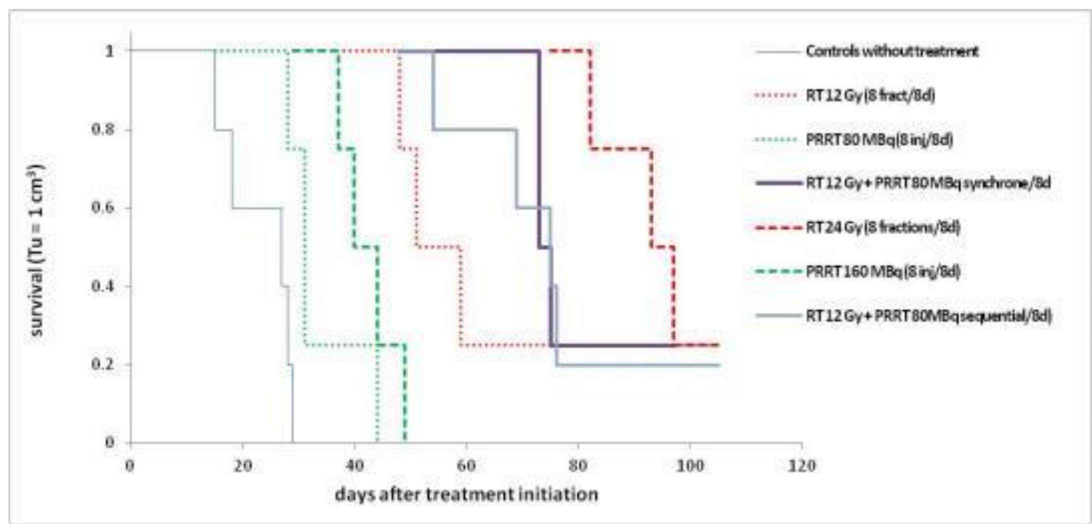
Systemic (intravenous) and external radiotherapy



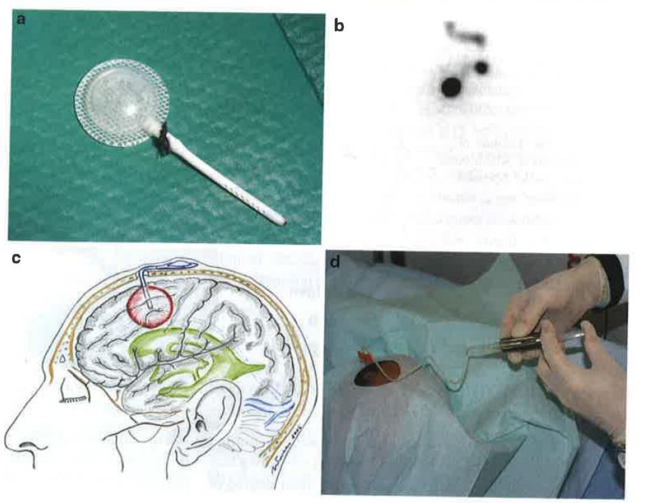


^{152}Tb-DOTA-RM6





Intracavity injection+resection of Glioblastoma



Targeted alpha-radionuclide therapy of functionally critically located gliomas with ^{213}Bi-DOTA-[Thi^{8},Met(O$_2$)^{11}]-substance P: a pilot trial

D. Cordier · F. Forrer · F. Bruchertseifer · A. Morgenstern · C. Apostolidis · S. Good · J. Müller-Brand · H. Mäcke · J. C. Reubi ·

Eur J Nucl Med Mol Imaging (2010) 37:1335–1344
DOI 10.1007/s00259-010-1385-5

ORIGINAL ARTICLE

Pat. No.	Age at Dx (years)	Diagnosis/location of tumour	Cycles/activity (GBq)	Tumour volume (cm^3)	Barthel Index pre-/post-therapeutic	PFS (months)	OS (months)
1	60	GBM frontal L callosal	1/1.07	41.6	75/ 90	2	16
2	40	GBM frontal L (SMA precentral)	1/1.92	76.0	80/ 90	11	19
3	55	Astro WHO grade III fronto-opercular L	4/7.36	74.3	100/100	24+	24+
4	33	Astro WHO grade II frontal R (SMA)	1/1.96	12.0	100/100	23+	23+
5	39	Astro WHO grade II occipital R	1/2.00	17.1	100/100	17+	17+

PFS progression-free survival, *OS* overall survival, + ongoing, *SMA* supplemental motor area, *L* left, *R* right, *Astro* astrocytoma, *GBM* glioblastoma multiforme, *Dx* diagnosis

