Cyclotrons (& more) for radioisotopes production

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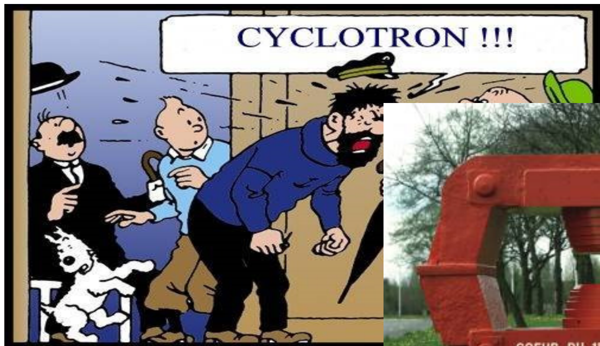
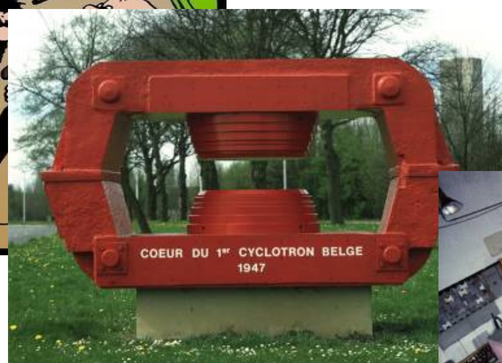
RADIO
PHARMA
SOLUTIONS

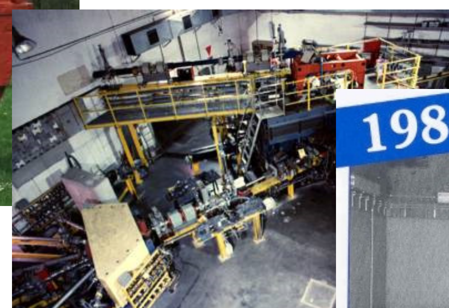
A Belgian story… Ion Beam Applications



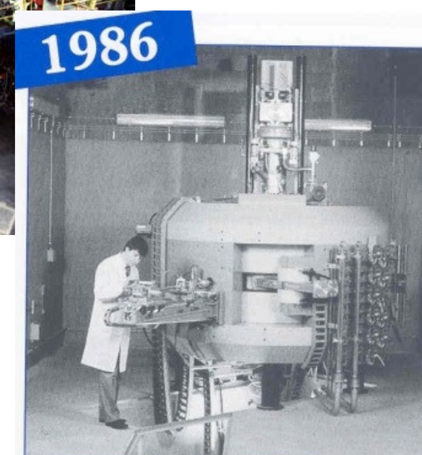
1947



1968



30 MeV Revolutionary cyclotron



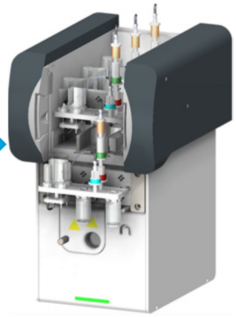
First 235 MeV commercial

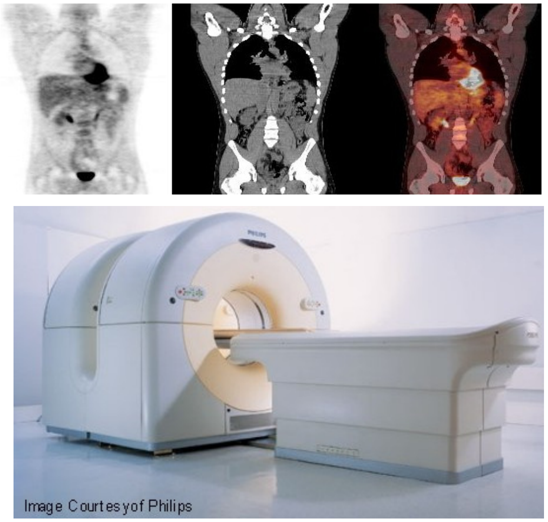
1999

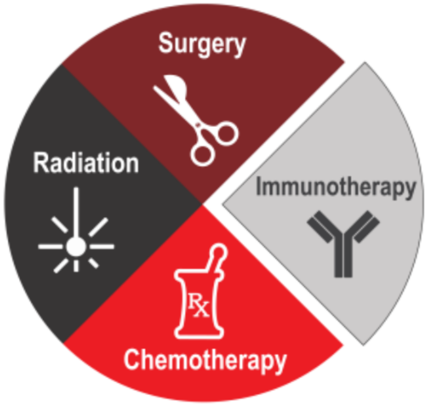
IBA created as spinoff in **1986**

IBA founder **Yves Jongen** still involved

Overview Radiopharmasolution







Cyclotrons

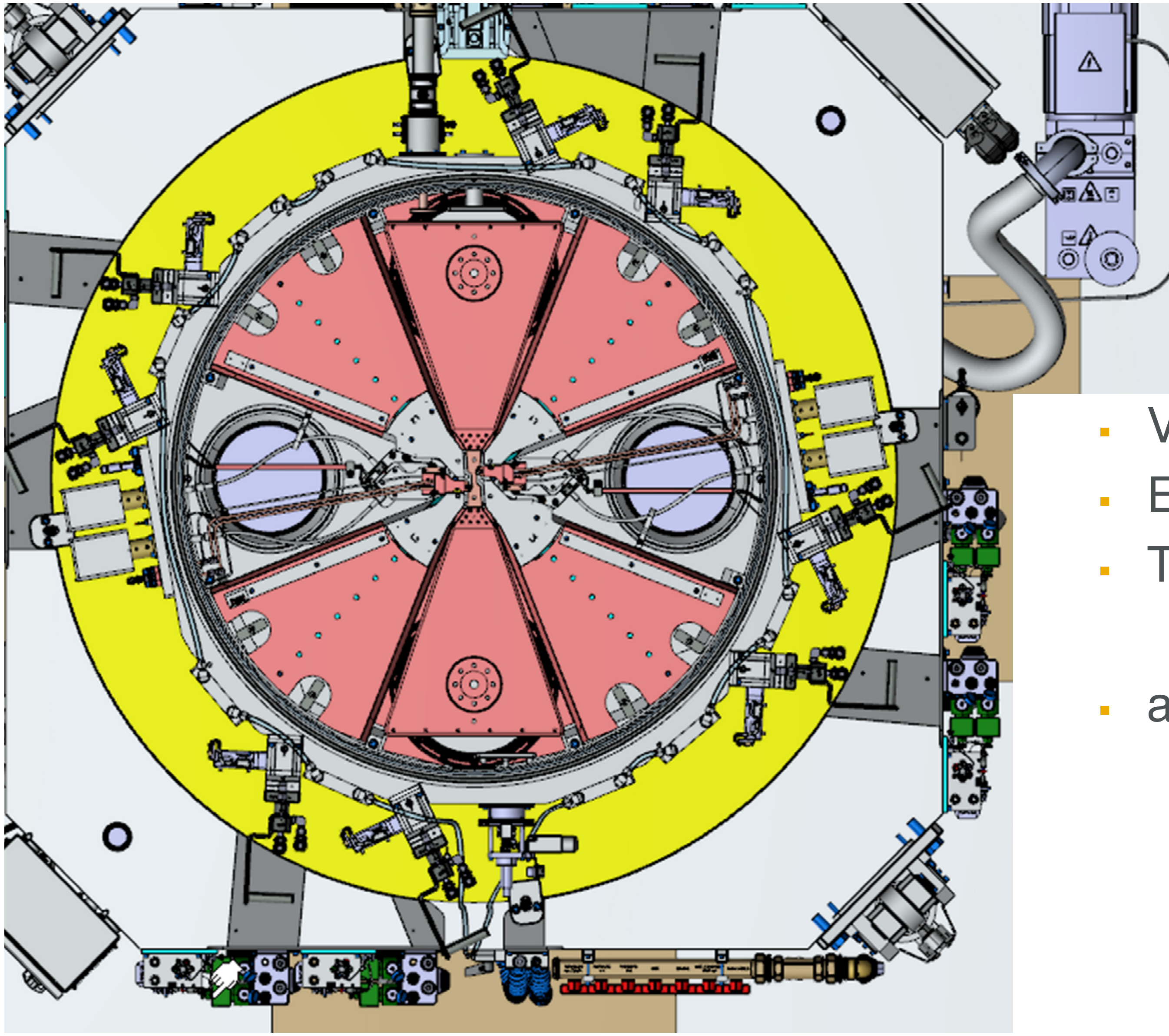
Radiochemistry

Imaging
for Diagnosis

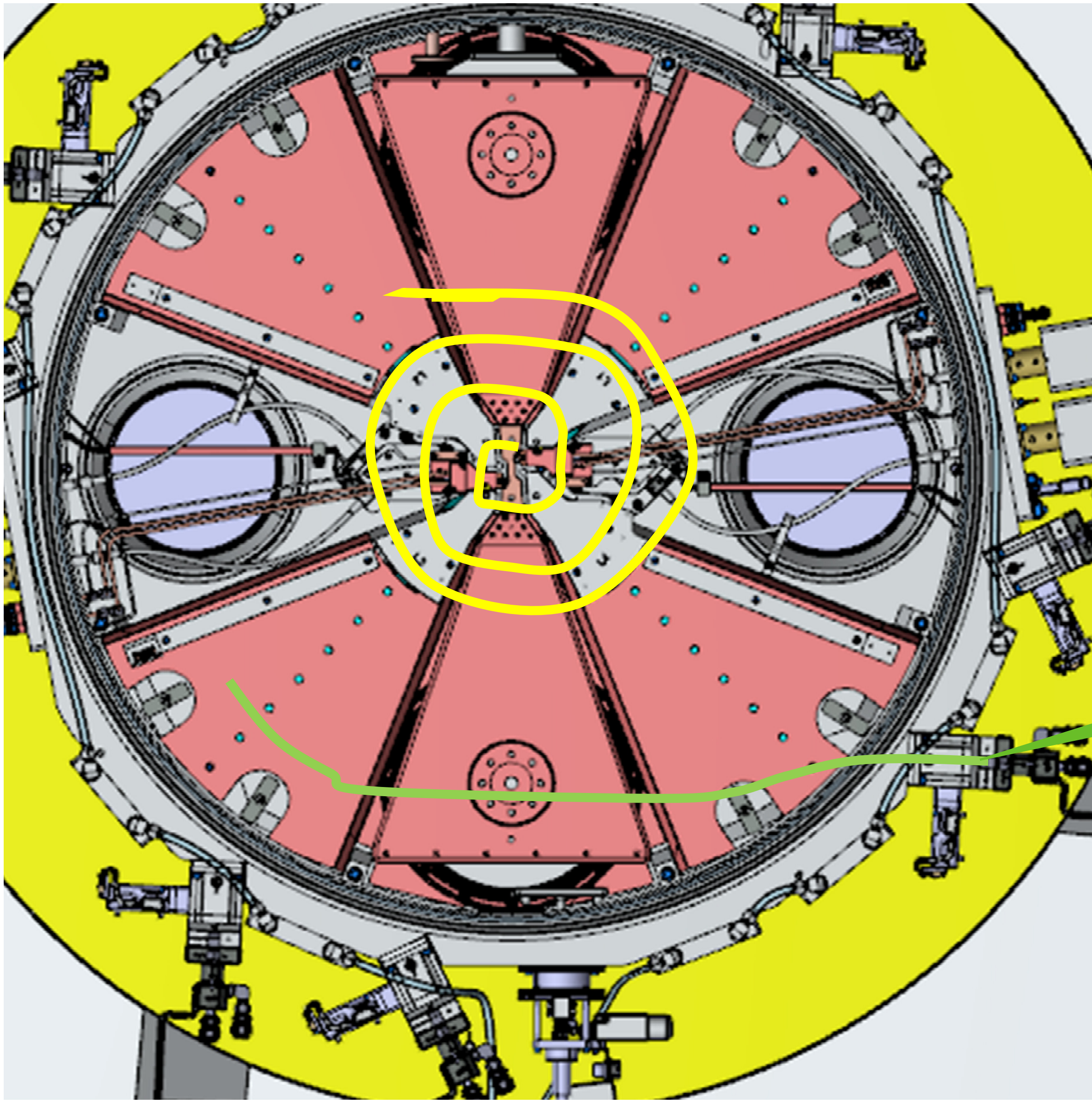
Therapy
Options

Cyclotron ?

- Magnet
  - Coils
  - Yoke / iron
- RF
- Ion source (H-)

