MEDICIS-Promed : radioisotopes production

Specialized Training - KU Leuven 5 sept 2017

Jean-Michel Geets; IBA RadioPharma Product Mngr

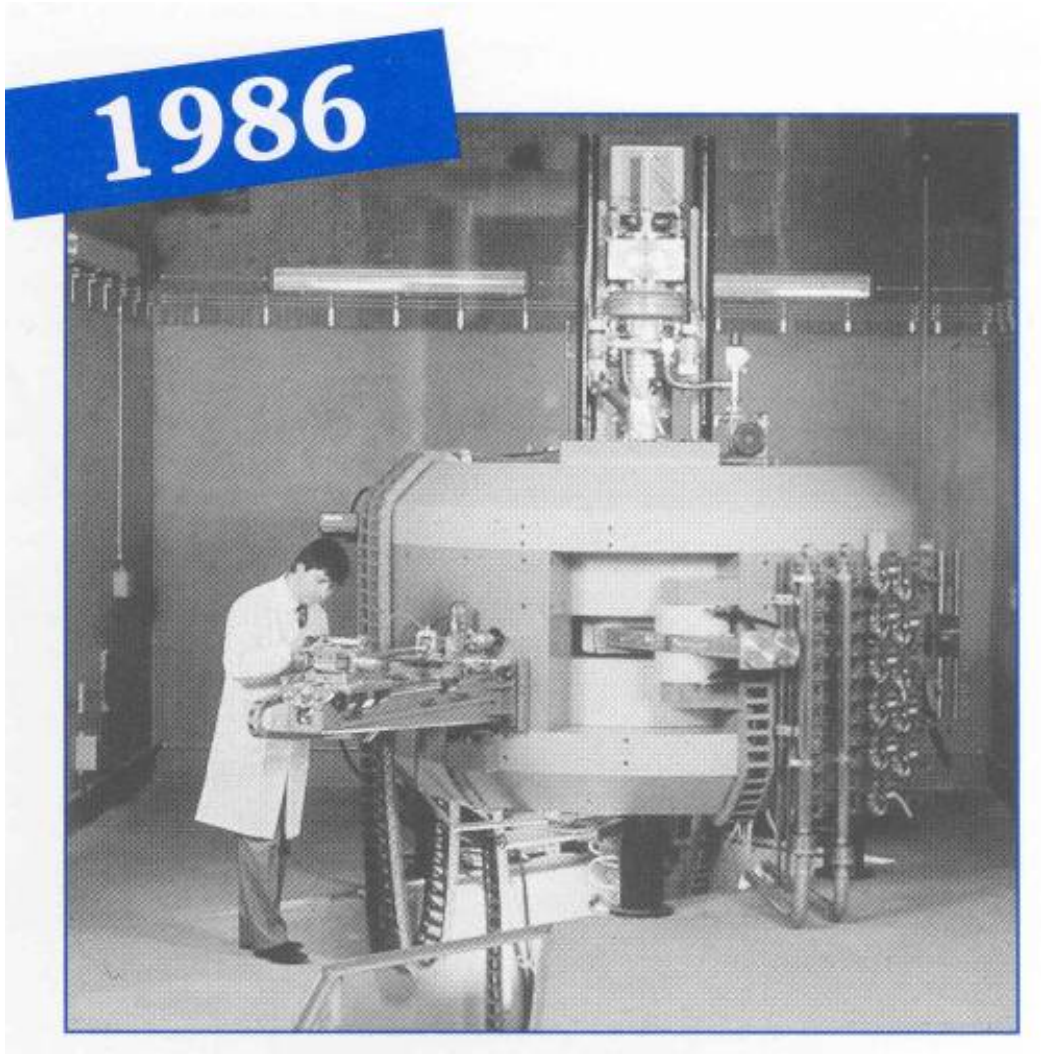
RADIO
PHARMA
SOLUTIONS

IBA solutions for medical Radioisotopes production

- TOTAL 45 min 5 sept 11 am
- About IBA
- Topics
  - Target selection
  - Target design
  - Energy range
  - Cyclotron : proton beam production
  - Mo99 solution with electron beam

- *Our affiliates come from a wide background with some students familiar with the production of radioisotopes but others rather invested in their end use. Please make sure you adapt your content to reach every member of the audience.*
- *The event will also be open to outside participants and many students from different background have already express interest*.

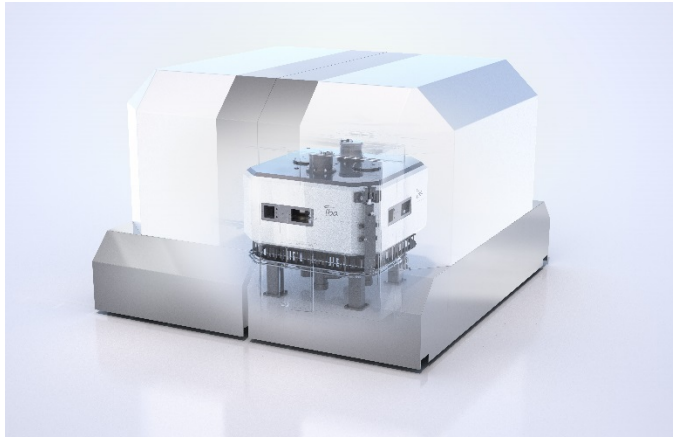
Once upon a time… in a Belgium physics research center



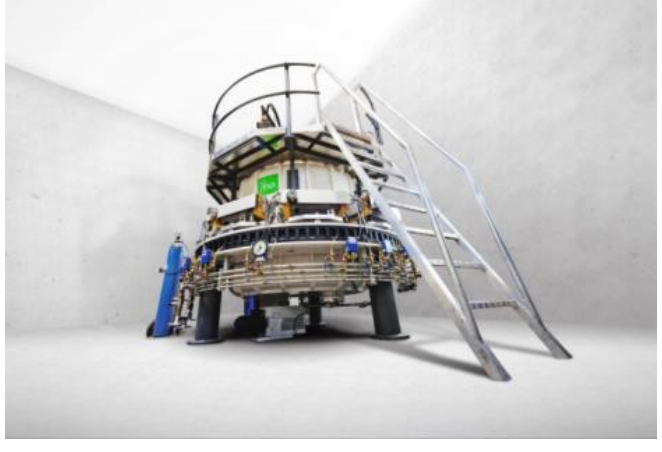
- A young researcher who had imagined a new cyclotron…
- Producing **5x more output**
- Consuming **3x less energy**
  than any existing cyclotrons…
- A revolutionary cyclotron ***Cyclone 30*** *was invented*