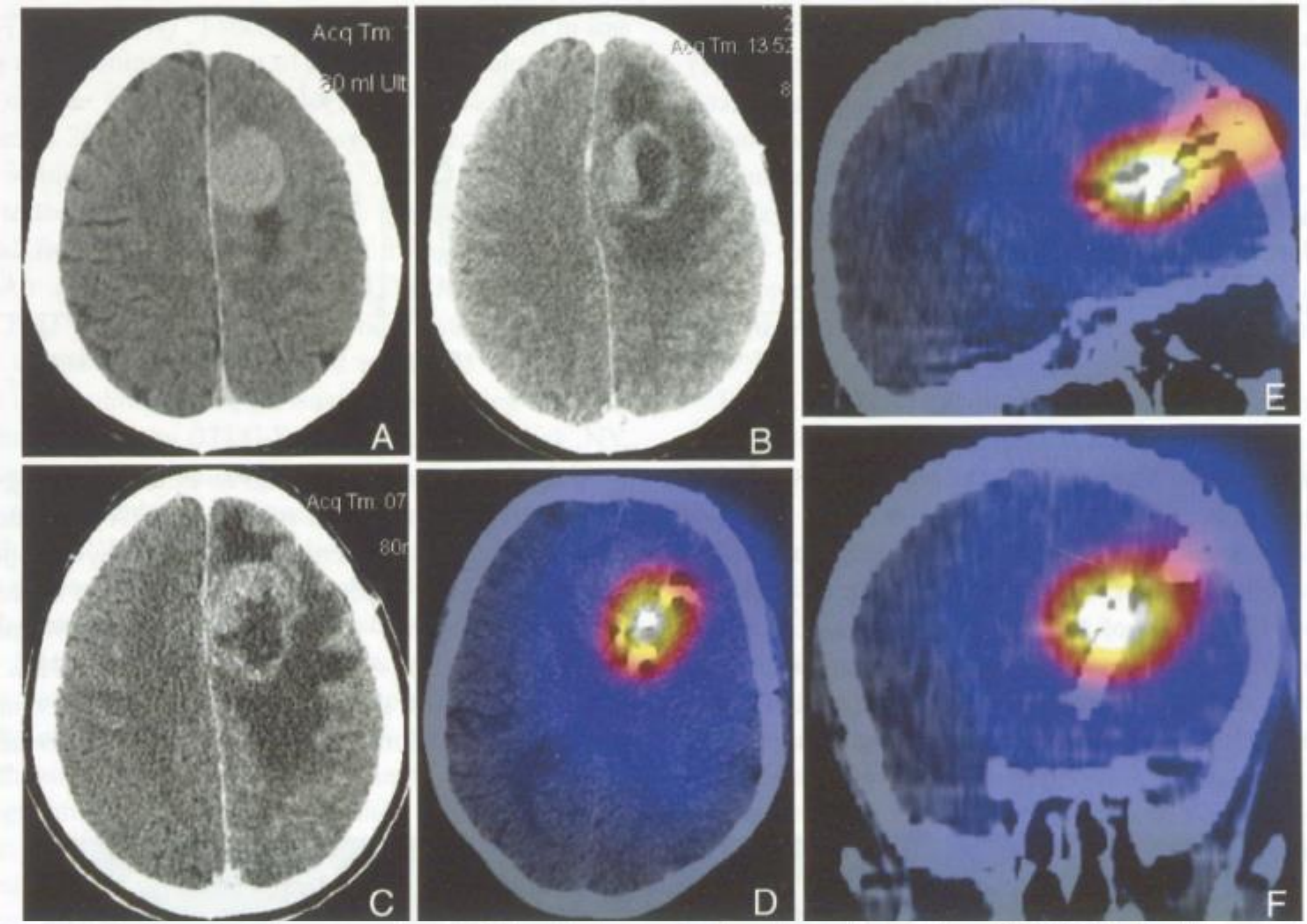


Fig. 4 Patient 2, left frontal GBM, contrast-enhanced CT imaging (**a**–**c**) and SPECT/CT (**d**–**f**). **a** Initial CT scan before stereotactic biopsy and catheter placement. CT scan at **b** 6 weeks and at **c** 10 weeks after radiopeptide treatment. Besides the intratumoural changes, please note the increasing perifocal oedema. SPECT/CT in **d** axial, **e** sagittal and **f** coronal planes with orthotopic dose distribution immediately after intratumoural application of ^{213}Bi-DOTA-substance P