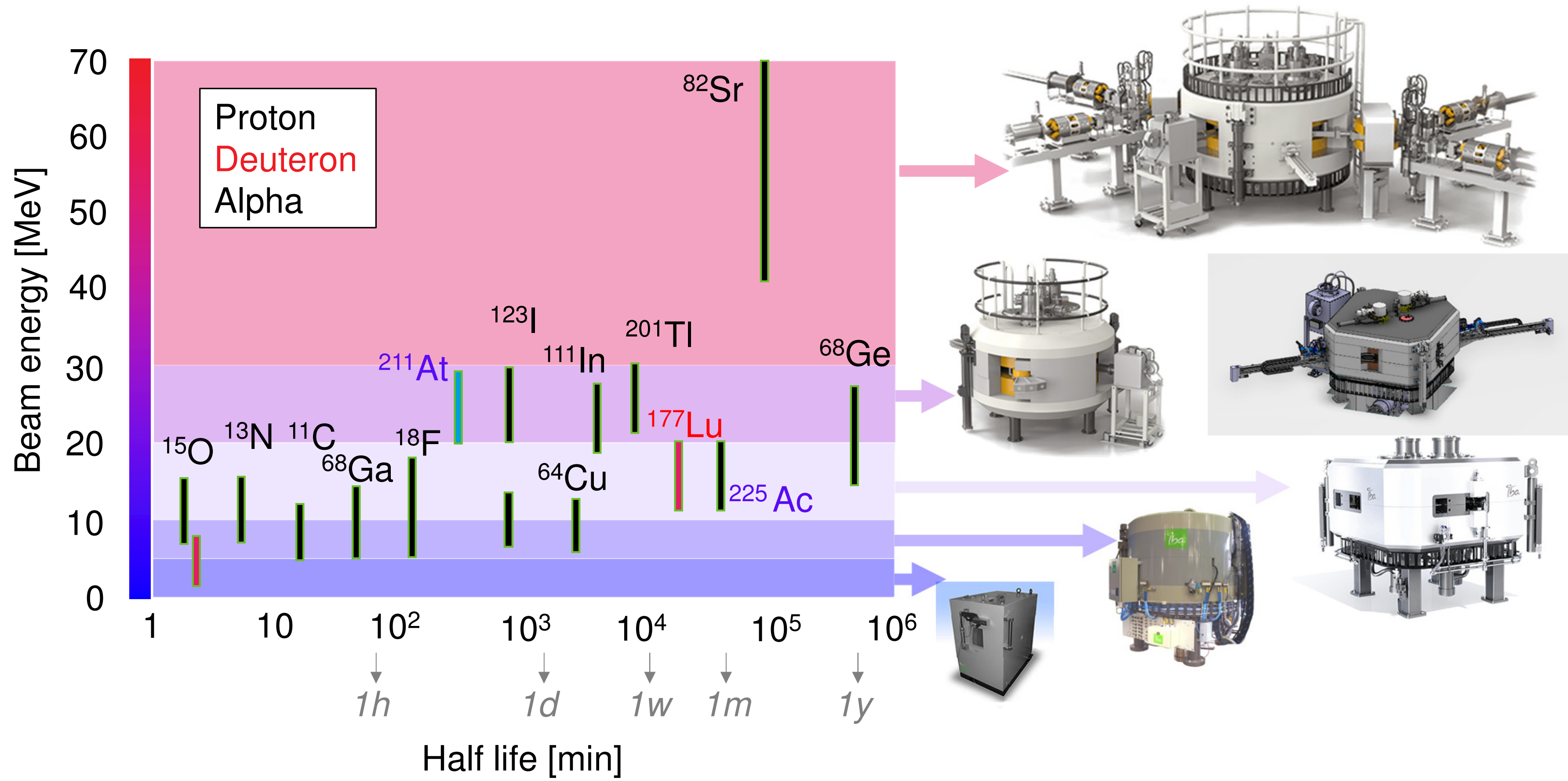


- Vacuum
- Extraction
- Targets
- auxiliaries



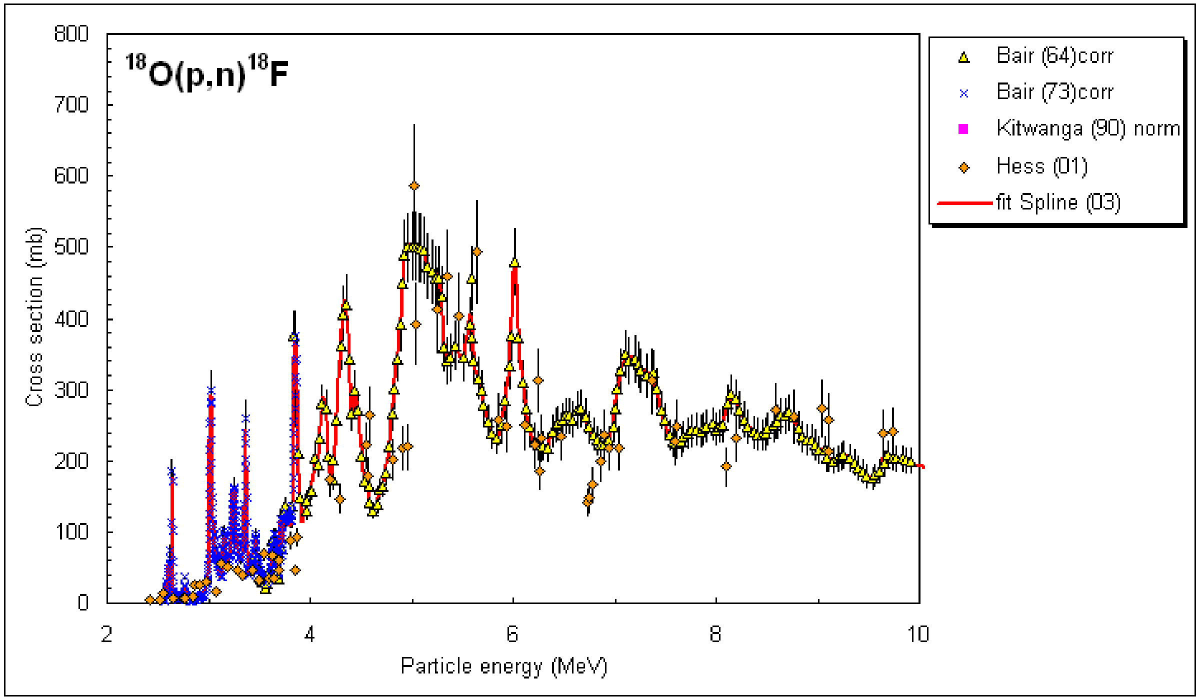
$^{18}O\ (p,n)^{18}F$

Energy ranges & example of IBA cyclotrons



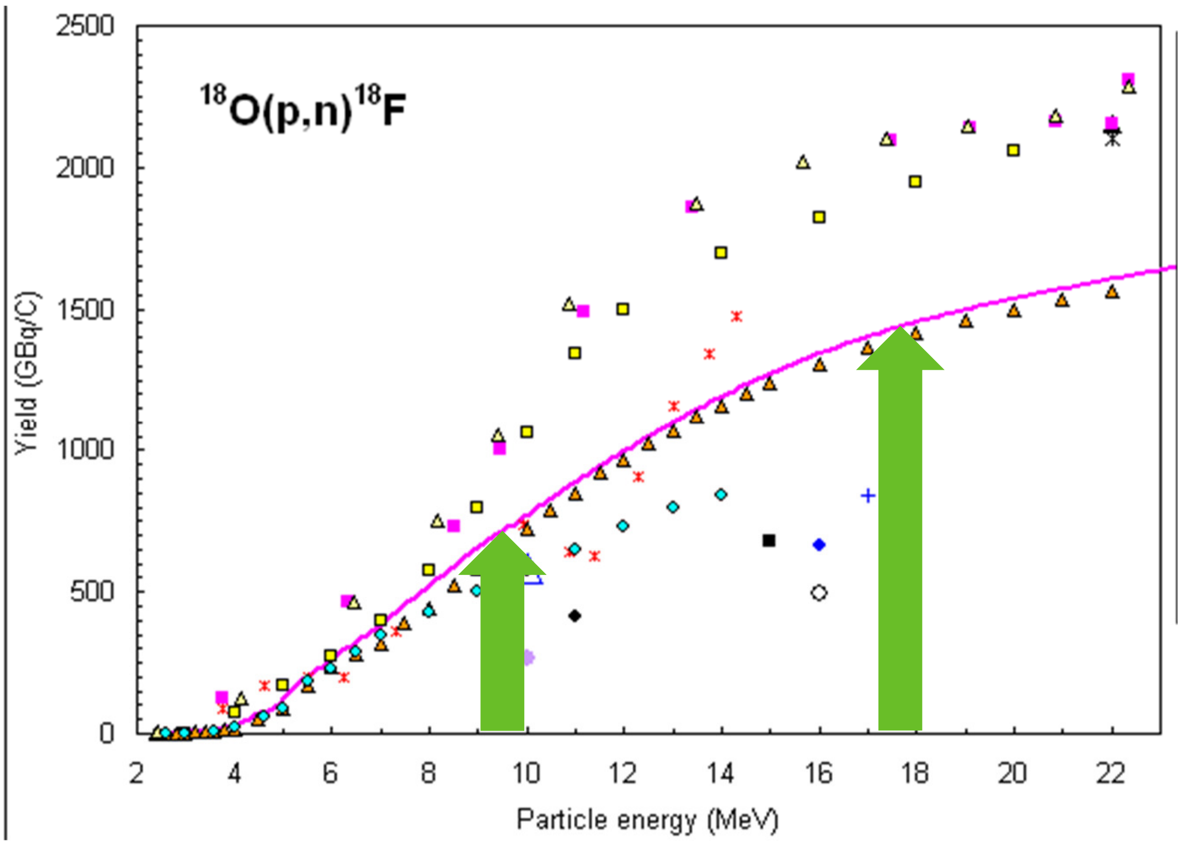
Isotope production

- ‘Yield’ based on nuclear cross section, particle energy
- Proportional to particle beam current
- Effect of beam time (Tirr) vs radioactive decay (T1/2)



Protect, Enhance and Save Lives

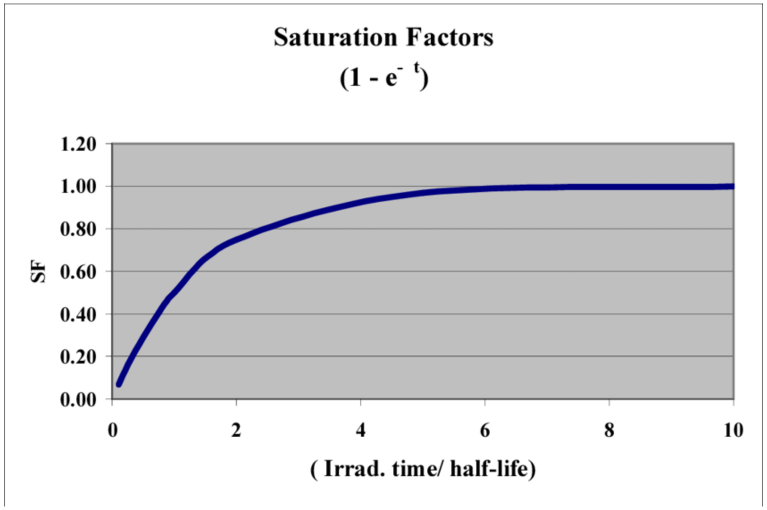
Ep on 18O(p,n)18F, cummulative yield ‘at saturation’



Factor 2 by choosing the right energy !

Activity EOB

$A_{EOB} = \mathbf{Y_{sat}} \times \mathbf{I_{\mu A}} \times (1-\exp(-\ln 2(\mathbf{T_{irr}}/T_{1/2}))$



- 18F (110min) – usual beam time 2 h
- 68Ge (271 days) – usual beam time 4-5 days

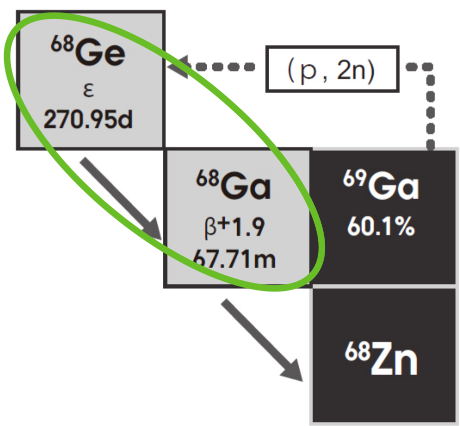
Cyclotron for PET : Cyclone® KIUBE

PET isotopes production

✓ Rather short-lived isotopes:
- local supply / in-house
- Small distribution radius

✓ Rather low E proton:
- Compact cyclotrons 16-18MeV

✓ Or Generator concept !



Radioisotope	Half-life	Decay (%)	β^+ Endpoint (MeV)	Principal Nuclear Reactions
^{11}C	20.3 min	β^+ 99.8, EC 0.2	0.961	$^{14}N(p,\alpha)^{11}C$
^{13}N	9.96 min	β^+ 100	1.190	$^{16}O(p,\alpha)^{13}N$
^{15}O	122 sec	β^+ 99.9, EC 0.1	1.723	$^{14}N(d,n)^{15}O$ $^{15}N(p,n)^{15}O$
^{18}F	109.8 min	β^+ 96.9, EC 3.1	0.635	$^{18}O(p,n)^{18}F$ $^{20}Ne(d,\alpha)^{18}F$
^{61}Cu	3.41 hr	β^+ 62, EC 38	1.205	$^{60}Ni(d,n)^{61}Cu$ $^{61}Ni(p,n)^{61}Cu$
^{62}Cu (gen.)	9.73 min	β^+ 97.8, EC 2.2	2.934	$^{63}Cu(p,2n)^{62}Zn$(9.1 hr) → ^{62}Cu
^{64}Cu	12.7 hr	β^+ 19, EC 41, β^- 40	0.657	$^{64}Ni(p,n)^{64}Cu$, *$^{64}Zn(n,p)^{64}Cu$*
^{82}Rb (gen.)	75 sec	β^+ 96, EC 4	3.35	$^{85}Rb(p,4n)^{82}Sr$(25 d) → ^{82}Rb
^{86}Y	14.7 hr	β^+ 34, EC 66	1.248, others	$^{86}Sr(p,n)^{86}Y$
^{124}I	4.15 d	β^+ 25, EC 75	1.533, 2.134	$^{124}Te(p,n)^{124}I$

Adapted from Gonzales, Cyclotope

A STORY OF CYCLOTRON INNOVATIONS

IBA Cyclone KIUBE, what to learn from it (2015-2016)

Optimization of "conventional cyclotrons" still possible and driven by new simulation tools !

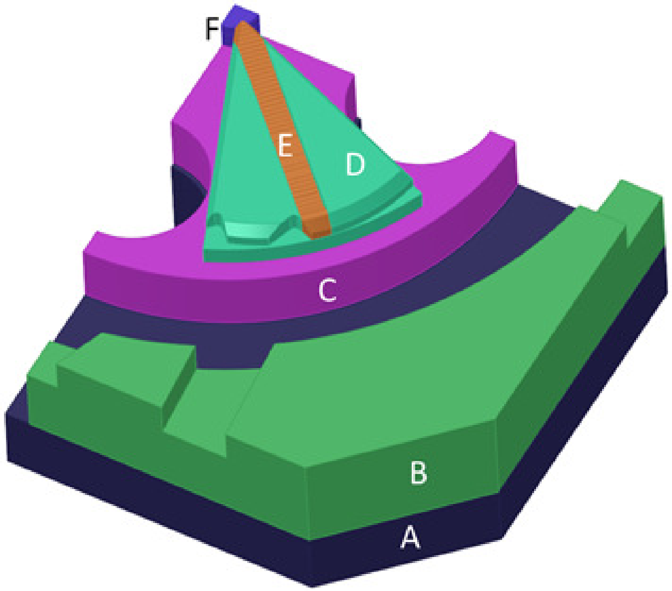
24 Tons

16 Tons

what to learn from it (1/6)

90's → 21st century tools

- Improved magnet design (OPERA3D)

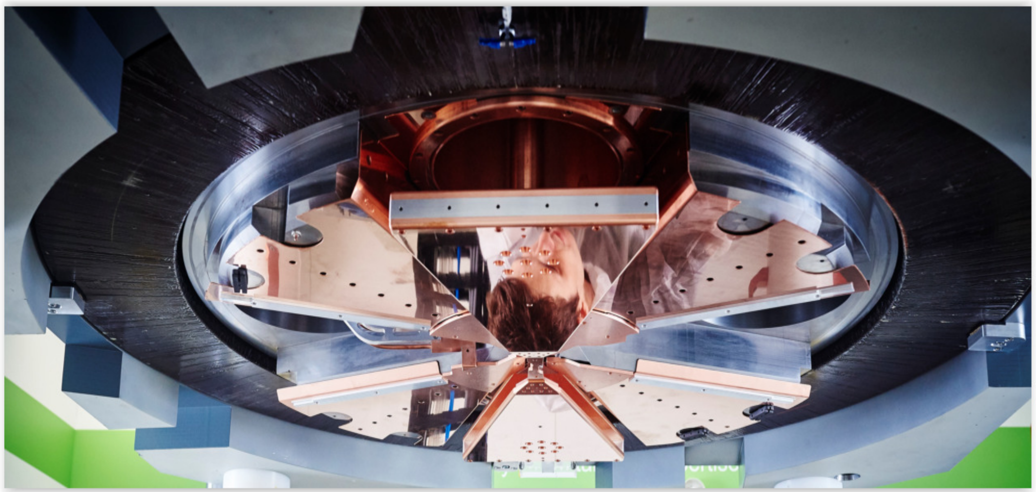


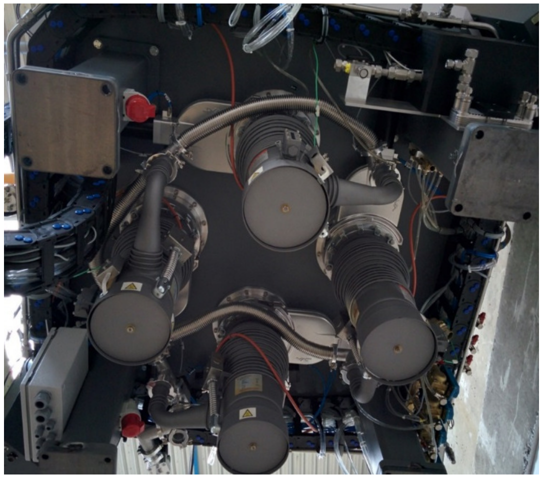
Protect, Enhance and Save Lives

what to learn from it (2/6)