IBA is a high-technology medical company with 4 BU's

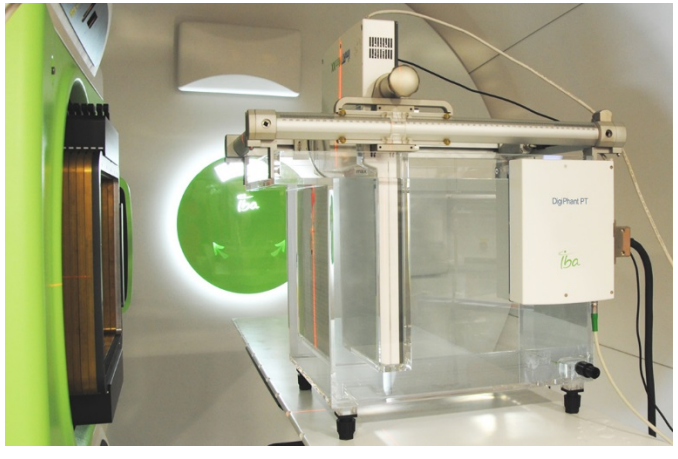
PROTON THERAPY



RADIOPHARMA SOLUTIONS



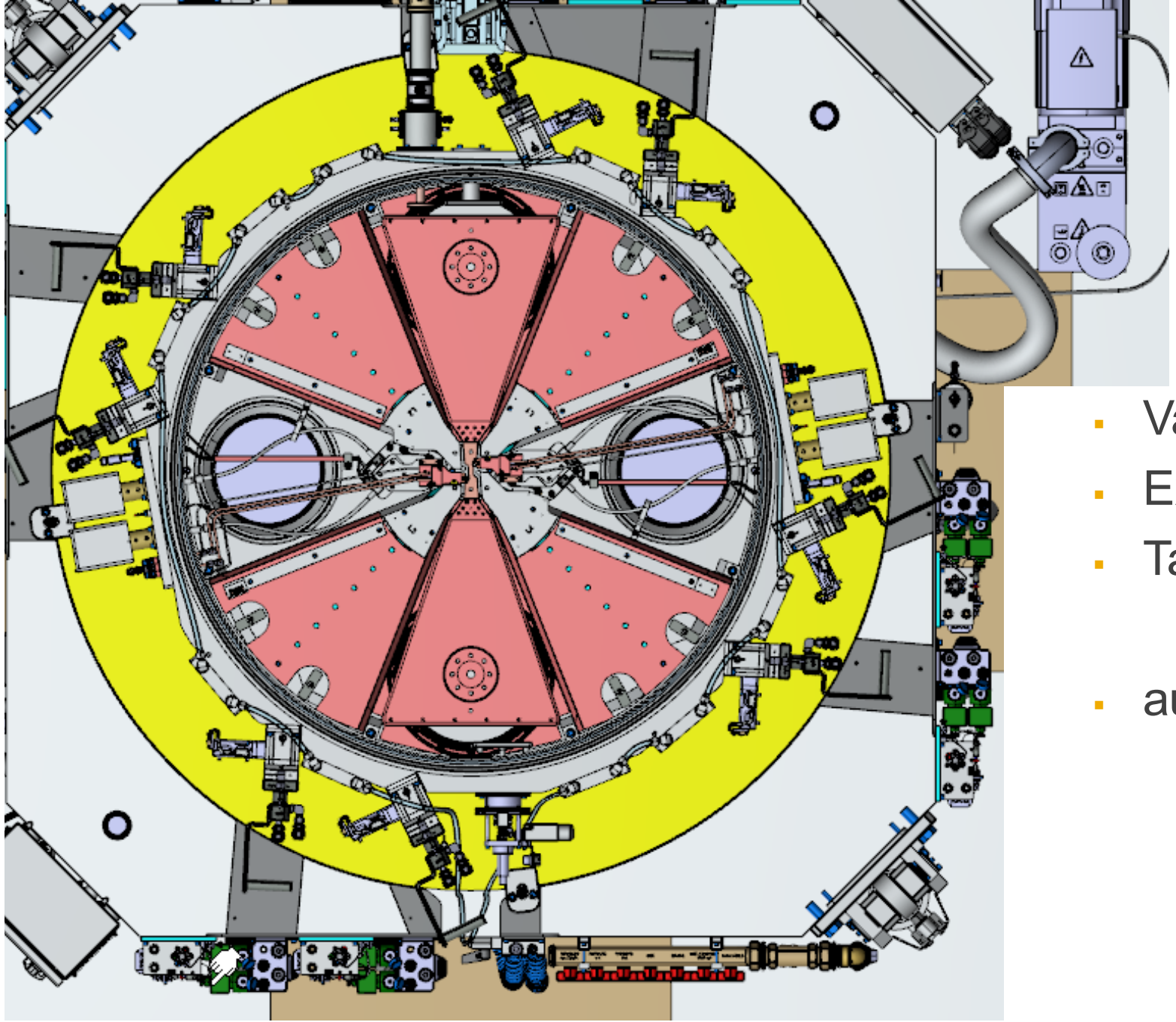
INDUSTRIAL SOLUTIONS



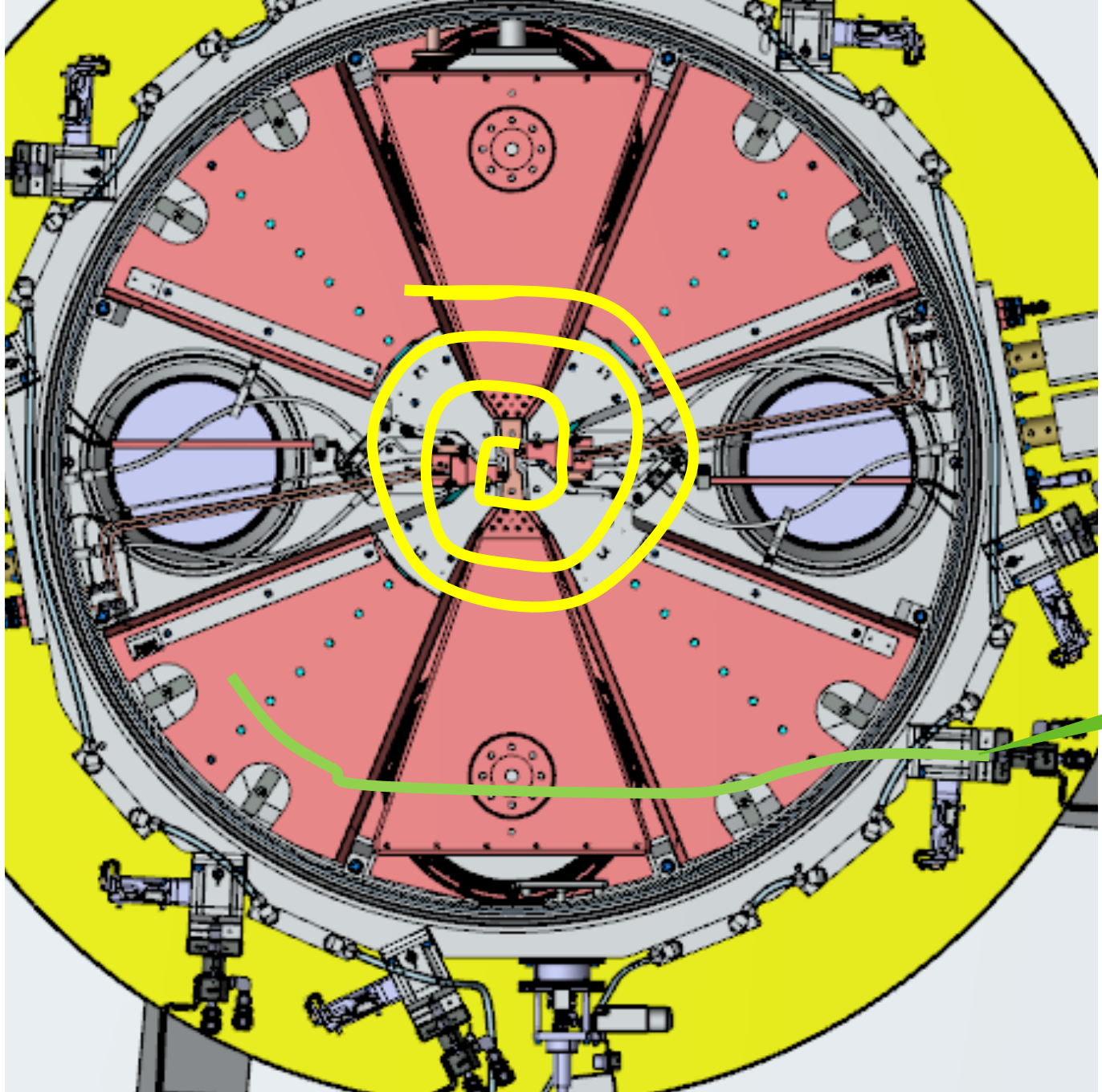
DOSIMETRY

Cyclotron ?

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



- Vacuum
- Extraction
- Targets
- auxiliaries



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

A STORY OF CYCLOTRON INNOVATIONS

1985
DEEP VALLEY CYCLOTRON
5 X MORE OUTPUT, 3 X LESS ENERGY
EP0227186

1990
VECTIO® BEAM
TRANSPORT LINE
FOR R&D

2000
NIOBIUM NIRTA® FLUOR TARGET
FOR BETTER ISOTOPE QUALITY
EP1716576

2002
NIRTA® SOLID TARGET
TO GIVE ACCESS TO NEW ISOTOPES
EP1570493

2003
DUAL BEAM REGULATION
FOR DOUBLED PRODUCTION
EP1566082

2005
HIGH CURRENT MACHINE 150µA
FOR INCREASED PRODUCTION
CAPACITY

2006
SHIELDED TARGET DOORS SHIELDING
CLOSURE FOR EASY DECOMMISIONING
EP200.199

2008
TWIN PROTON SOURCES
TO MAXIMIZE UPTIME
EP2196073

2011
NIRTA® FLUOR CONICAL TARGET
FOR REDUCED ENRICHED WATER USE
WO 2012/058970

2012
ZEPHIROS® CYCLOTRON
CONTROL SYSTEM
FOR EASE OF USE
EP2581914

2016
CYCLONE® KIUBE
EP16169489, EP16169490
EP16169494, EP16169497
EP16171282

Towards High beam current

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DEEP VALLEY CYCLOTRON
5 X MORE OUTPUT, 3 X LESS ENERGY
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2016
CYCLONE® KIUBE
EP16169489, EP16169490
EP16169494, EP16169497
EP16171282

80 µA

100 µA

150 µA

300 µA


solid target
conical target
1990
VECTIO® BEAM TRANSPORT LINE FOR R&D
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NIRTA® SOLID TARGET TO GIVE ACCESS TO NEW ISOTOPES
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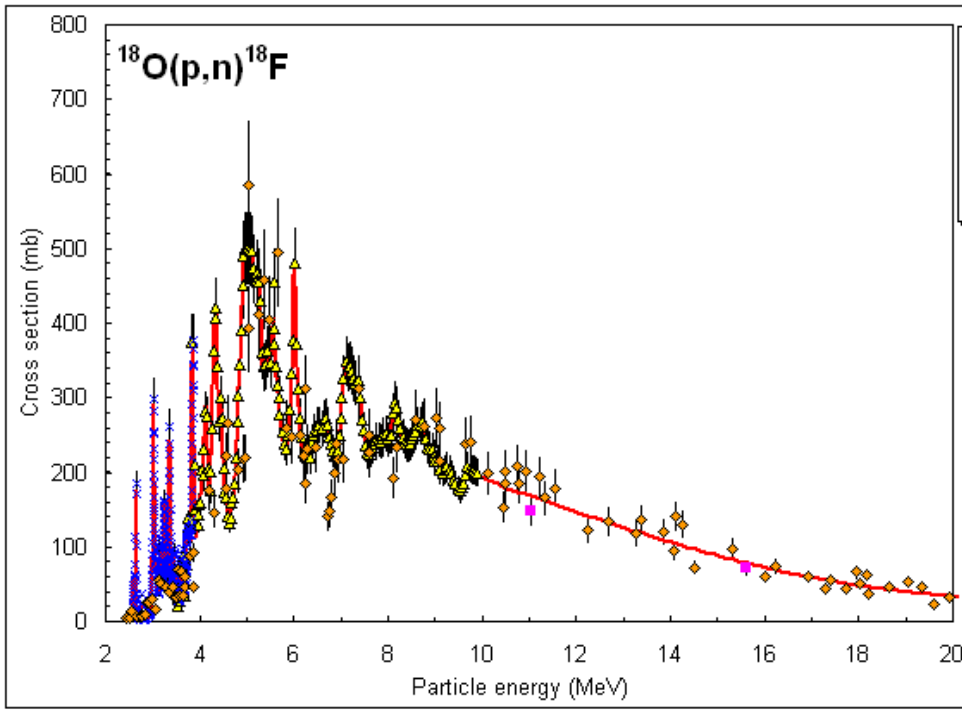
2012
ZEPHIROS® CYCLOTRON CONTROL SYSTEM FOR EASE OF USE
EP2581914
80 µA
Nb target
100 µA
150 µA
User's benefits
300 µA

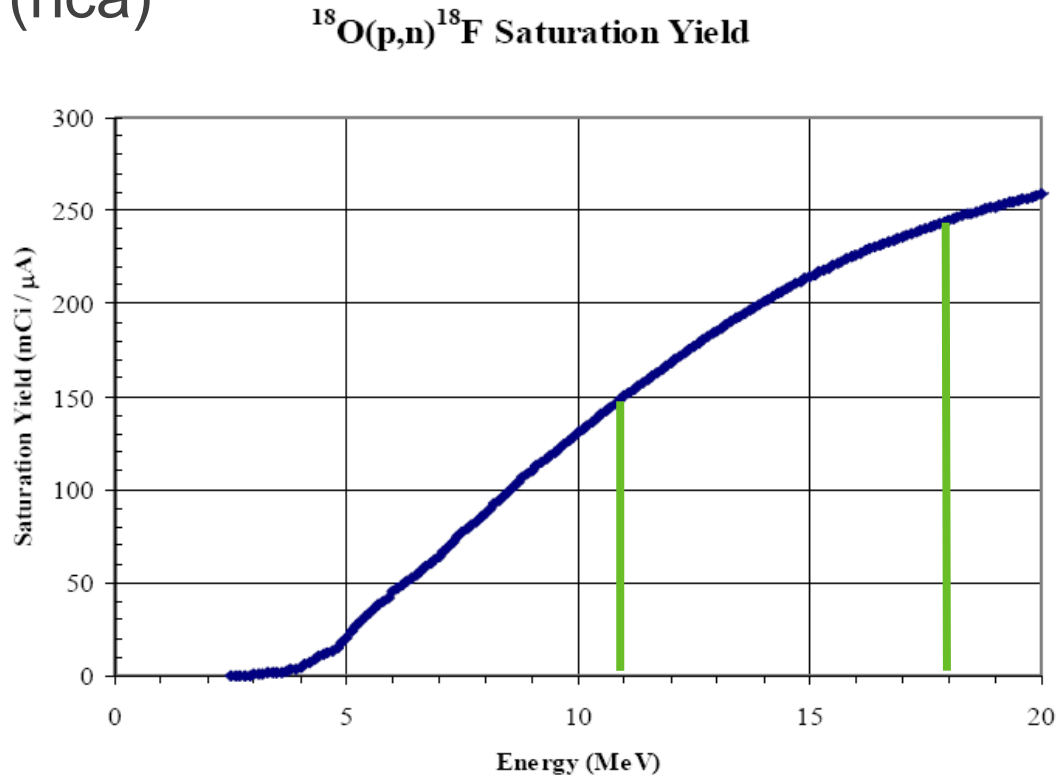
Radioisotope production, Target design, .. & the right energy