90's → 21st century tools

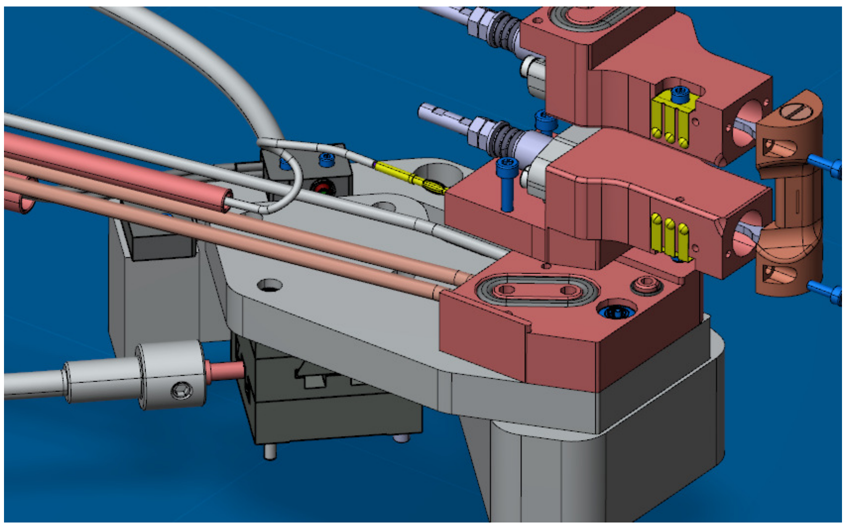
- Improved magnet design (OPERA3D)
- Improved vacuum design (Comsol) : **H-** (transmission 50% -> 70%)

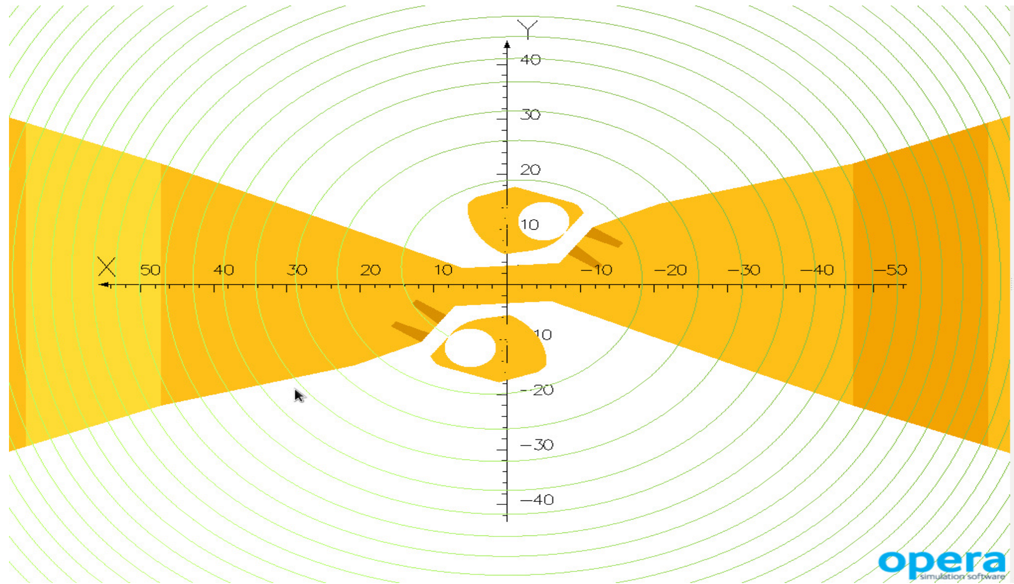




what to learn from it (3/6)

90's → 21st century tools
- Improved magnet design
- Improved vacuum design (Comsol)
- Optimized central region



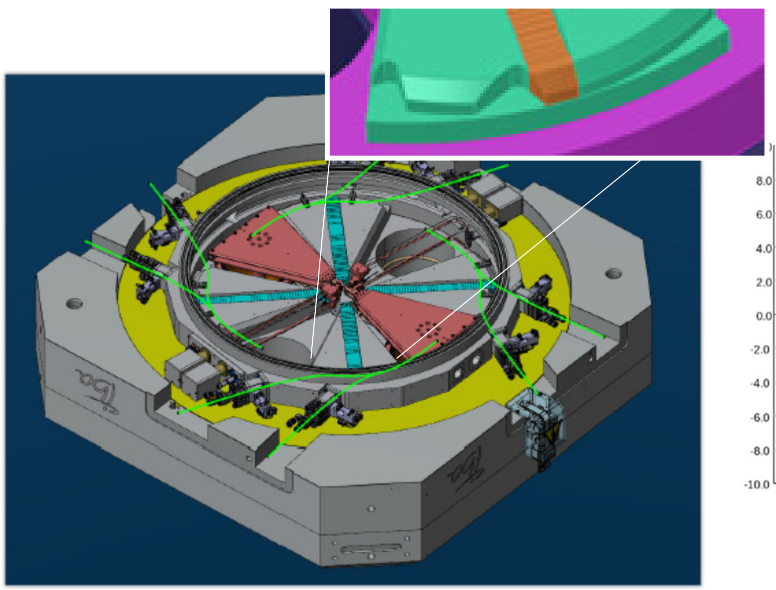


- *Motorized source positioning for better orbit centering & ease of maintenance*

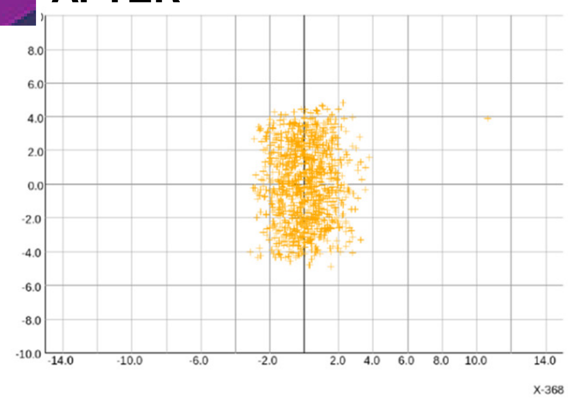
what to learn from it (4/6)

90's → 21st century tools

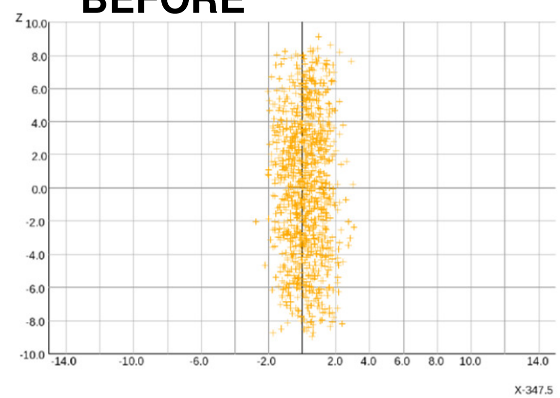
- Improved magnet design
- Improved vacuum design
- Optimized central region
- Optimized extraction optics



AFTER



BEFORE



A compact, internal Twin source cyclotron 18 MeV

Performance

300 µA

Vacuum

40 min
4 pumps

Flexibility

13-18 MeV
8 ports

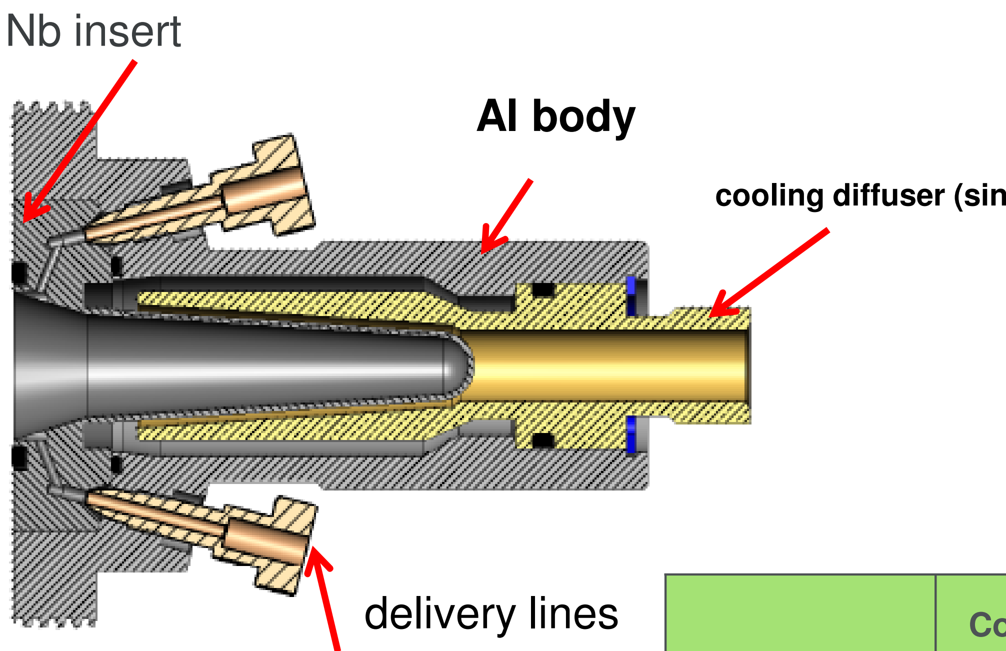
CYCLONE® KIUBE

EP16169489, EP16169490
EP16169494, EP16169497
EP16171282

Reliability

2 ion sources
4 strippers /port

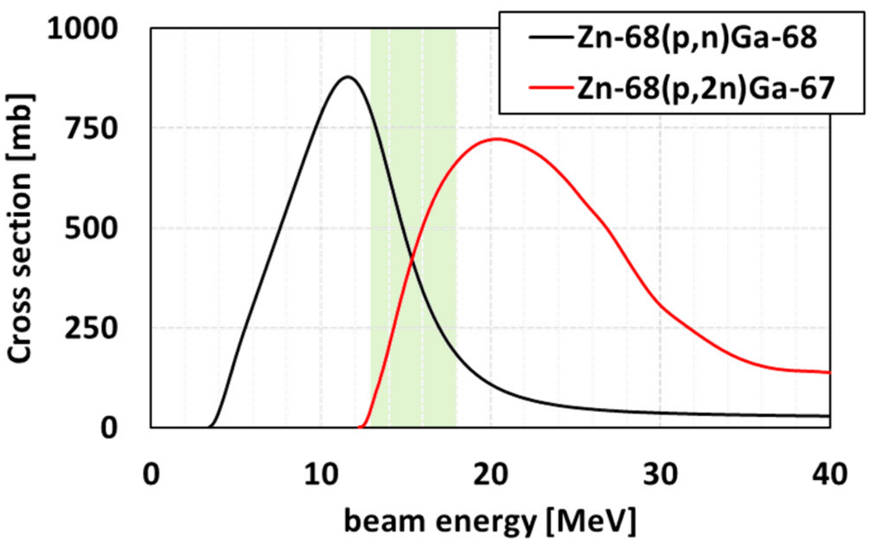
LIQUID target 18F : 2,4 kW in 4 ml of 18O- water



	Conical 5	Conical 8	Conical 12	Conical 16
Filling volume	**1,8ml**	**~2.3 ml**	**~2.7 ml**	**~4 ml**
Current	45 µA	70 µA	100 µA	135 µA
Activity output (2h)	**5 Ci** 185 GBq	**8 Ci** 296 GBq	**12 Ci** 444 GBq	**16 Ci** 592 GBq

Optimize Ep on target

Isotope	Energy on target [MeV]
Zr-89	14-15
Cu-64	11-14
Ga-68	13

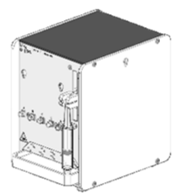


OPTIMIZATION of Ep for the product quality (Ga68 direct production)

- **Energy degrader foil**
- **Variable E on machine**

Novel routes of production: ^{68}Ga & ^{64}Cu

Complete ^{68}Ga production process from **liquid target** up to the final injectable drug for human use:



^{68}Ga
$GaCl_3$

^{68}Ga
PSMA
DOTATATE
DOTANOC

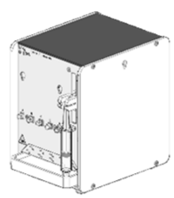
Cyclone® KIUBE

Ga-68 target

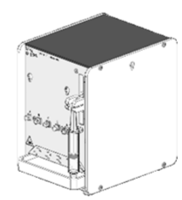
Cu-64/61 target

Purification:
Synthera® Extension

Labelling: Synthera®



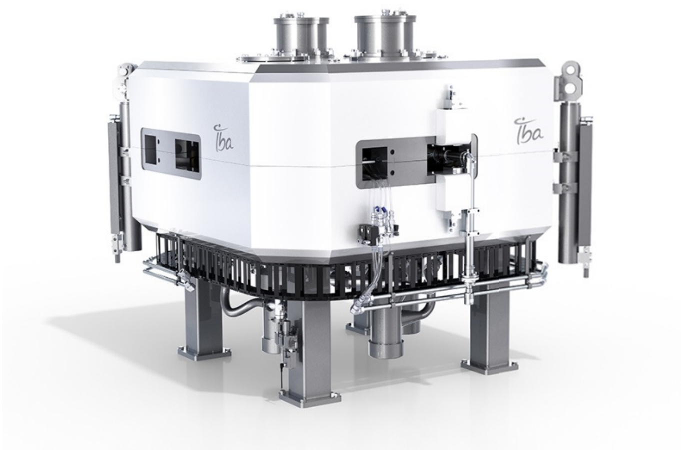
^{64}Cu
$CuCl_2$



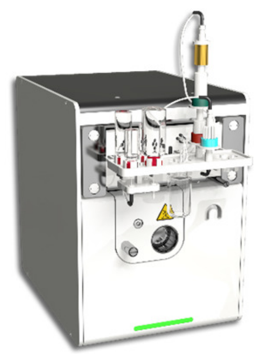
^{64}Cu
ATSM

Collaboration with the University of Coimbra

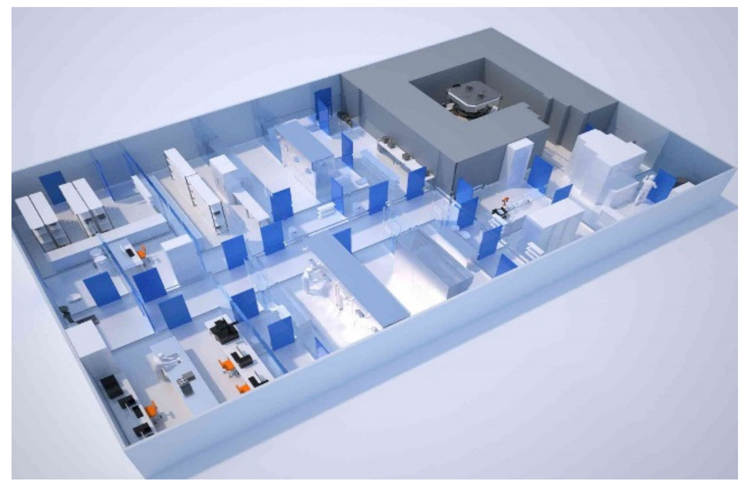
RadioPharma Solutions : INTEGRALAB



CYCLONE® **KIUBE**



SYNTHERA®+



INTEGRALAB®

RadioChemistry- Synthera®+ Family for 18F-chemistry

+800 Synthera® worldwide

- **BETTER**
  Multiple runs of multiple tracers
- **SMARTER**
  Accessory-based ‘IFP’
- **STRONGER**
  Consistent yield and high uptime

Protect, Enhance and Save Lives

Cyclone KIUBE extended option (beam line + solid target)

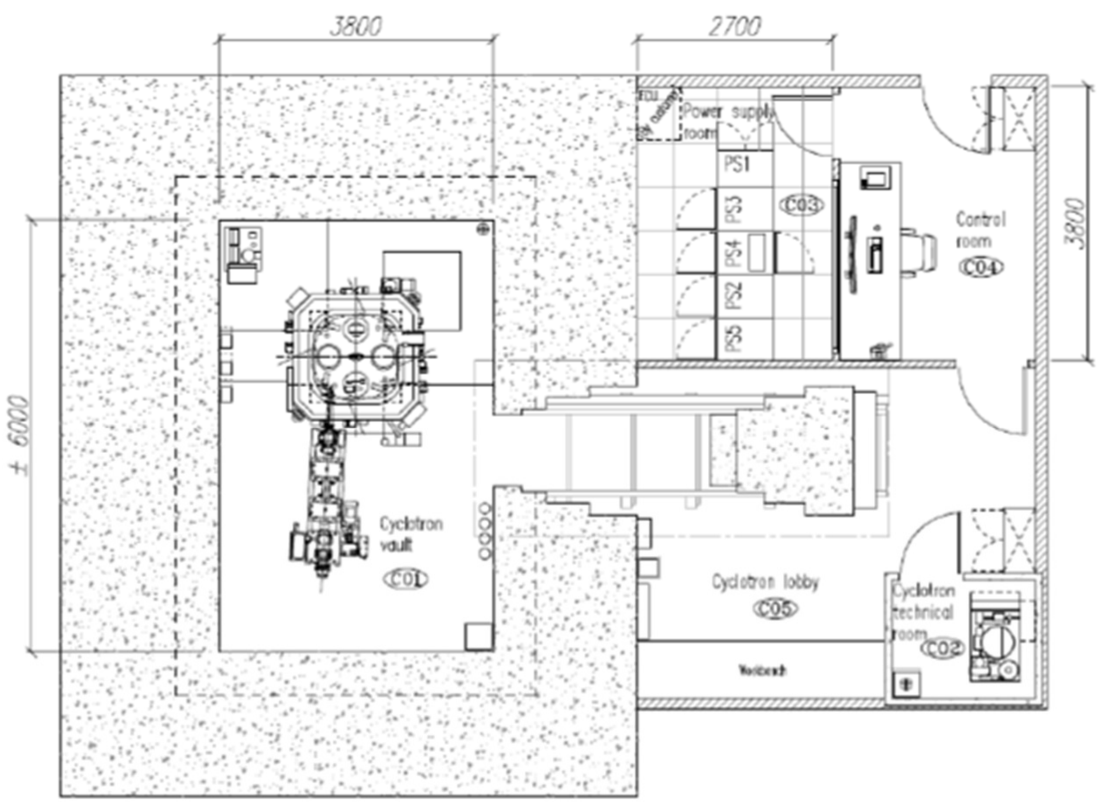
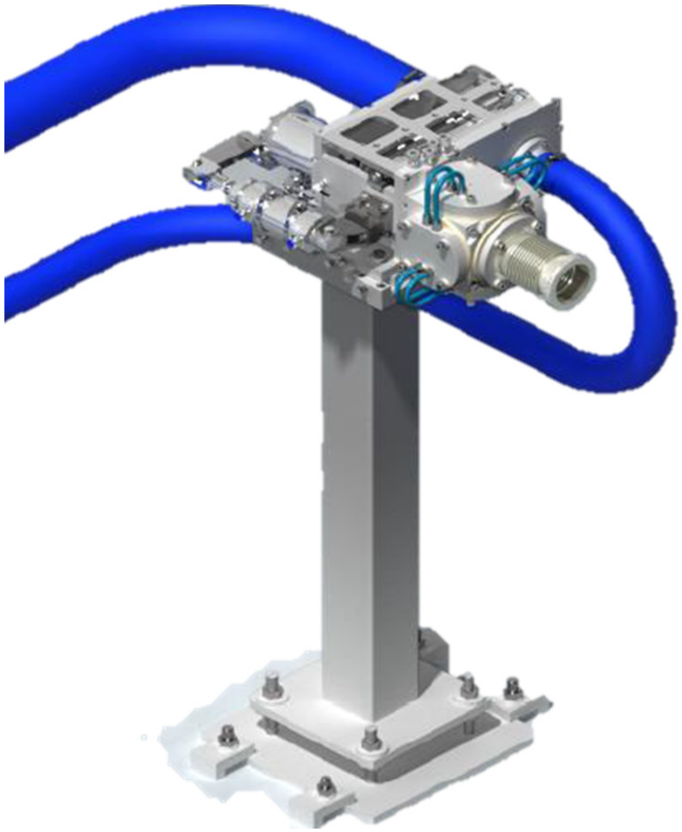
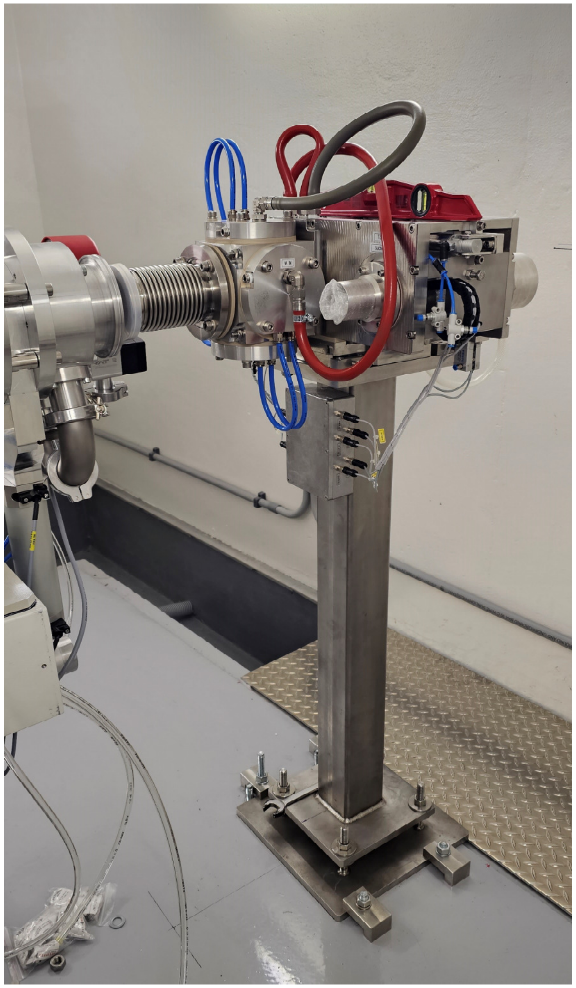


Figure 23: Cyclone® KIUBE with short beam line (vault)

- Bunker 12m x9 m
- + Power house 8x4m
- One bunker door
- Maintenance = total off

Solid target system high-power/ compact ~18 MeV





IBA Nirta® High Power Solid target – Isotopes range

List of isotopes that could be produced with IBA Nirta® High Power solid target

- ^{89}Zr (78h) from ^{89}Y(p,n) ~14-15 MeV
- ^{64}Cu (12.7h) from ^{64}Ni(p,n) ~11-14 MeV
- ^{124}I (4.15 d) from ^{124}Te(p,n) 14.5 MeV
- ^{123}I from ^{123}Te(p,n) 14.5 MeV
- ^{76}Br (16h) from ^{76}Se(p,n) 16 MeV
- ^{86}Y (14.7 h) from ^{86}Sr(p,n) 15 MeV
- ^{66}Ga (9.5h) from ^{66}Zn(p,n) 16 MeV
- ^{68}Ga (68 min) from ^{68}Zn(p,n) ~ 13 MeV

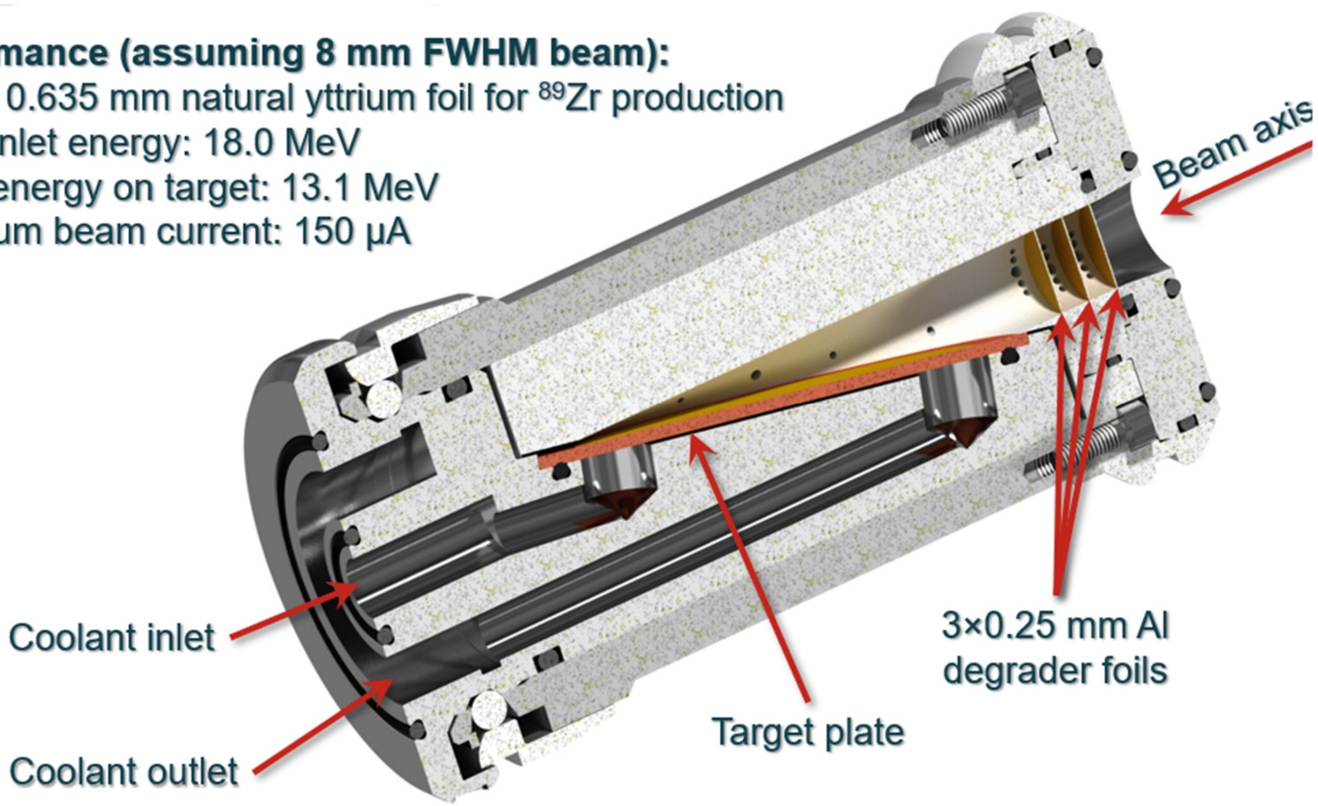
- ^{100}Mo(p,2n) Tc^{99} ~18 MeV

(Energy ON TARGET)

Nirta® - High Power Solid Target – capsule configuration for 89Zr – Cu64

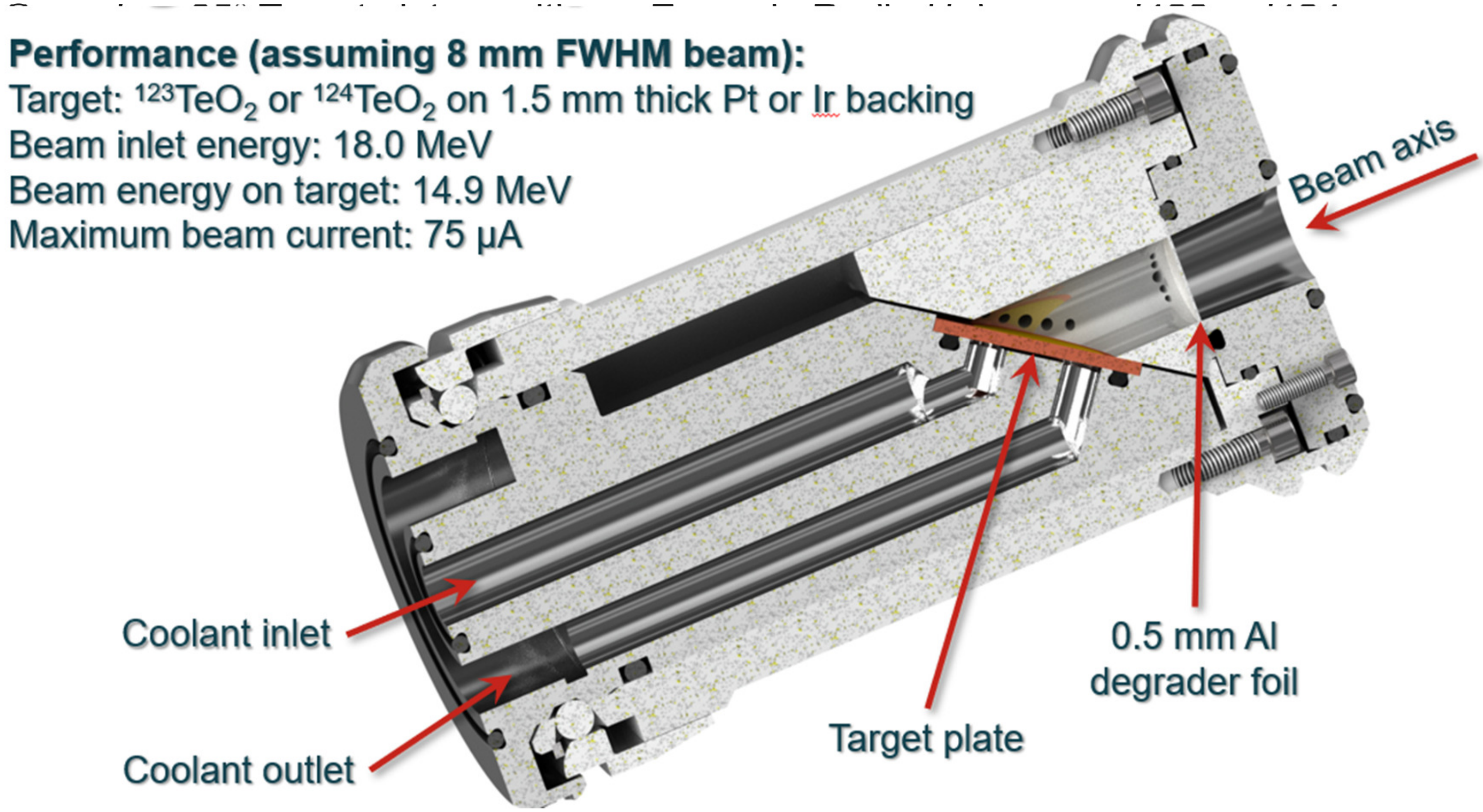
Irradiation Capsule – 10° Target plate position – Radio-Metal Production, e.g. Zr89 and Cu64