RADIO
PHARMA
SOLUTIONS

Target & production / energy : exemple of ^{18}F

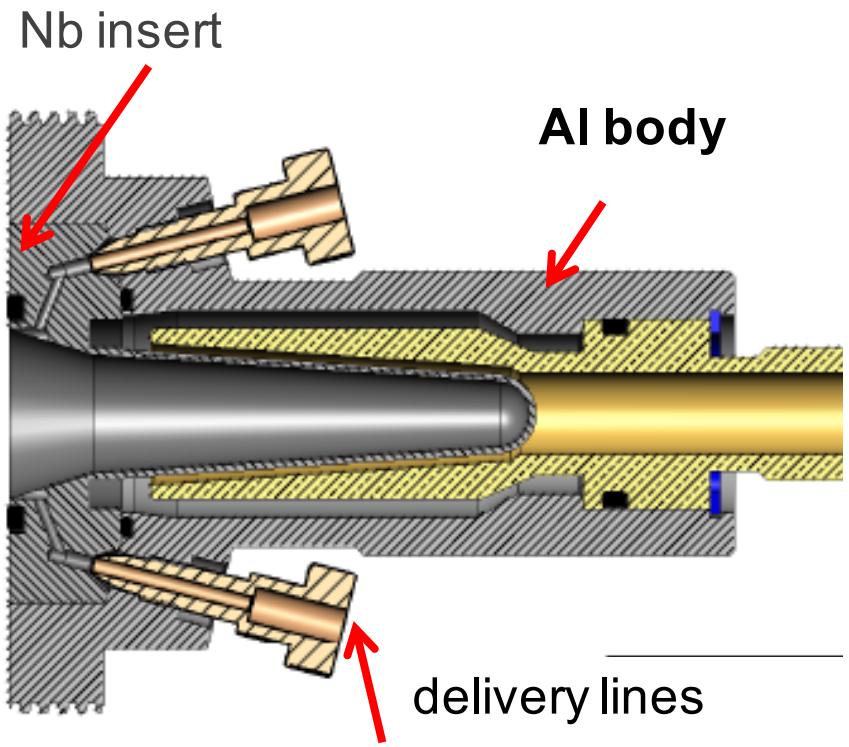
- From cross section to thick target yield
  - Physical properties & constraints
  - Chemicals properties & constraints
  - Contaminants, carrier added or not (nca)

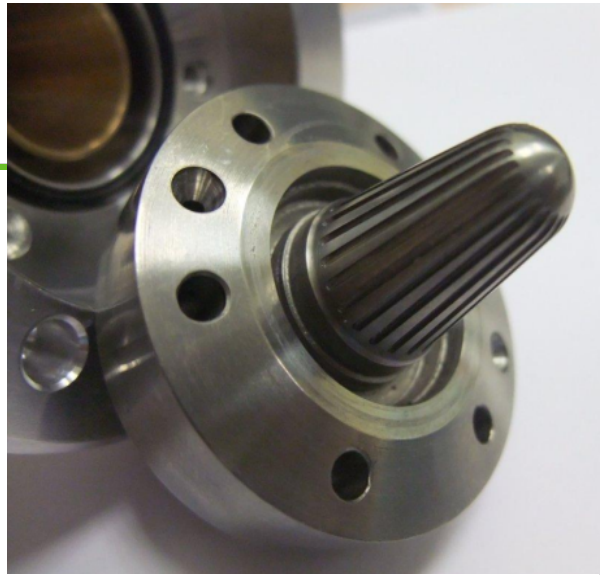


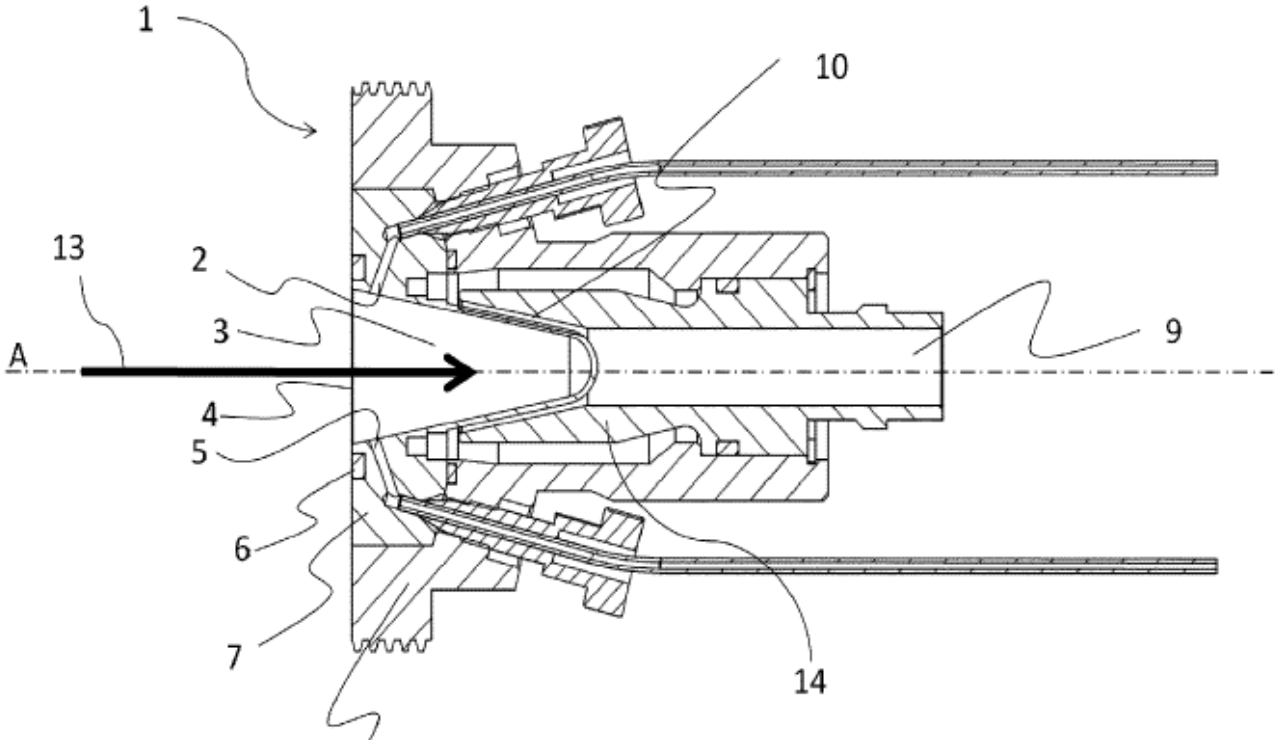


C.Gonzalez, Cyclotope & MD Anderson CC, Texas

LIQUID target 18F : 2,3 kW in 4 ml







New Nirta® Conical target performances

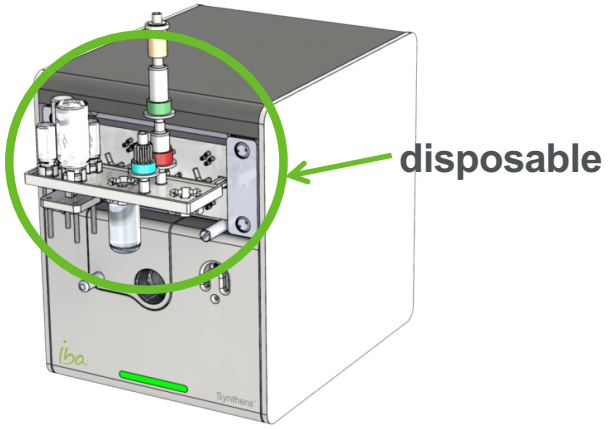
Data 18 MeV - need of HIGH CAPACITY 18F- : price erosion of FDG dose.

	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	130 µA
Average yield @ sat	230 mCi/µA 8.5 GBq/µA	230 mCi/µA 8.5 GBq/µA	230 mCi/µA 8.5 GBq/µA	230 mCi/µA 8.5 GBq/µA
Activity output (2h)	**5 Ci** 185 GBq	**8 Ci** 296 GBq	**12 Ci** 444 GBq	**16 Ci** 592 GBq
Target pressure	~40 bar	~30 bar	~30 bar	~30 bar

Synthera® Complete offering in 18F chemistry system

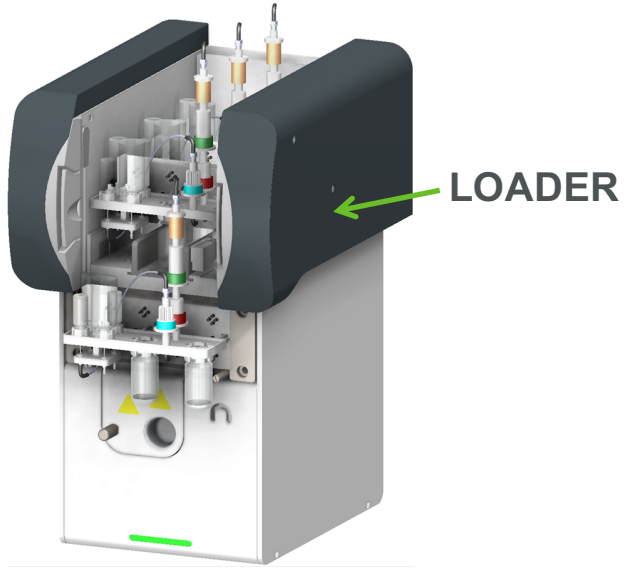
BASE MODULE

- High-activity tolerance
- High yield 60% FDG
- Multi-tracer



MULTI-RUN

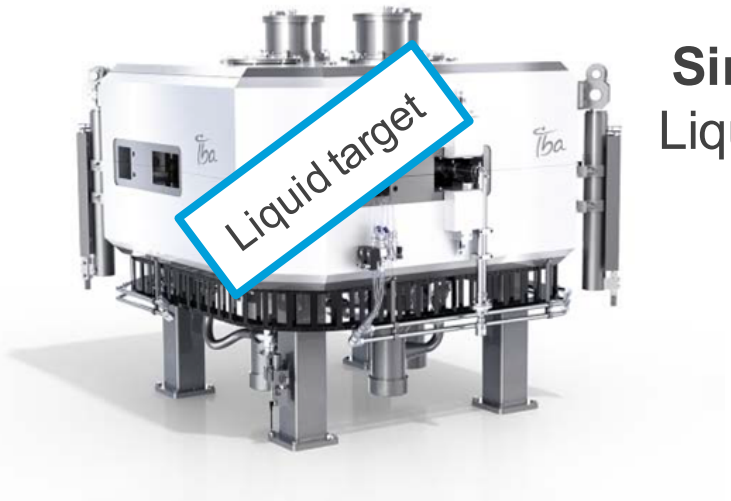
- High-activity tolerance
- High yield
- **Multi-run of FDG & multi-tracers**