Performance (assuming 8 mm FWHM beam):
Target: 0.635 mm natural yttrium foil for ^{89}Zr production
Beam inlet energy: 18.0 MeV
Beam energy on target: 13.1 MeV
Maximum beam current: 150 µA



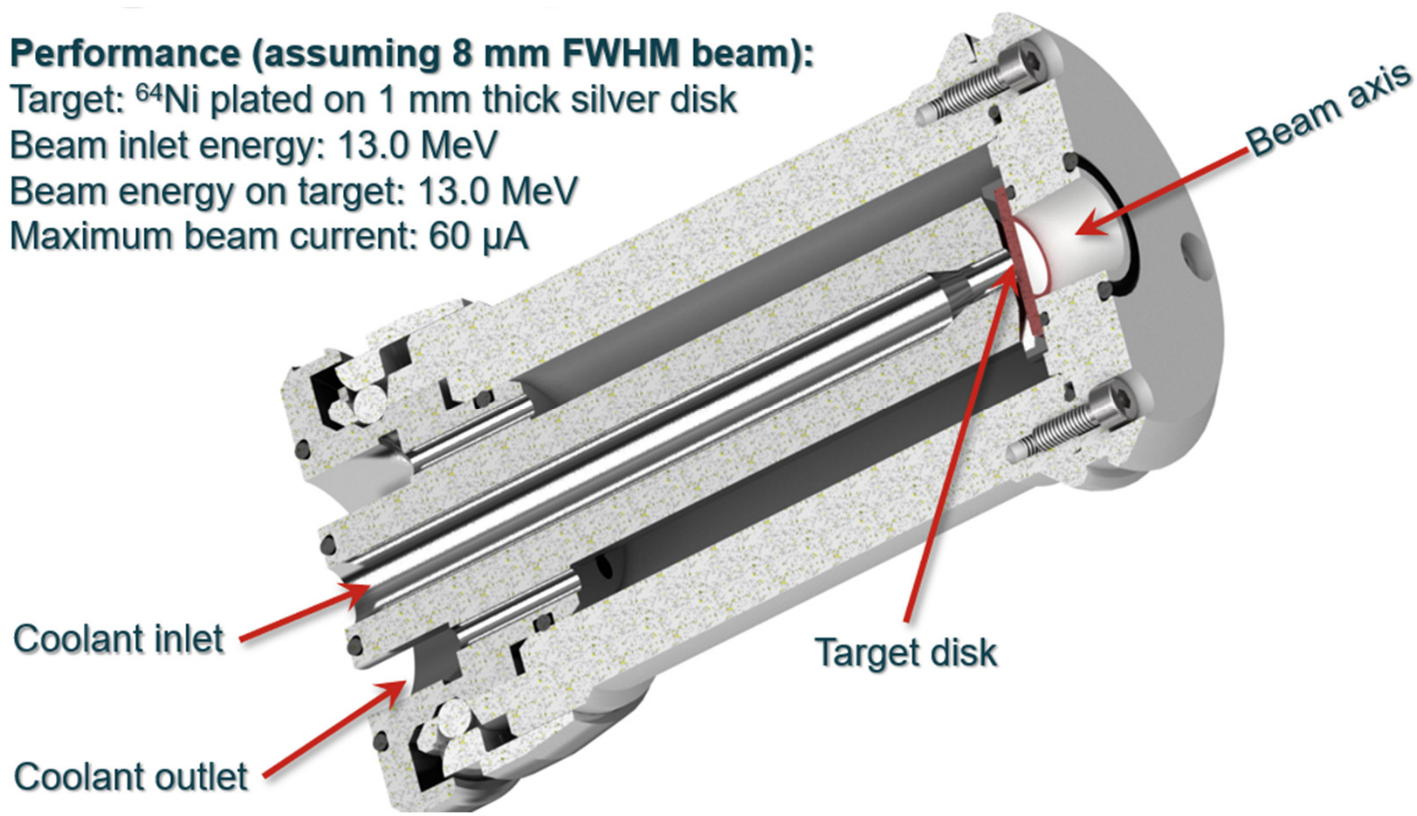
Nirta® - High Power Solid Target – capsule configuration for 123I and 124I

Irradiation



Nirta® - High Power Solid Target – capsule configuration for 64Cu low current

Irradiation Capsule – 90° Target plate position – Example Radio-Metal Production, e.g. Cu64



Cyclone® IKON 13-30 MeV

30 MeV for 'SPECT' isotopes production

Isotope	Energy	Beam	Reaction
Tl-201	28-30	p	Tl-203(p,3n)Pb-201
In-111	25-28	p	Cd-112(p,2n)In-111
Ga-67	25-28	p	Zn-68(p,2n)Ga-67
I-123	22-30	p	Xe-124(p,2n)Cs-123

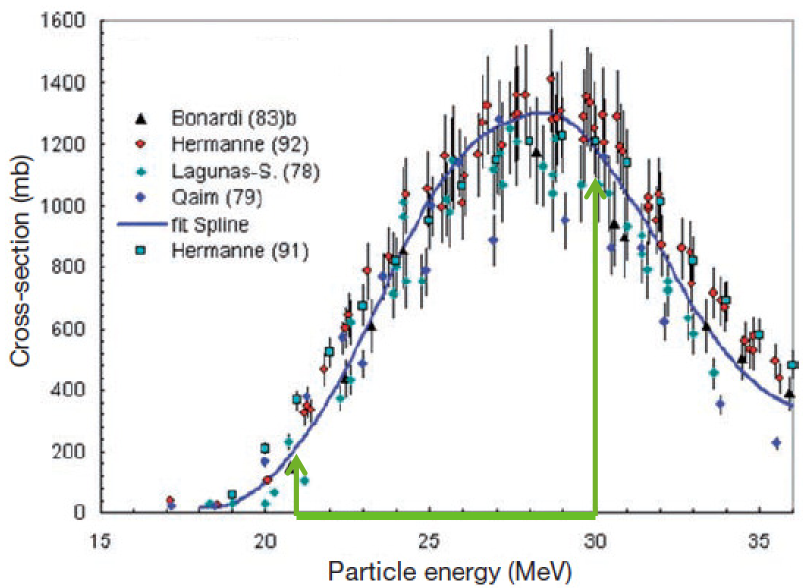


FIG. 2.40.1. Excitation function for the $^{203}Tl(p, 3n)^{201}Pb$ reaction.

✓ Rather long-lived isotopes:
- Centralized supply
- Overseas shipment
- Gov – Large pharma cmpy

✓ Higher power and often fragile targets :
- **External targets in dedicated vault**
- Extraction to long beam lines
- Beam optics to manage
- Beam losses to avoid

Table 4

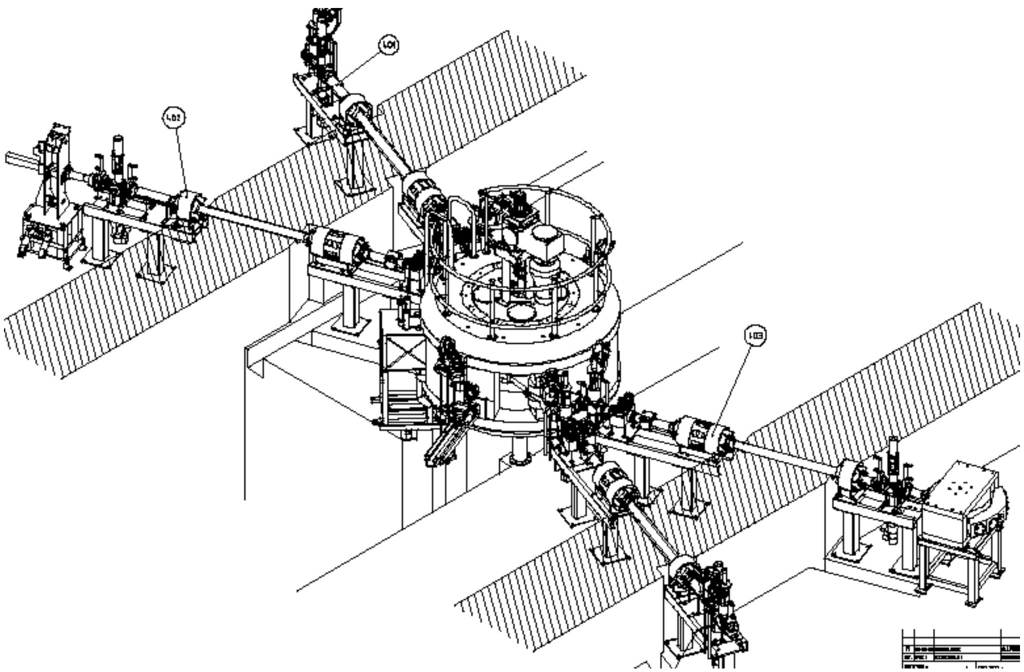
Specification of thallous (Tl-201) chloride injection

Half life	73.1 hours
Energy of gamma rays	0.068 to 0.082 (Hg K X rays)
Radionuclidic impurity	Tl-202 < 1.9% Tl-200 < 1.0% Pb-203 < 0.25%

Protect, Enhance and Save Lives

Cyclone 30 MeV proton for SPECT

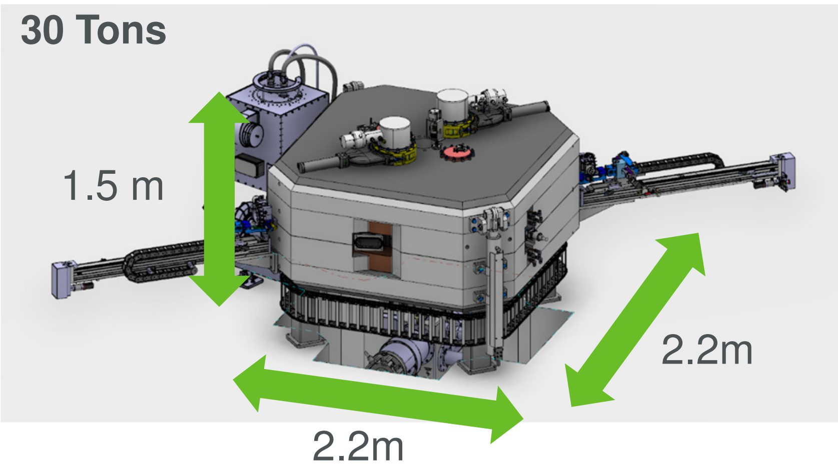
- 15- 30 MeV variable Energy proton
- Up to 1.2 mA proton (~ 36 kW)
- Mainly for SPECT isotopes (p,2n) (p,3n)
  - ~ Compact cyclotron (60 Tons)



IBA Cyclone 30

Capitalizing on the Cyclone® KIUBE design

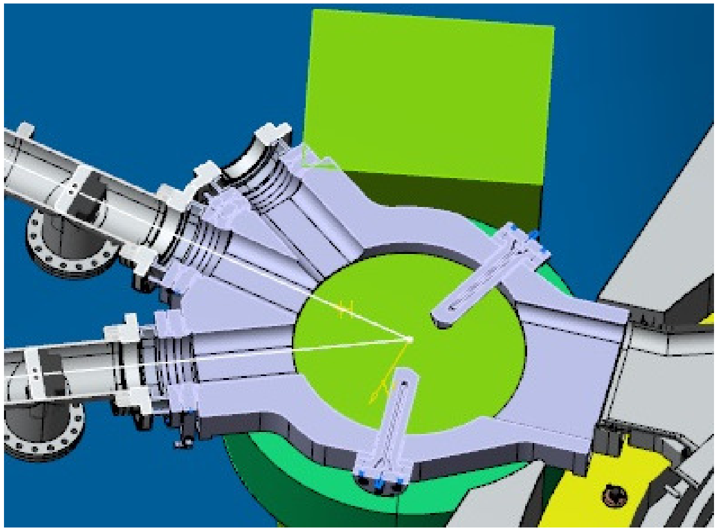
- to create a **compact, high-energy** and **high-current** Cyclotron

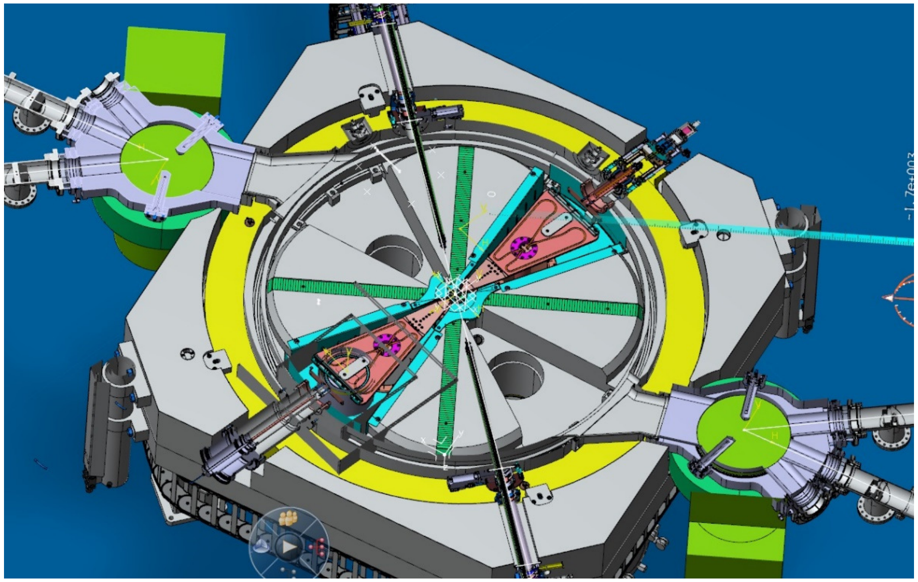


- Industrial cyclotron
  - >15% injection efficiency
  - >97% acceleration transmission
  - >99% extraction efficiency
  - >99% beam line transmission

Two exits – 3 ports each

- Up to 2x 2 long beam line 13-30 MeV
- Up to 2x 1 target at 18 MeV

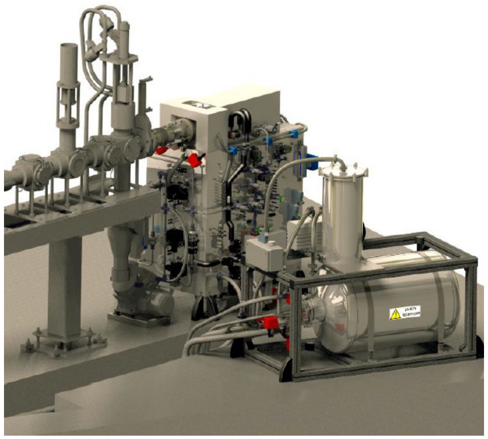




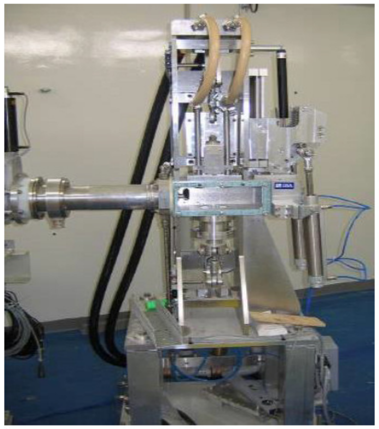
Installation first site ongoing (beam on tgt sept 2023)