FLEXIBILITY

- High-activity tolerance
- High yield
- **Fixed IFP**

One way of obtaining Ga-68 for NET imaging



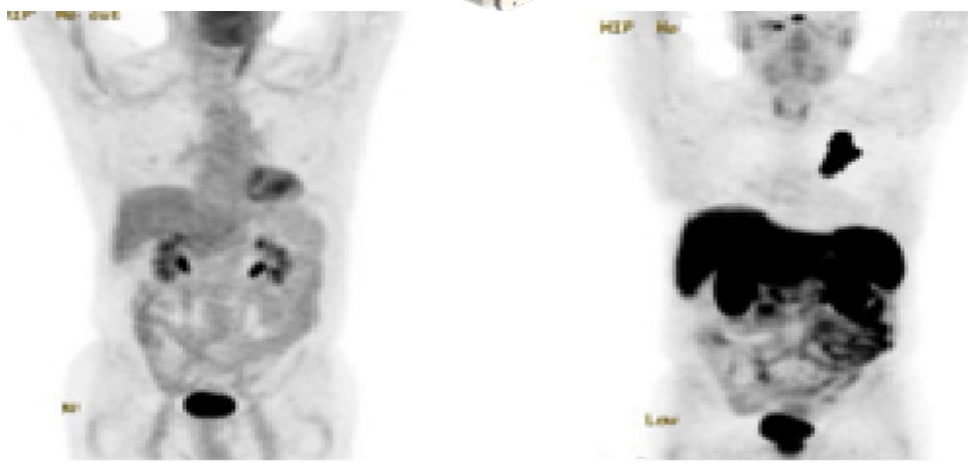
Ga-68 Nirta® target system

Similar to ^{18}F-FDG production

Liquid transfer & cartridge purification

^{68}Zn (p,n) ^{68}Ga

Post-processing & Labelling
on the Synthera® platform



F-18 FDG PET scan

Gallium DOTATATE PET scan

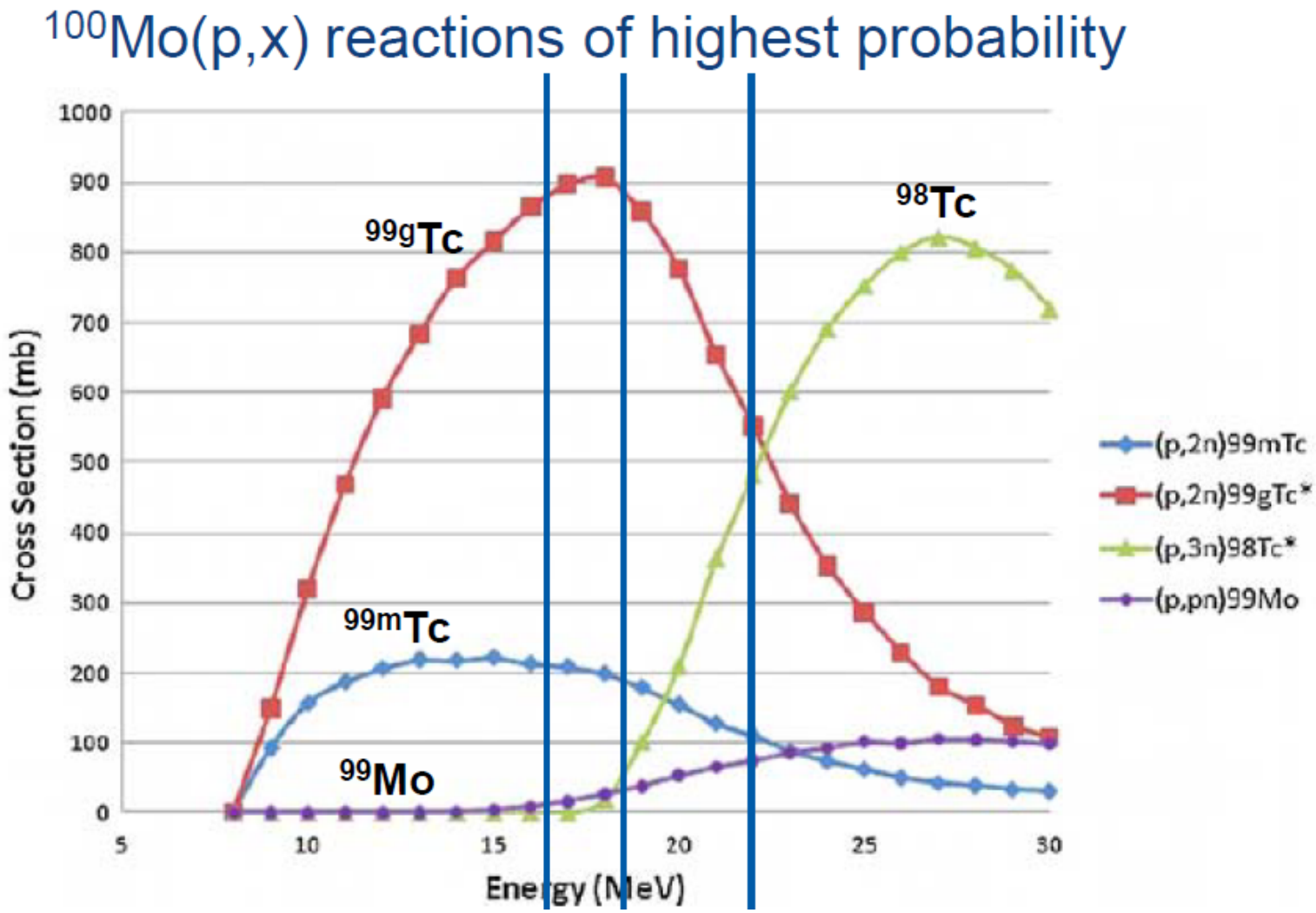
Gallium-68 DOTATATE PET/CT

F-18 FDG PET scan of a patient with Neurendocrinetumour did not reveal any abnormality. However, Gallium-68 DOTATATE PET scan demonstrates tumour in the left lung.

in collaboration with the University of Coimbra

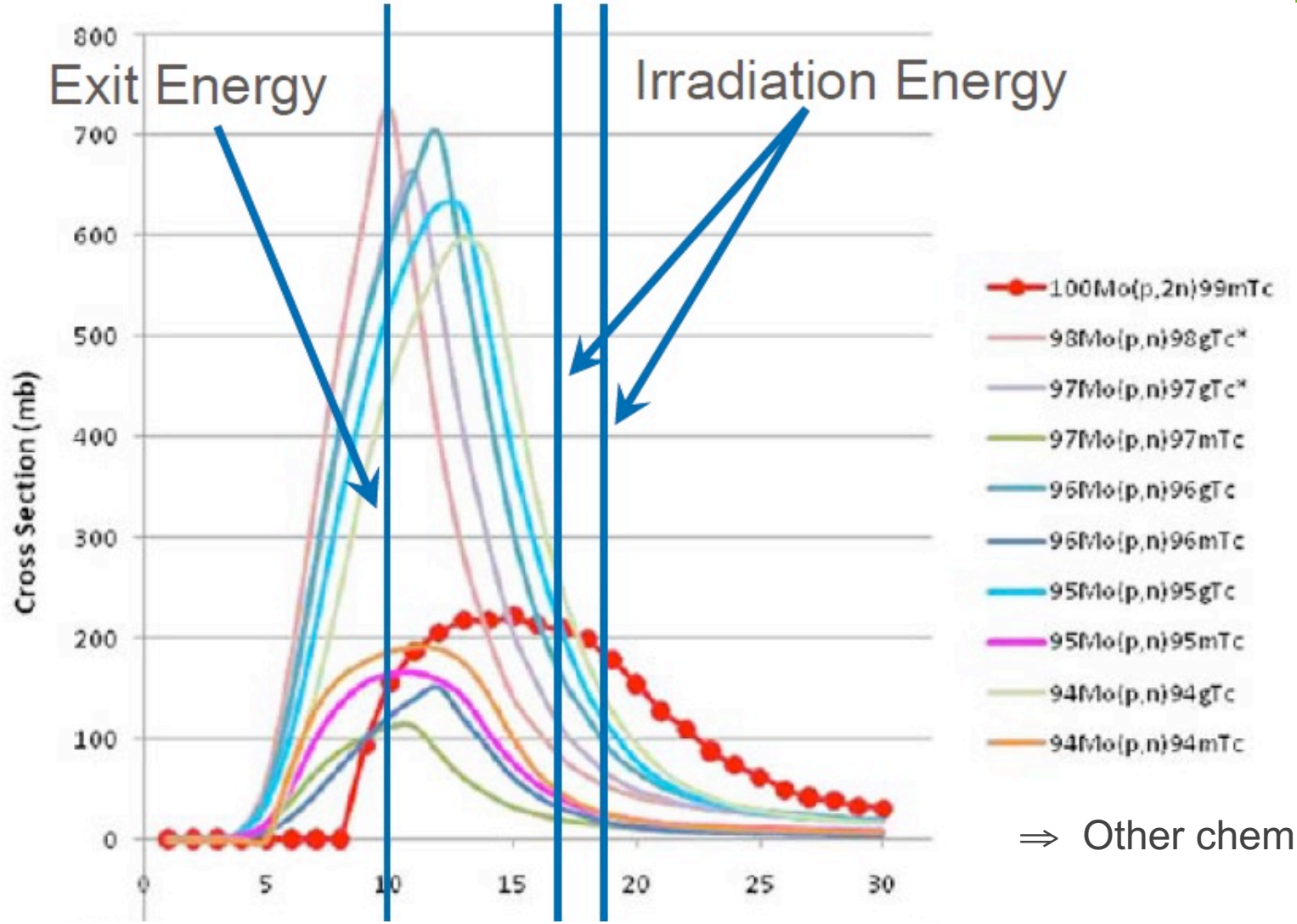
IBA patent application : EP15170854.2

Mixed reactions in one target.. $^{100}Mo\ (p,2n)Tc^{99m}$



A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

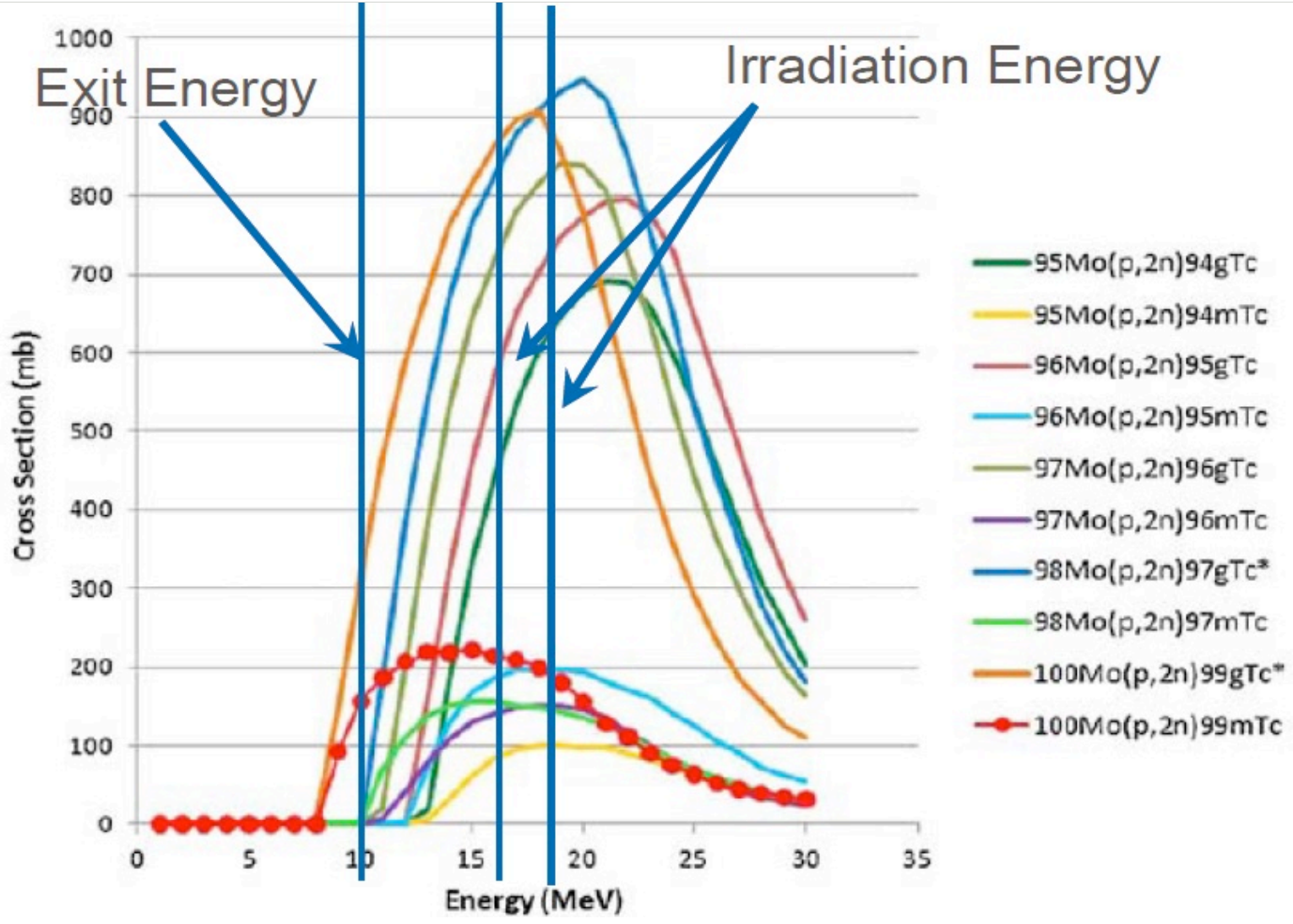
Side reaction (p,n) on Mo ^{9x} => Tc ^{9x}



⇒ Other chemicals removed by purification

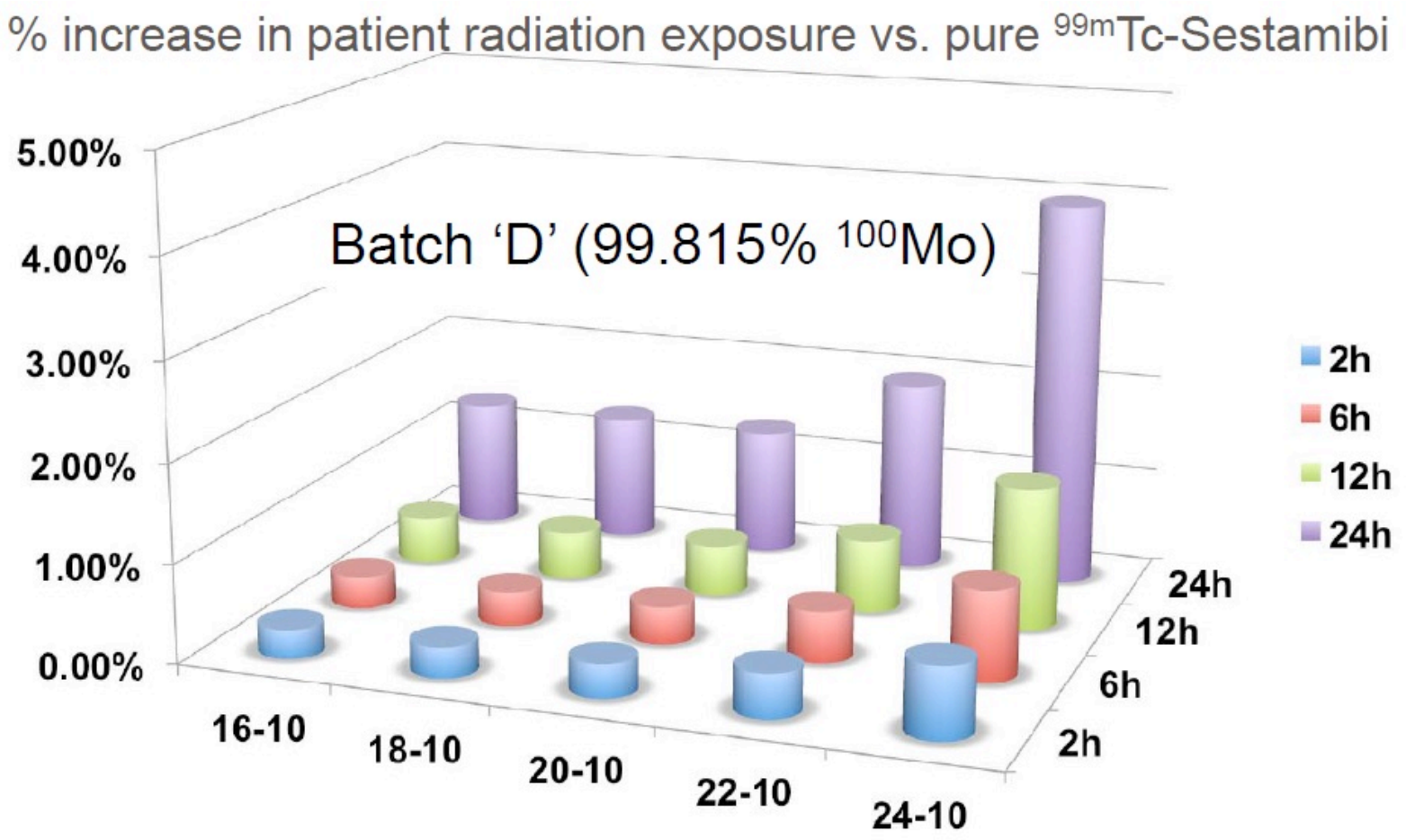
A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

Side reaction (p,2n) on Mo 9x => Tc 9(x-1)



Optimal energy range: 16-19 MeV

Effect of impurities on the patient exposure !



A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

IBA Cyclone® 18 MeV is the right solution for PET

- Access to common PET
  - 18F
  - 11C
  - 13N
  - 15O
- Access to new RI on solid target
  - 64Cu,
  - 89Zr,
  - 124I / *123I*
  - *Scandium..*
  - *Tc99m*
- new system for Ga68 in ‘solution-liquid target’

Production with Two-steps process Tl^{201} cardiac spect

- **Tl-203(p,3n) Pb-201**
  - & others
- **Pb-201 => Tl-201**
- Need 2 separations
- ‘growth time’ ~ 24h