Machine with complete target range & IBA chemistry

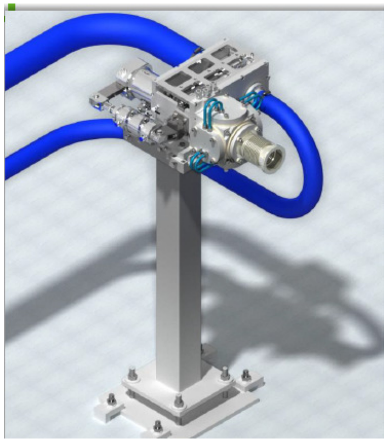
Xenon gas target
for ^{123}I



High power 30 MeV
solid target



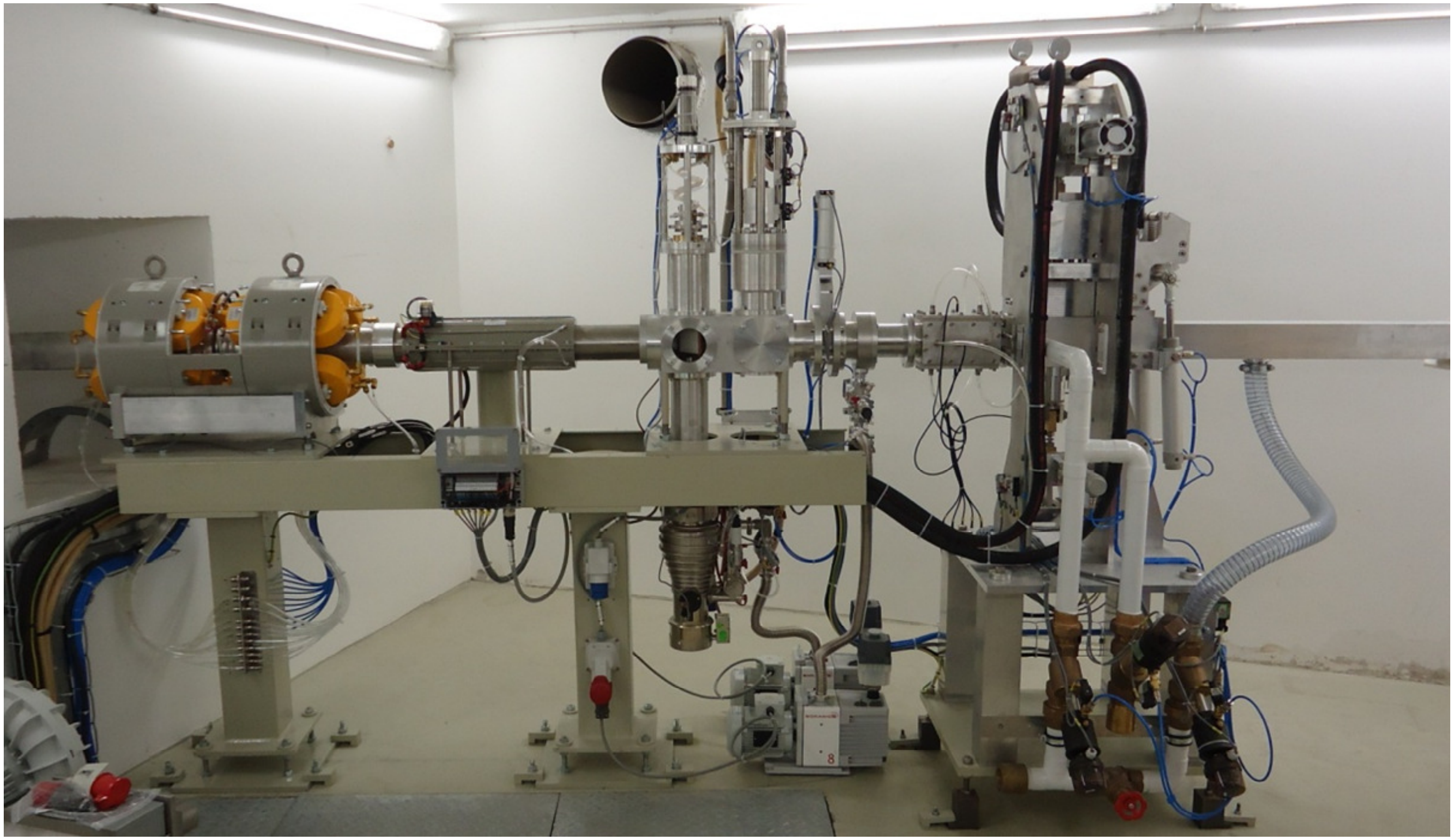
High power PET
solid target



Nirta® PET liquid
and gas targets

Solid target & beam line – target vault

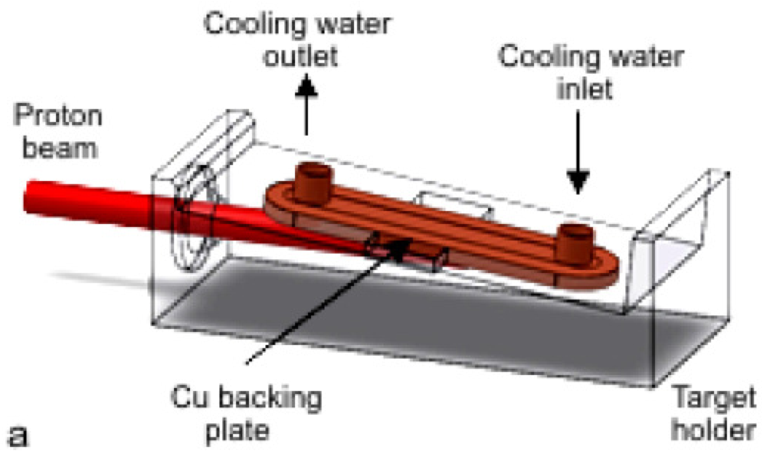
Need to control the beam on target

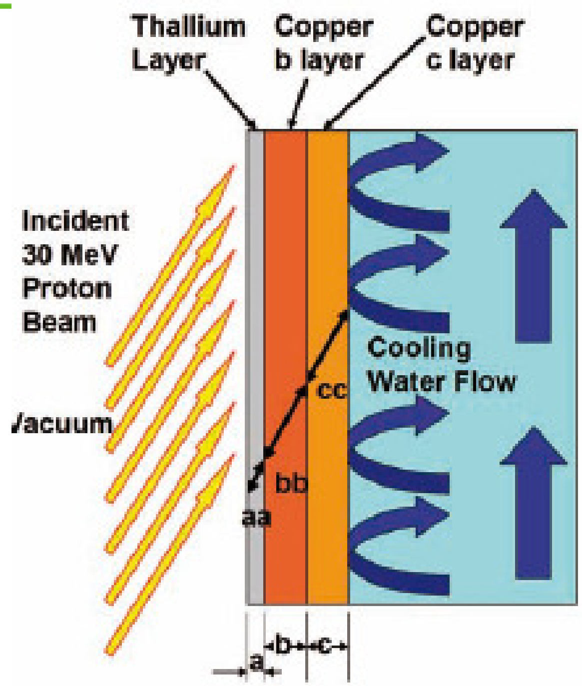


Protect, Enhance and Save Lives

Solid target process and constraints

- Avoid melting/evaporation





Element	Density $(g \cdot cm^{-3})$	Melting point (°C)	Thermal conductivity $(W \cdot cm^{-1} \cdot K^{-1})$
Copper	8.96	1083	4.03
Thallium	11.85	303	0.46

NUKLEONIKA 2011;56(4):283–289 & **IAEA TRS 465**

Solid target process and constraints

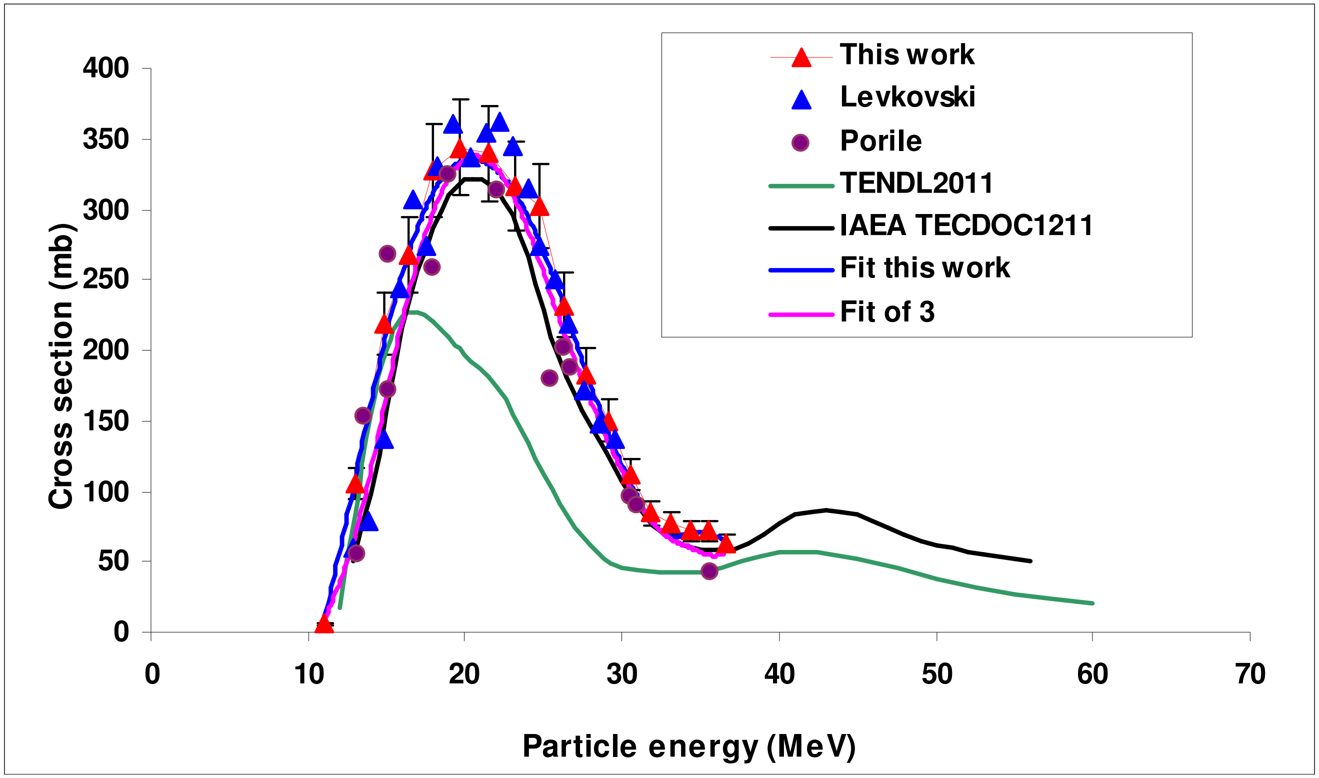
- Adherence to carrier up to T°irr
- Smooth & dense (no dentrites, no occlusions)
- Stress free & homogenous +/-5%
- No bath additives @ interface

- **No toxic (CN-)**
- **Time controlled layer thickness**
- **No post process (mechanical, thermal)**

IAEA TRS 432 – cyclotron solid target / Nukleonika 2010 / Rad Chem 2010

Production of PET generator : Ge68 / Ga68

Ge-68	18-30	p	nat Ga(p,x)Ge-68



Low yield reaction
Long lived Ge68:

⇒ Need high beam current ~500µA

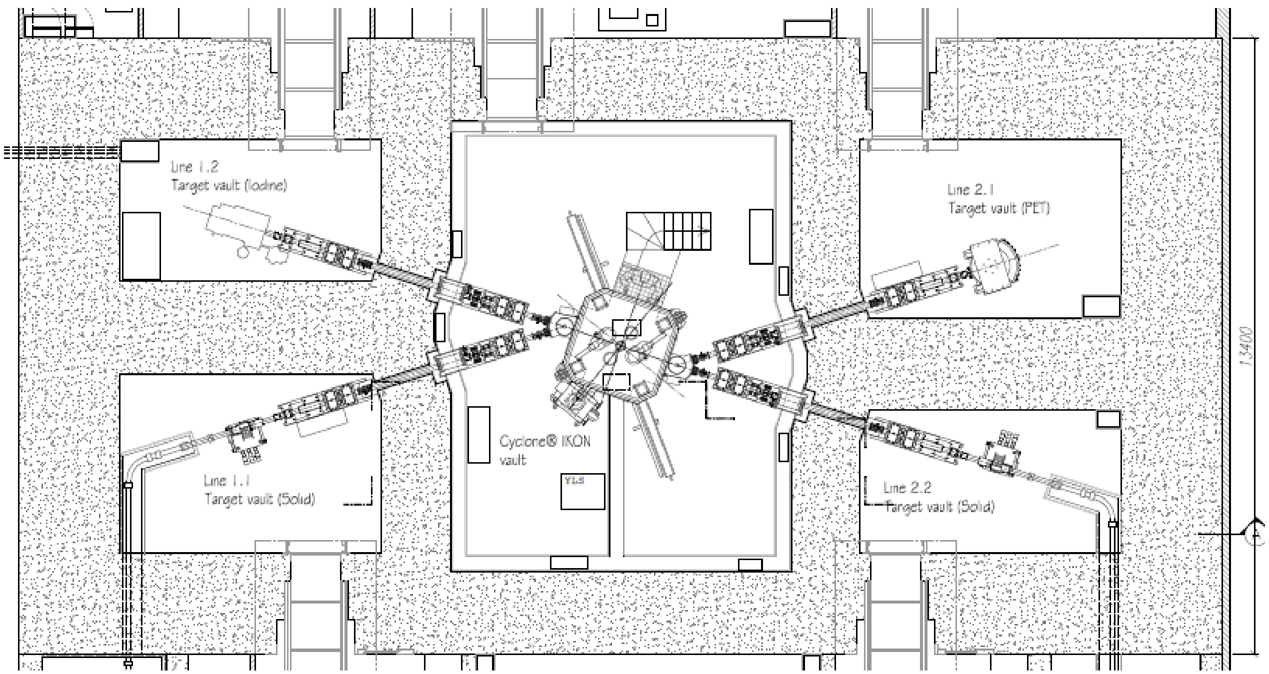
⇒ Long beam time ~4-5 days

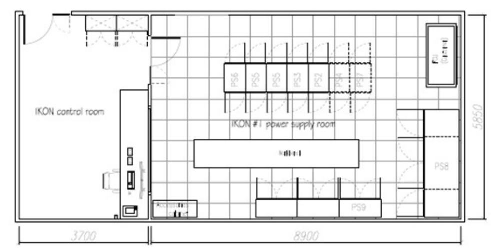
⇒ And low melting point of Ga !