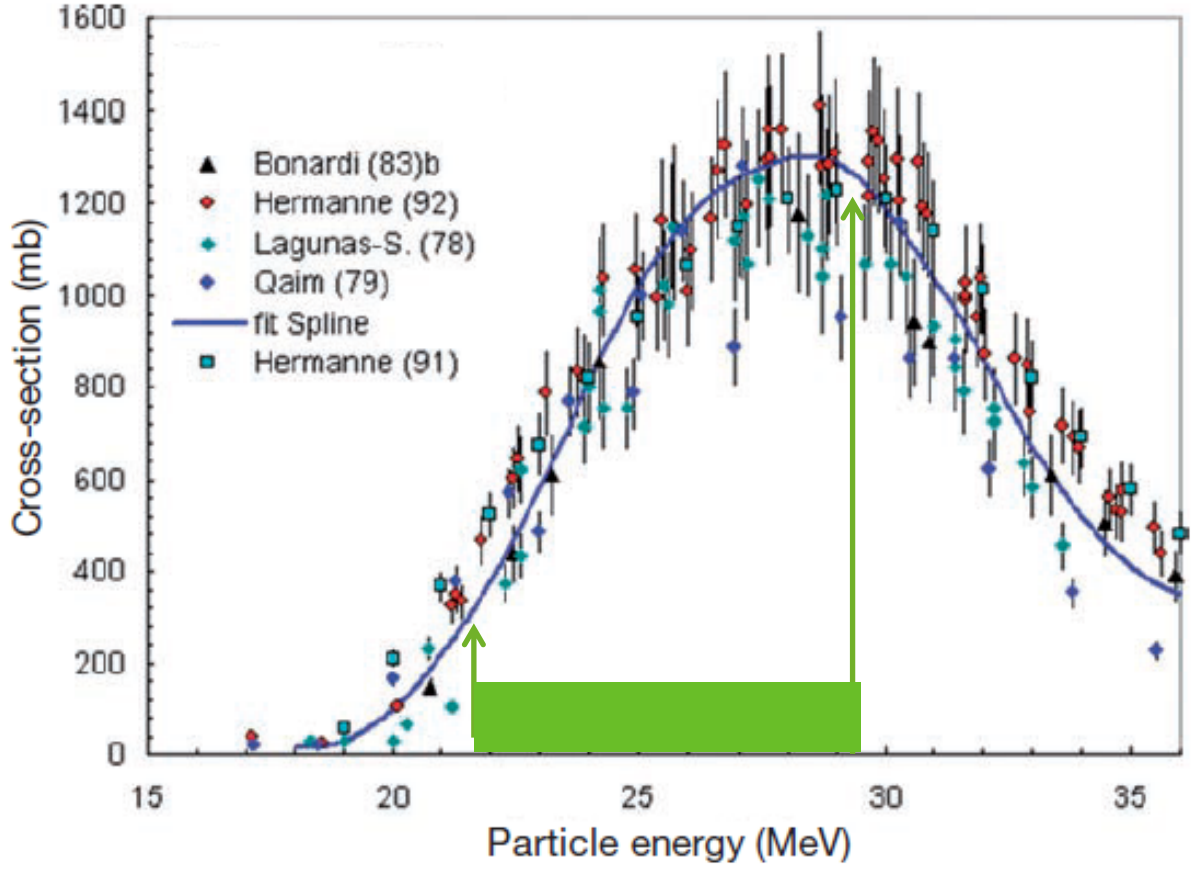
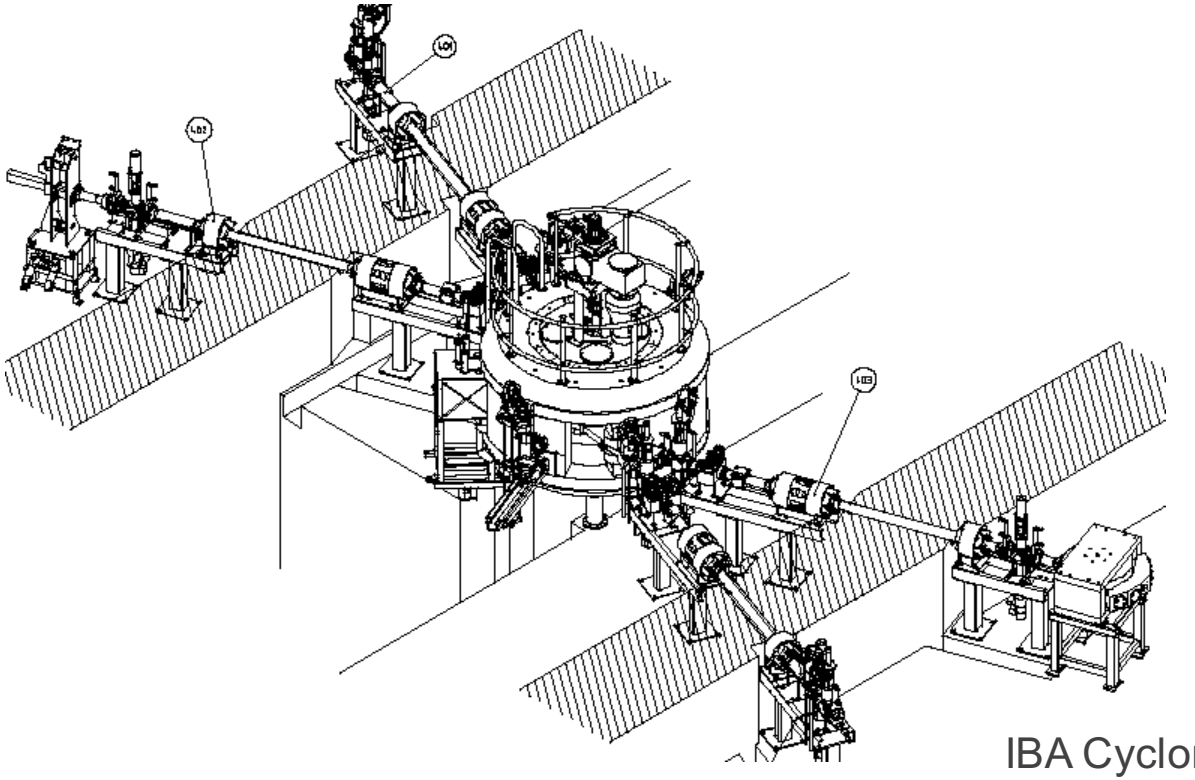


FIG. 2.40.1. Excitation function for the $^{203}Tl(p, 3n)^{201}Pb$ reaction.

Cyclone 30 MeV proton for SPECT & more

- 15- 30 MeV variable Energy proton
- Up to 1.2 mA proton (~ 36 kw)
- Mainly for SPECT isotopes **(p,2n) & (p,3n)**



IBA Cyclone 30

30 MeV typical production of SPECT isotopes

- Solid target

30 MeV / 250 µA ~ 7,5 kW

Isotope	Energy	Production
Tl-201	28-30 MeV	Tl-203 (p,3n) Pb-201 --> Tl-201
In-111	25-28 MeV	Cd-112 (p,2n) In-111
Ga-67	25-28 MeV	Zn-68 (p,2n) Ga-67

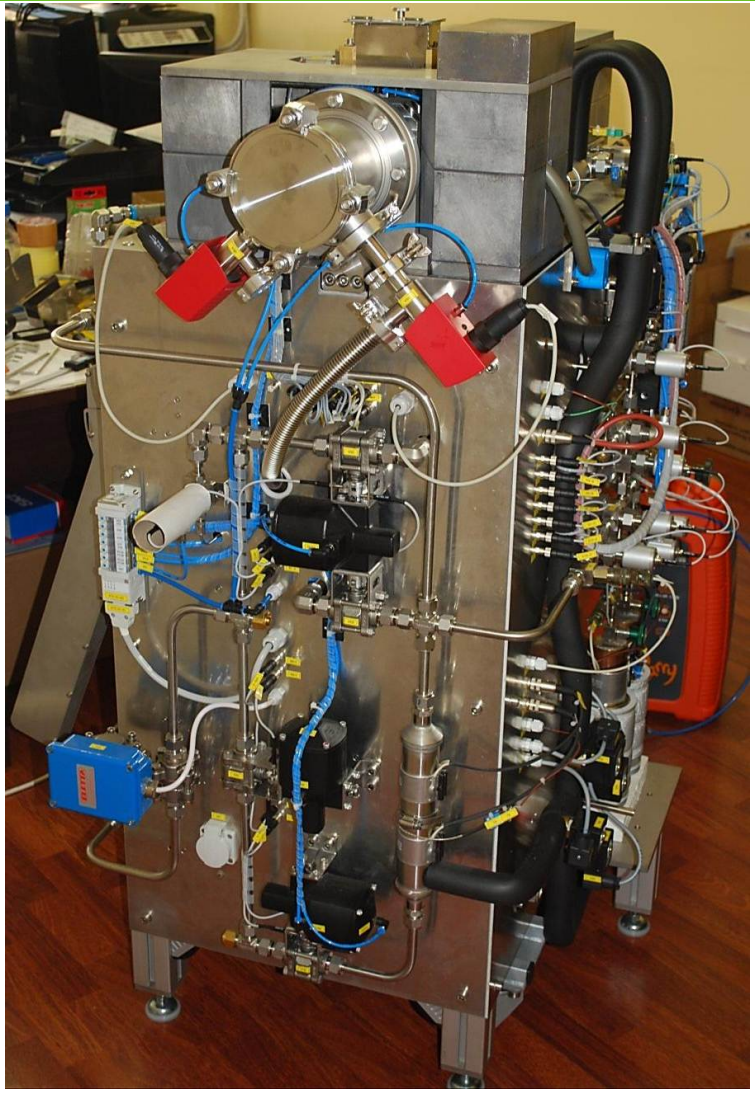
- Addition of:

Ge-68	25-30 MeV	Ga (p,2n) Ge68

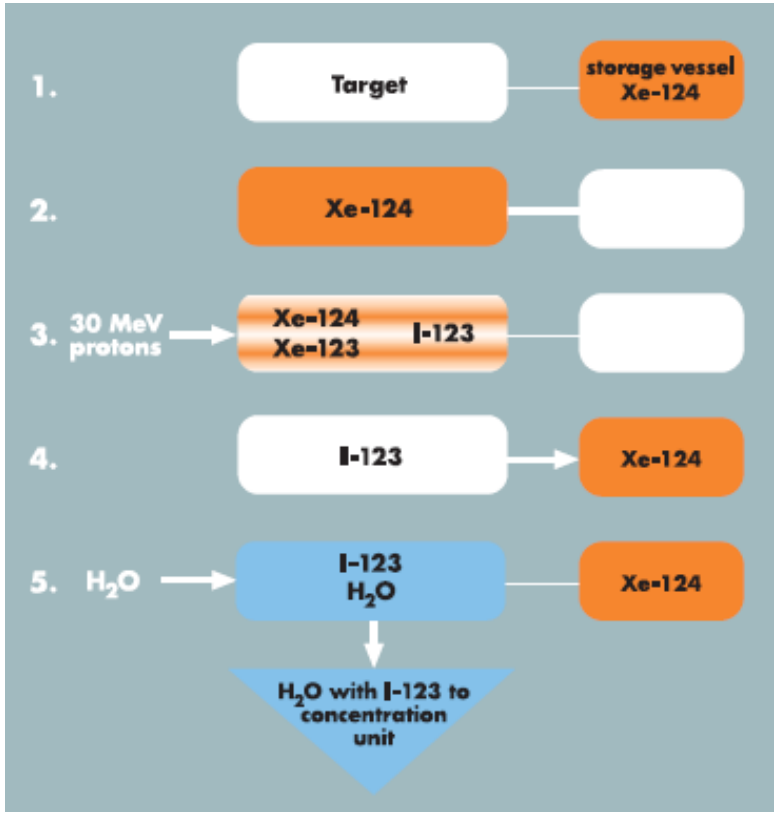
- Gas target

I-123	22-30 MeV	Xe-124 (p,xn) Cs-123 --> I-123

Production of ^{123}I : IBA target + chemistry module

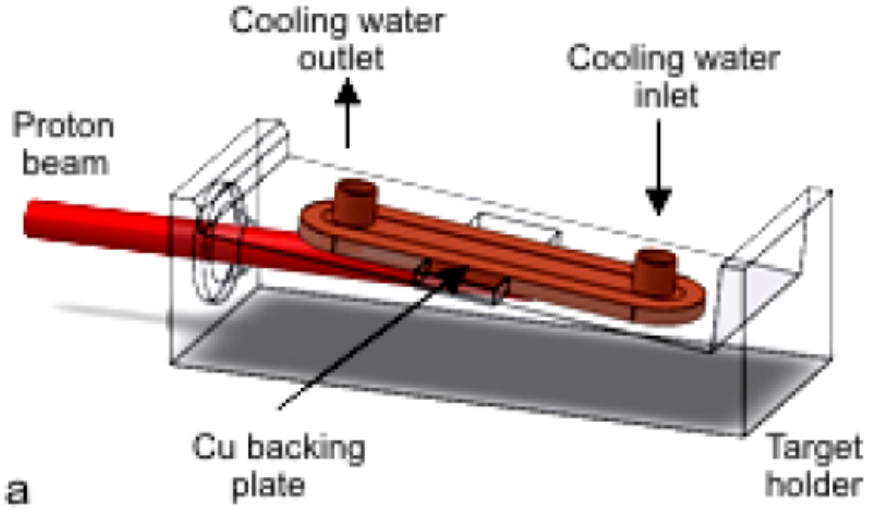


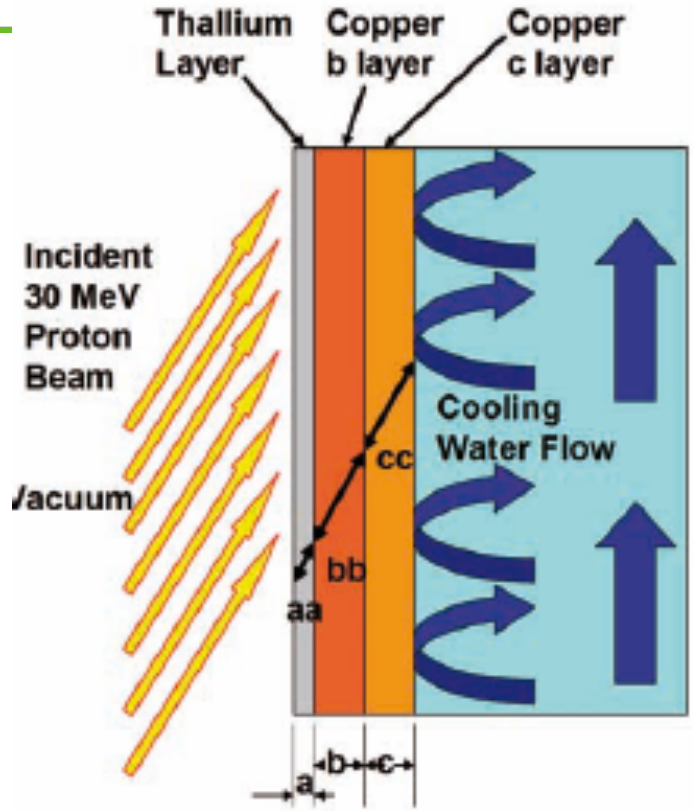
- Gaseous ^{124}Xe target for 30 MeV cyclotrons (Cyclone 30)
- High current targetry
- ^{124}Xe safety and recovery system



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**

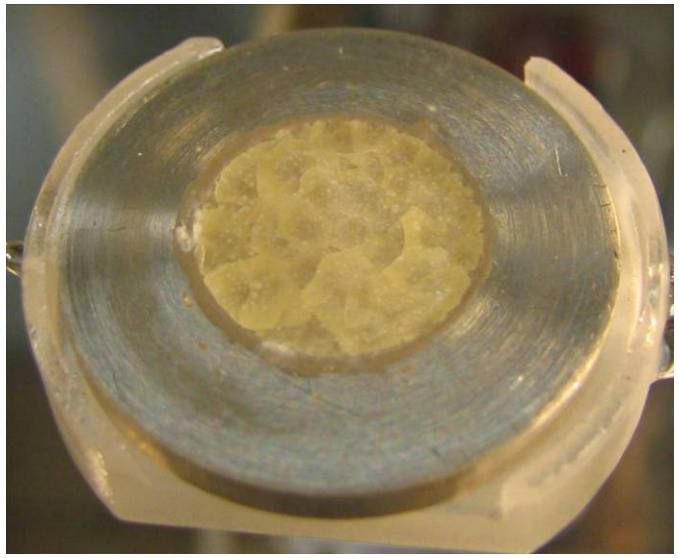
Solid target process and constraints

- 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

Solid target : (1/2) effect of beam optics on TeO_2

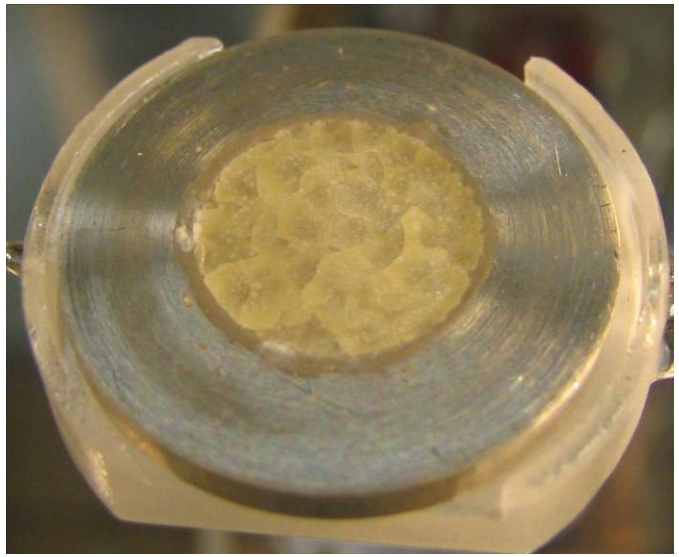


$^{124}Te\ (p,n)\ ^{124}I$

$^{123}Te\ (p,n)\ ^{123}I$

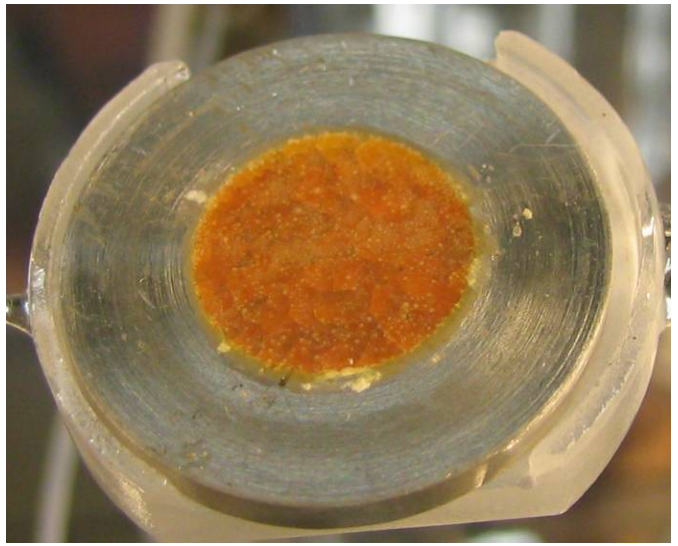
- Irradiation of a glassy matrix of TeO_2 and Al_2O_3 melted in a Pt disk
- Beam strike area dia 12 mm
- Up to 40 µA – 13 MeV (after degrador)