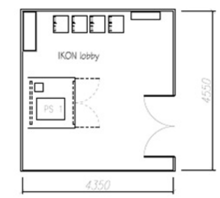
Protect, Enhance and Save Lives

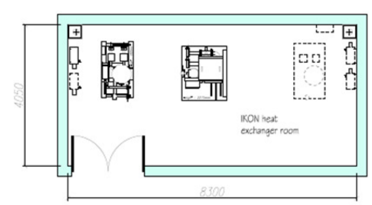
Cyclone IKON layout – fully redundant layout

- extended 26 m x 24m inc doors





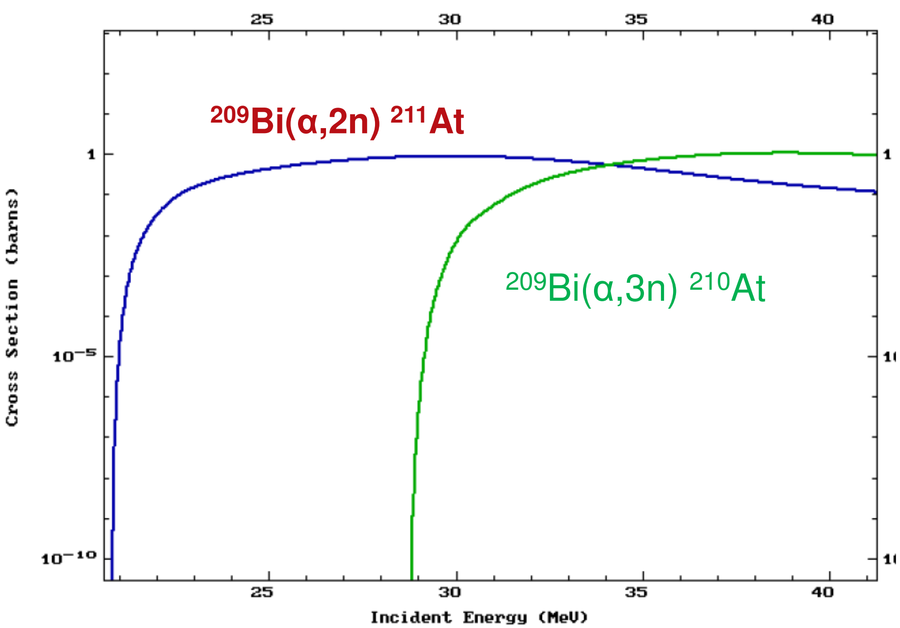


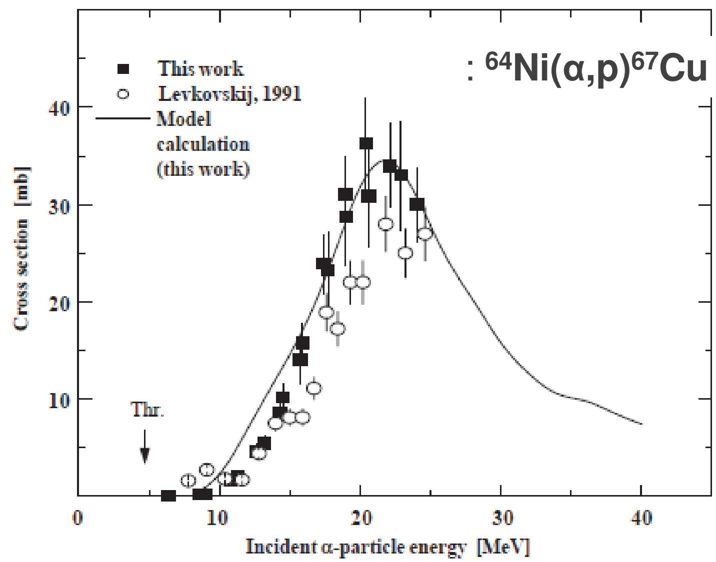


Rooms to be placed o

Extended family: Cyclone 30 XP (now in Julich & Polatom

- Cyclone 15- 30 MeV proton + 15 MeV deuteron
- Addition: 28- 30 MeV alpha beam (in positive ion)
- Production of ^{211}At & ^{67}Cu for Therapy



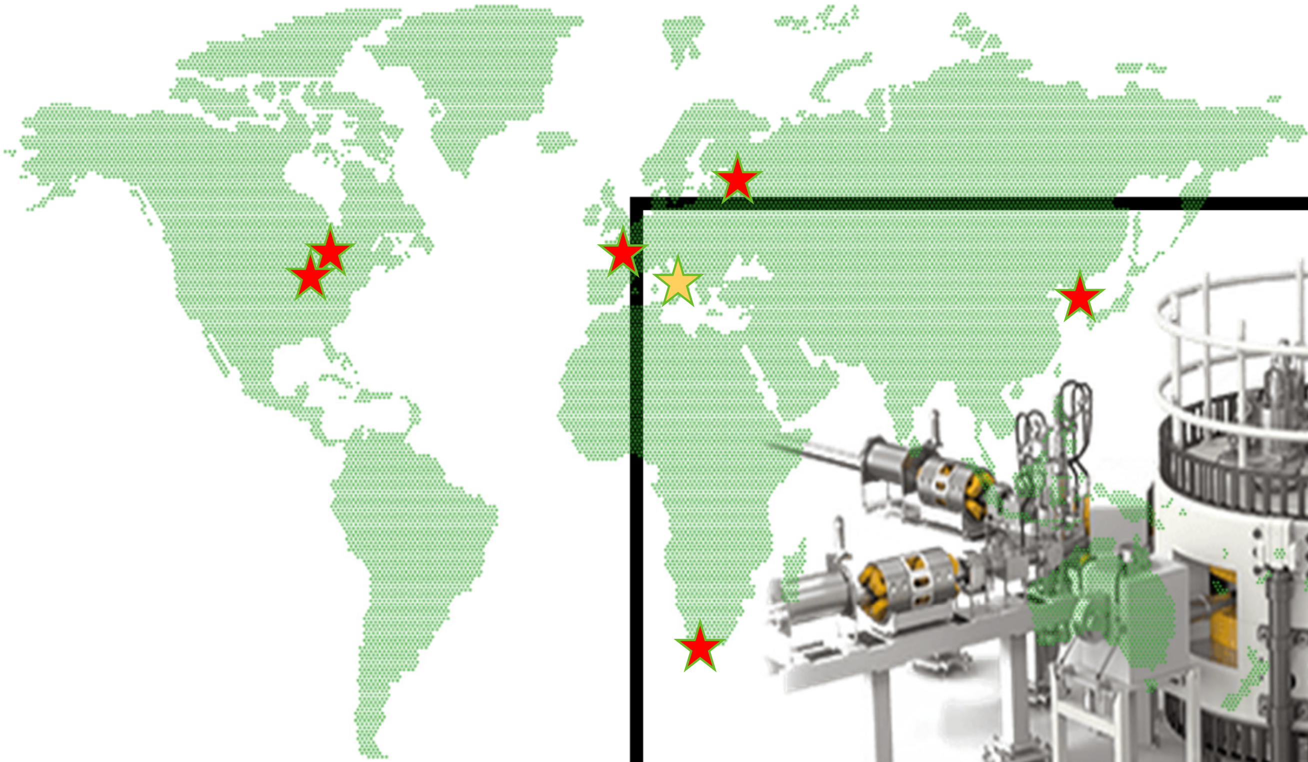


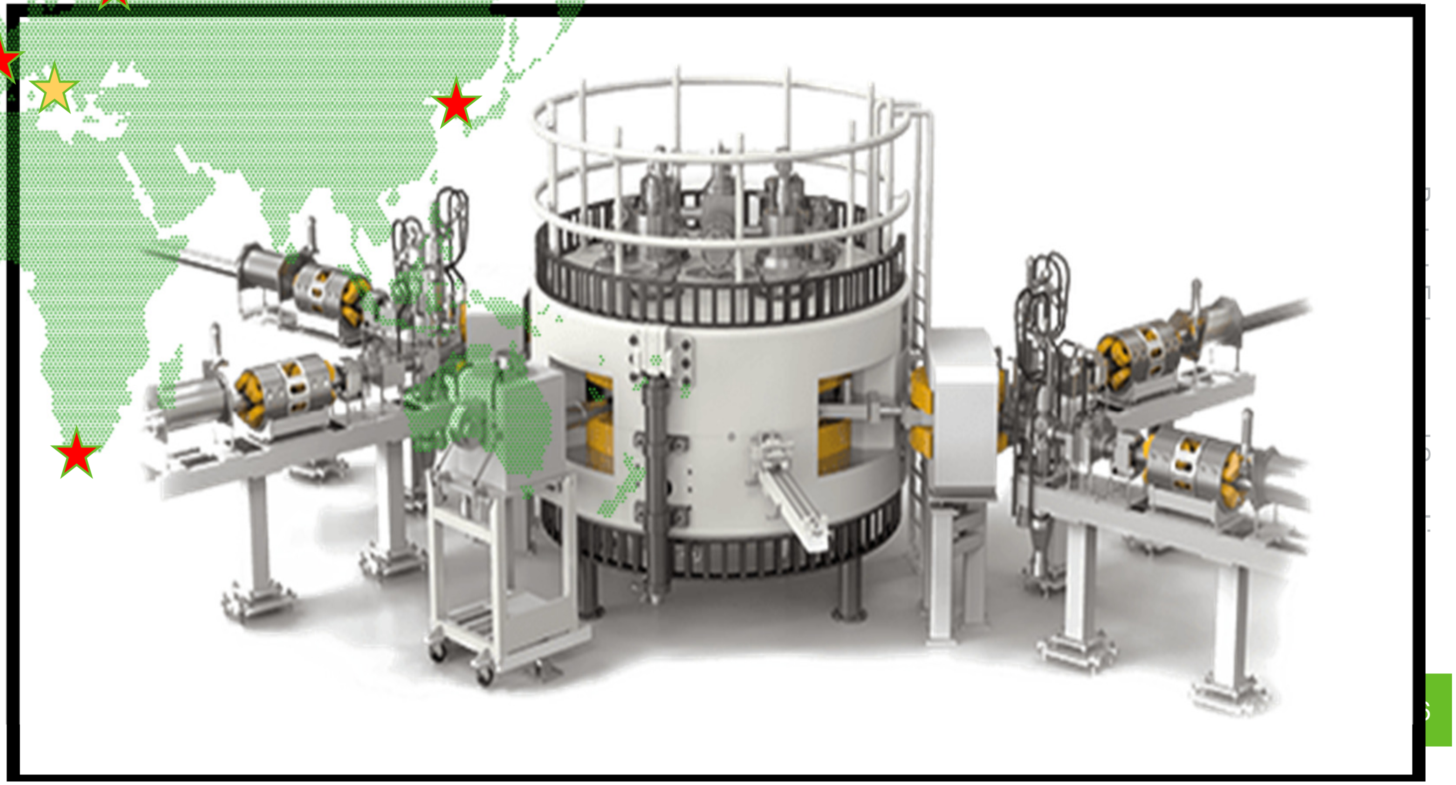
EANM 2010, # 7, session P14, Sunday Oct 10, geets et al.

Cyclone® 70P - specific use

Cyclotron High Energy segment 30- 70 MeV proton

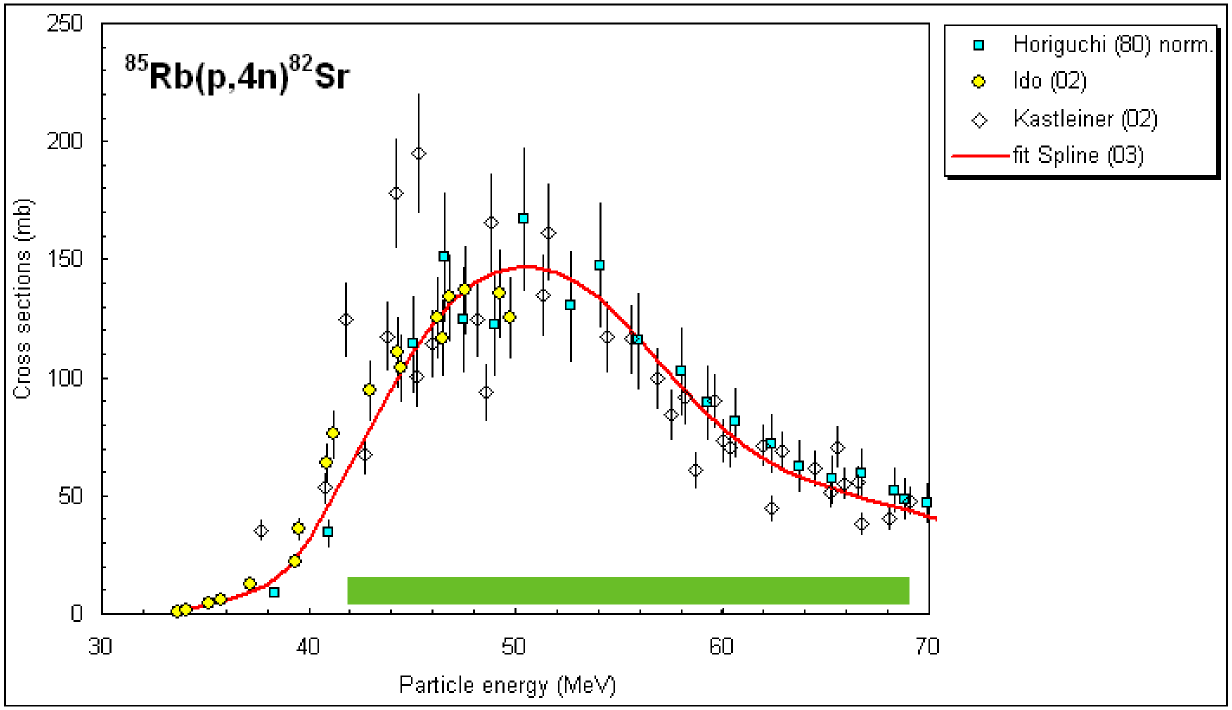
^{68}Ge ^{82}Sr





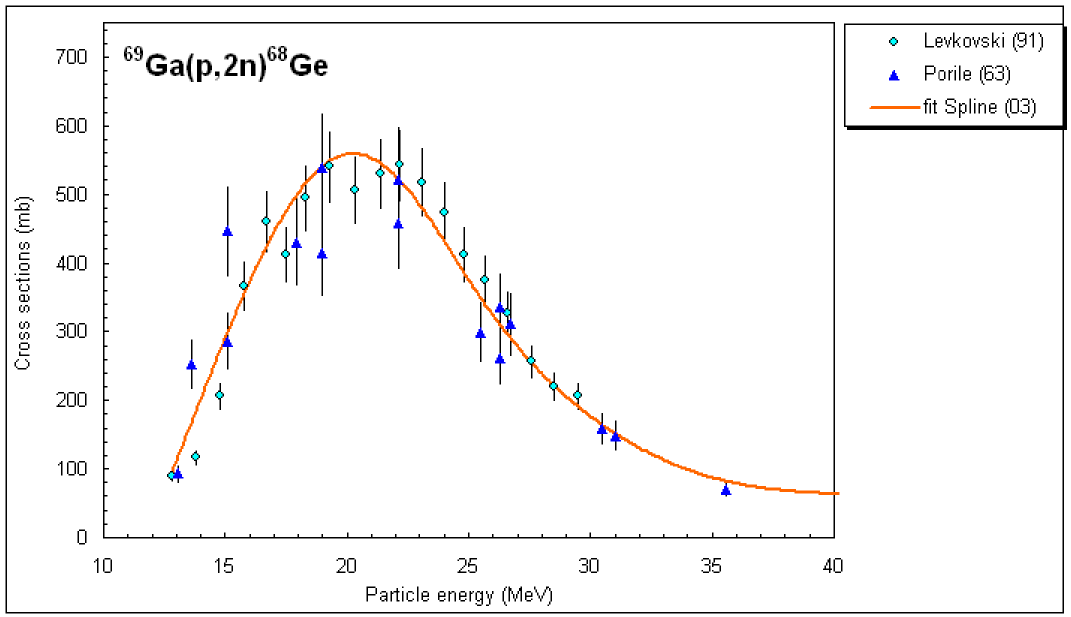
Sr/Rb : generator from cyclotron (or Linac..)

- ^{82}Sr (25d)/ Rb (1.2 min)
  - **$^{85}Rb(p,4n)\,^{82}Sr$** 42-65 MeV
  - Avoid (p,3n).. (< 41 MeV, proton energy lost)



Ge/Ga; generator from cyclotron

- ^{68}Ge (270d) /^{68}Ga (68 min) PET generator
  - Nat Ga(p,x)^{68}Ge 18- 50 MeV
  - ^{69}Ga(p,2n) ^{68}Ge 15- 40 MeV
- Gallium is liquid at ~room temp
  - Specific encapsulated tgt OR GaNi solid



Co production of interesting PET generators

Example: iThemba Labs target system

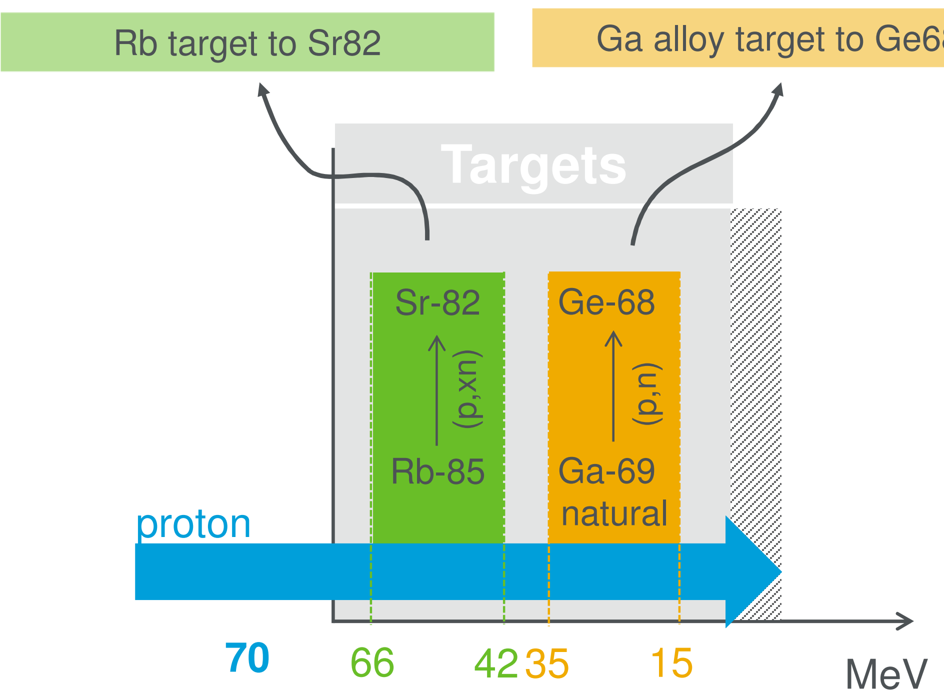
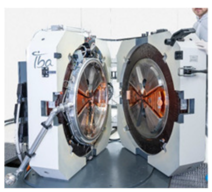


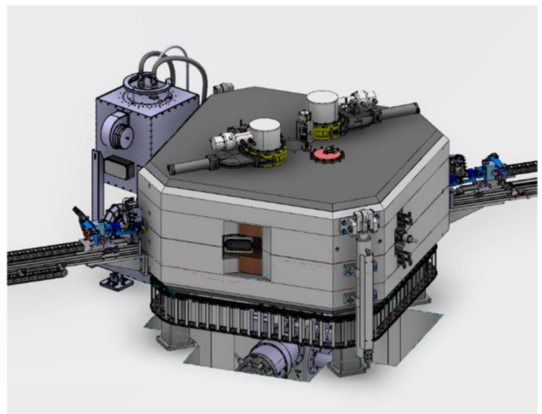
Figure 6. The tandem Rb/Ga targets mounted on a bayonet-mount plug.

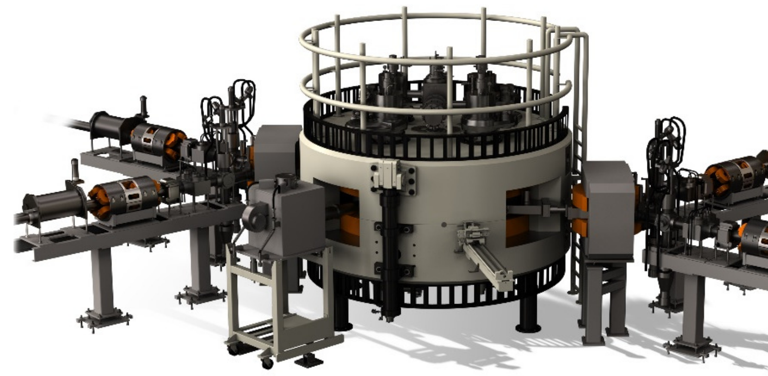
Instruments 2018, 2, 29; doi:10.3390/instruments2040029

Cyclone KEY; KIUBE, Cyclone IKON and the 70P

PET isotopes	SPECT & PET & Generators Ge68	PET Generators & SPECT







9 MeV

^{18}F ^{13}N

18 MeV

^{18}F ^{11}C ^{13}N ^{99}Tc

^{68}Ga ^{89}Zr ^{123}I ^{64}Cu

13 - 30 MeV

^{68}Ge ^{211}At ^{123}I

^{225}Ac ^{111}In ^{201}Tl

30 - 70 MeV

^{123}I ^{68}Ge ^{82}Sr

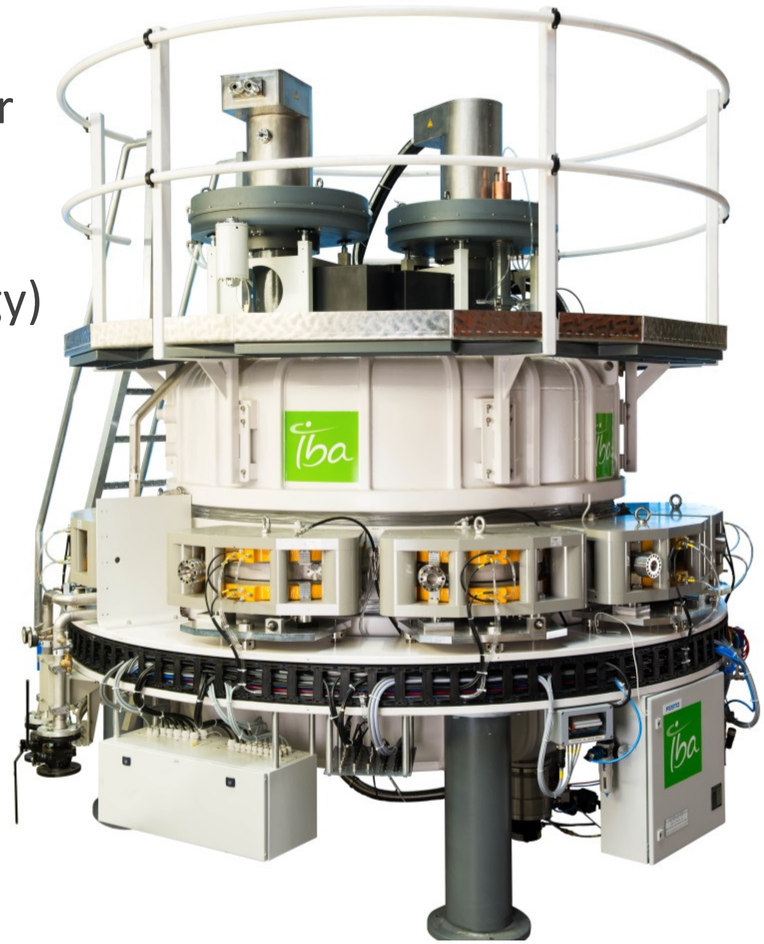
and Save Lives

PRODUCTION WITH ELECTRON - ACCELERATORS

- Slides courtesy of NorthStar, LLC (USA) & IBA INDUSTRIAL

40 MeV electron 'Rhodotron' accelerator

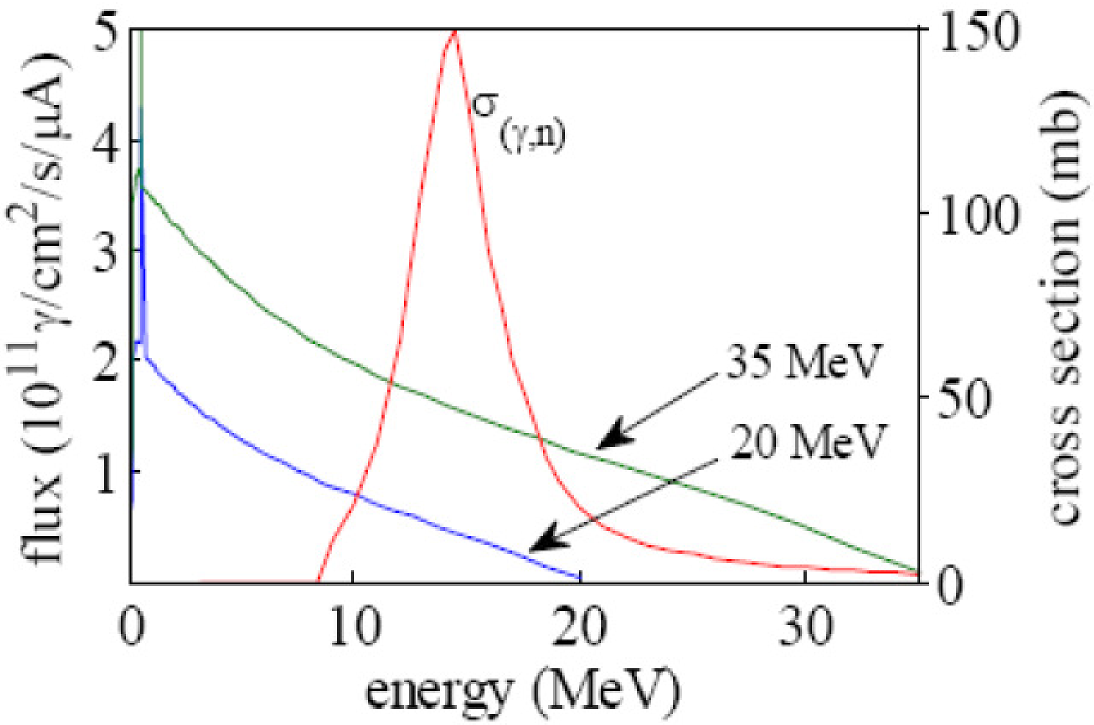
- **Feasible & reliable**
  - More than 3MW of beam power installed all over the world **running 24-7 with >99% availability**
  - Exit window crash proof
  - No activation (>99.9% transmission at high energy)
- **Economical** alternative to Linac
  - Half the consumption of a Linac
  - Small footprint
  - Low maintenance cost



Upraded 10 MeV to 40 MeV

Photonuclear reaction (g,n) in Mo100 target

Accessible with electron- photon conversion



N_m – atom density of material m
E_{th} – threshold energy in m
$\Phi_{E0}(E)$ – photon fluence spectrum
$\sigma(\gamma,n)$ – cross section

Average bremsstrahlung photon spectra produced with 20- and 35-MeV electron beams in a Mo target compared to the photonuclear cross section of ^{100}Mo.

Review of main ^{225}Ac production routes

- ^{225}**Ac**: viable production routes
  - ^{229}Th generators
  - High energy proton spallation on ^{232}Th
  - 16MeV proton on ^{226}Ra
  - Photoreaction on ^{226}Ra

IBA equipment
Cyclone proton 18 or 30 MeV ;
Rhodotron 40 MeV / 125 kW

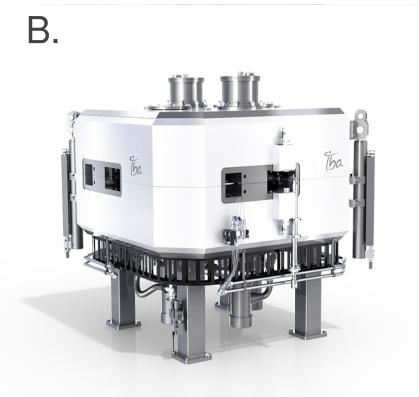
	Production Method	Facility	Capabilities	Monthly ^{225}Ac Production [GBq (Ci)]
Current Sources	^{229}Th generator	ORNL ITU IPPE	0.704 g (150 mCi) of ^{229}Th 0.215 g (46 mCi) of ^{229}Th 0.704 g (150 mCi) of ^{229}Th	2.2 (0.06) 1.1 (0.03) 2.2 (0.06)
Potential	^{232}Th(p, x)^{225}Ac	TRIUMF	500 MeV, 120 µA	11266.5 (304.05)
		BNL	200 MeV, 173 µA	2675.84 (72.32)
		INR Arronax	160 MeV, 120 µA 70 MeV, 2×375 µA	1002.0 (27.08) 462.1 (12.49)
		LANL	100 MeV, 250 µA	444.0 (12.00)
		iThemba LABS	66 MeV, 250 µA	127.7 (3.45)
Future	^{226}Ra(p, 2n)^{225}Ac		20 MeV, 500 µA cyclotron 15 MeV, 500 µA cyclotron	3983.1 (107.65) 1157.4 (31.28)
Sources	ISOL		TRIUMF (existing) TRIUMF (potential upgrades)	0.37 (0.01) 190.6 (5.15)
	^{226}Ra(γ, n)^{225}Ra	medical linac ALTO	18 MeV, 26 µA 50 MeV, 10 µA	48.1 (1.3) 55.5 (1.5)
	^{226}Ra(n, 2n)^{225}Ra		fast breeder reactor	~37 (1)

Source: Radchenkoa V. et al,**Current Radiopharmaceuticals*, 2018, *11***

Manufacturing tools

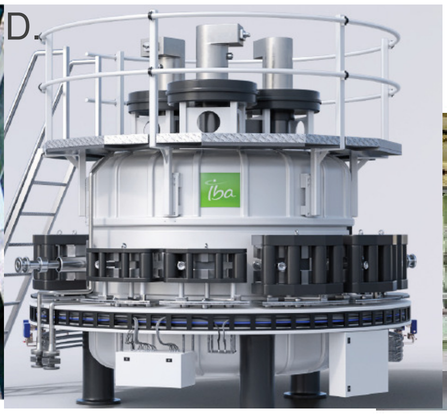
A.

B.



C.

D.



Generators for on-site RI
^{99m}Tc
^{188}Re,
^{82}Rb,
^{68}Ga

Cyclotrons

^{123}I-^{201}Tl-^{111}In

^{18}F-$^{64/61}$Cu-^{89}Zr
^{68}Ga

^{225}Ac

Reactor
Radiotherapeutics or precursors
^{177}Lu-^{99}Mo-^{131}I

Linacs
Rhodotron
Radiotherapeutics
^{225}Ac-^{67}Cu-^{47}Sc

Thank you

Geets Jean-Michel

Domain Expert

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