Solid target : (2/2) effect of beam optics on TeO_2



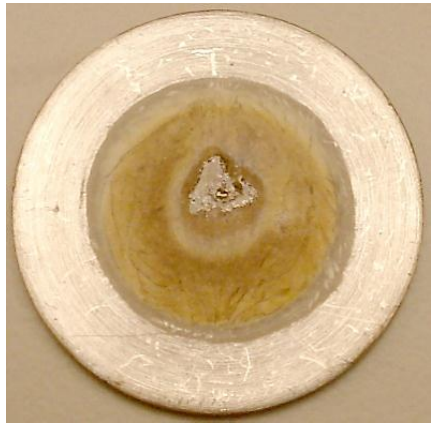
$^{124}Te\ (p,n)\ ^{124}I$

$^{123}Te\ (p,n)\ ^{123}I$



Inhomogeneous but acceptable irradiation

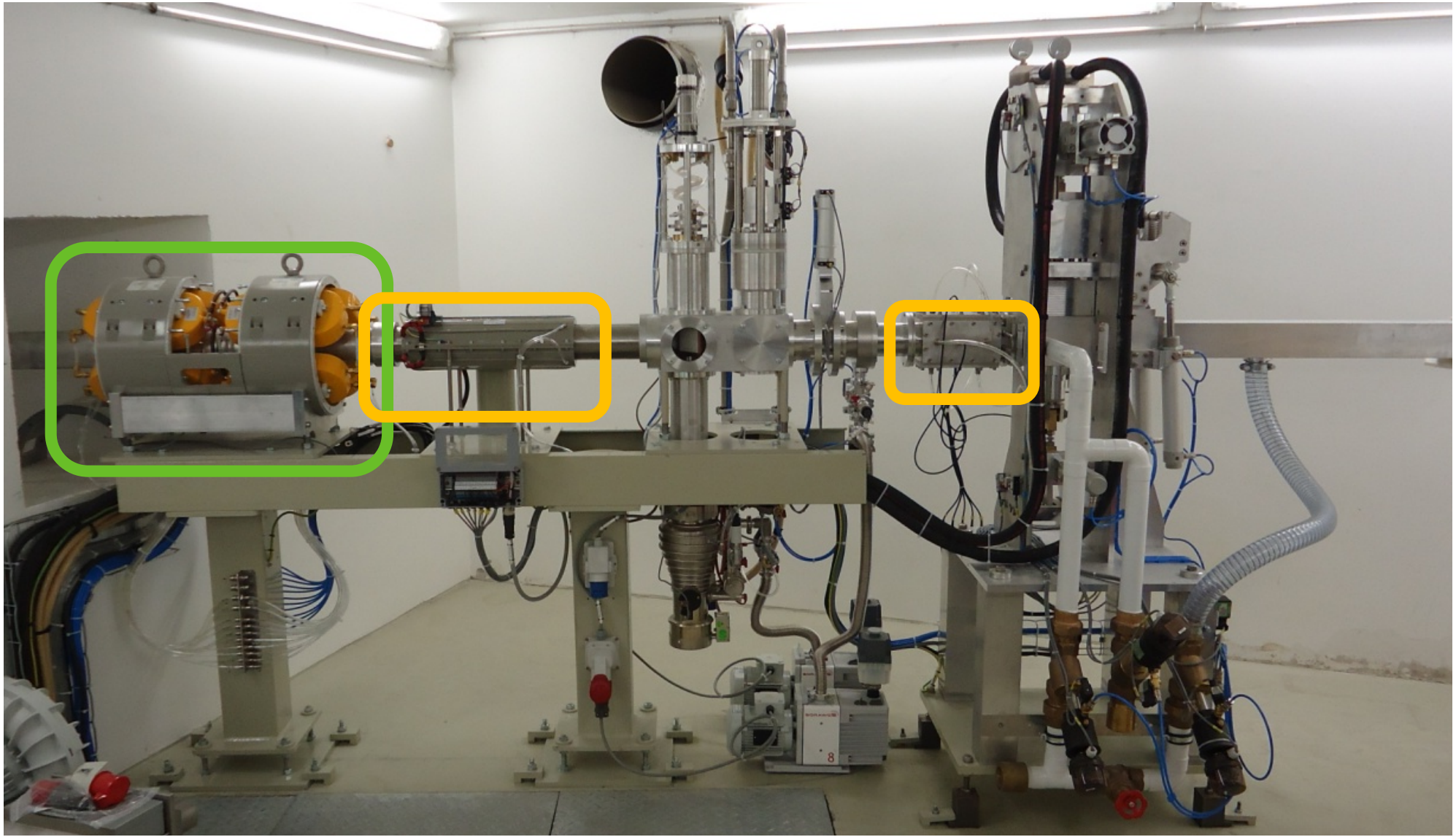
At the physical limits



Thermally damaged target

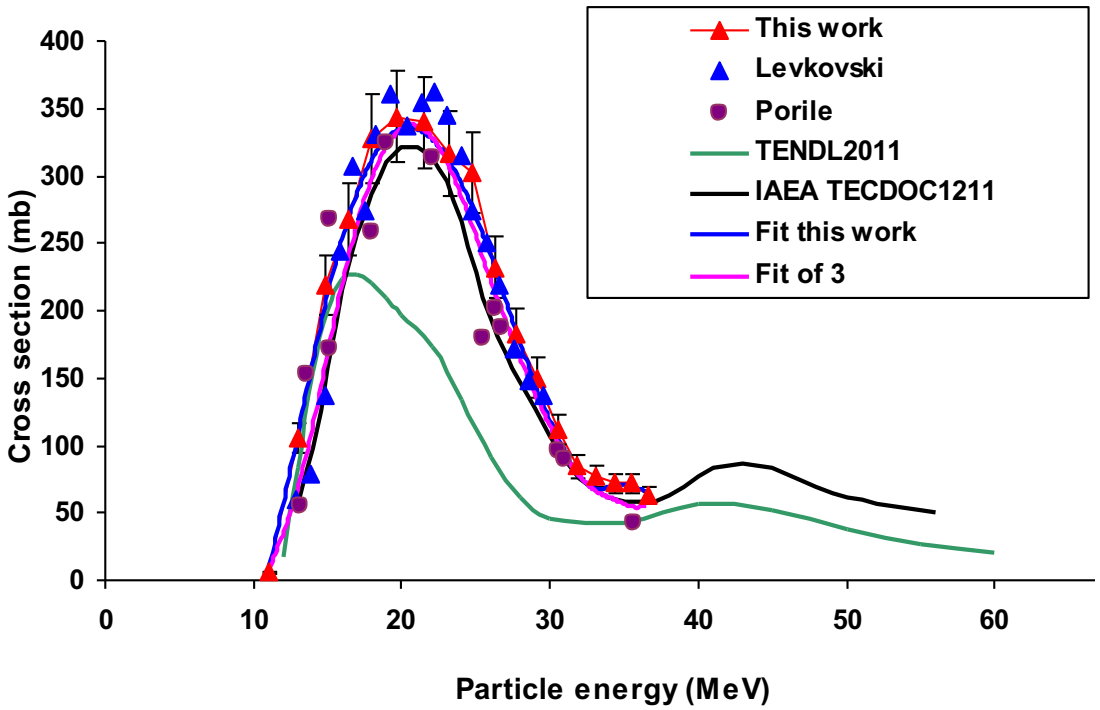
Solid target & beam line – target vault

Need to control the beam on target



Development of 68Ge production on 30 MeV cyclotron

high melting point
Ga-Ni alloy
&
Separation chemistry



Preferred production route
$^{nat}Ga(p,2n)^{68}Ge$ (^{69}Ga: 60.1%)

Vrije Universiteit Brussel

Ref: AccApp, Brugge 2013; 68Ge production (Adam Rebeles) & EUChemMS; 68Ge excitation curve and yield (Hermanne)

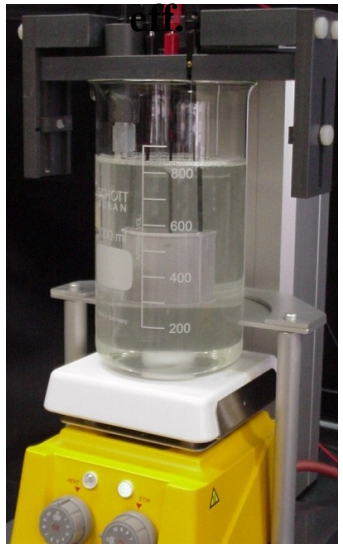
Enriched material PLATING 99% eff.

Cyclotron irradiation

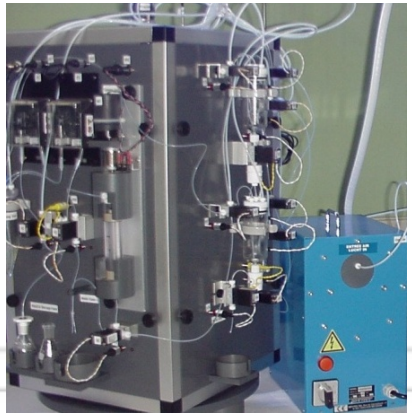
Target DISSOLUTION

IBA- VUB Solid Target Automated Process

Enriched material RECOVERY 90%



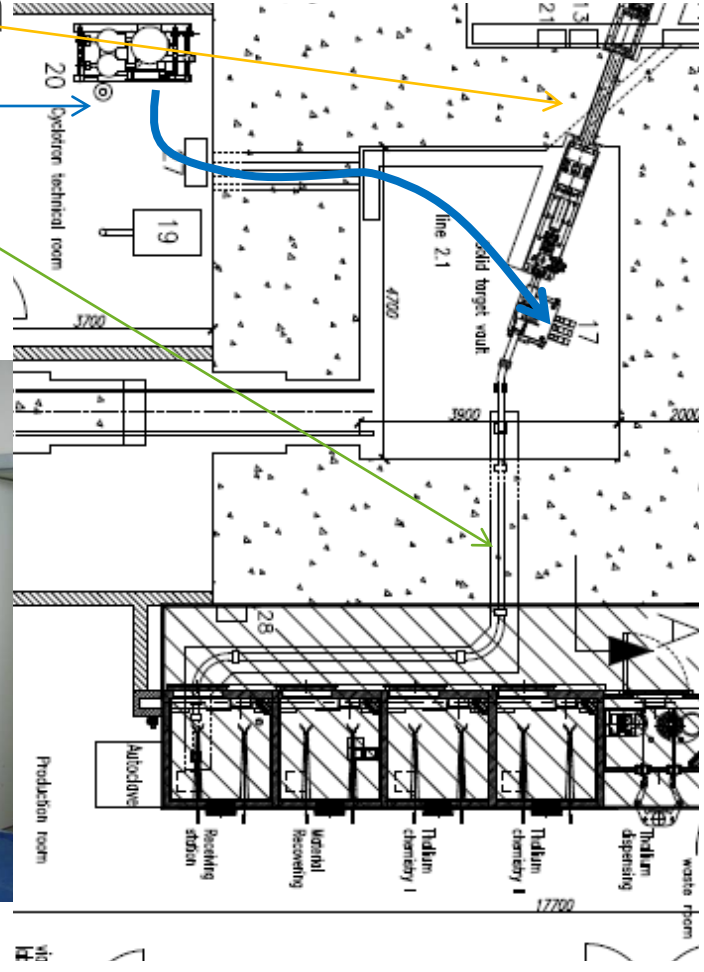
Radioisotope SEPARATION & PURIFICATION > 85%



2nd SEPARATION & PURIFICATION (201Tl only)

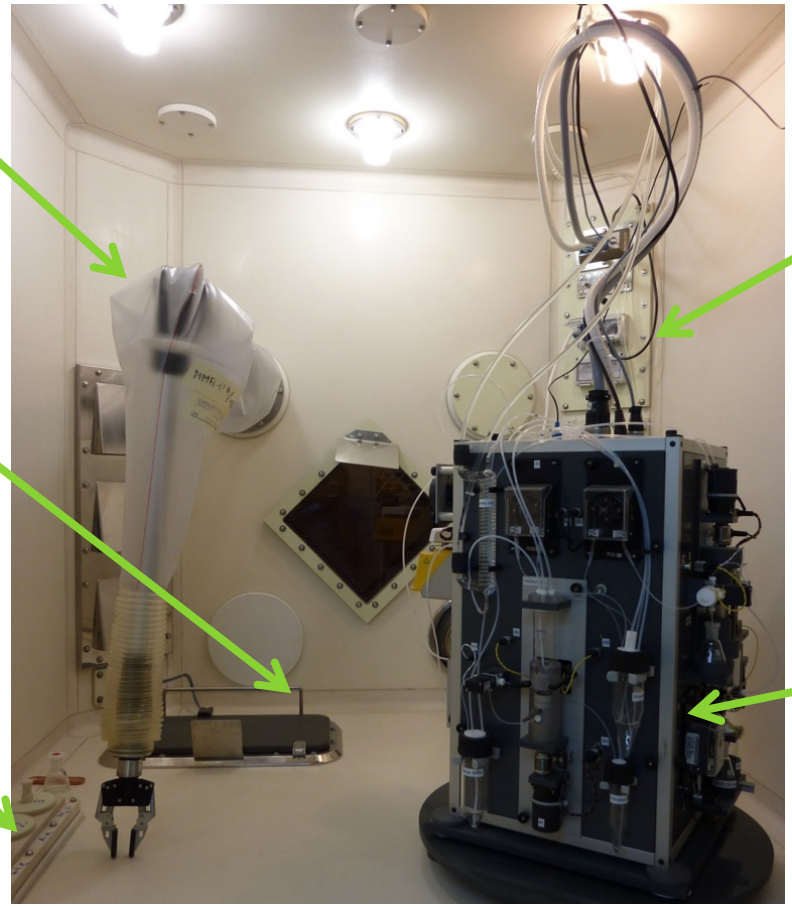
Bulk for DISPENSING

- Interface to beam line-cyclotron
- Water cooling system
- Pneumatic Transport system



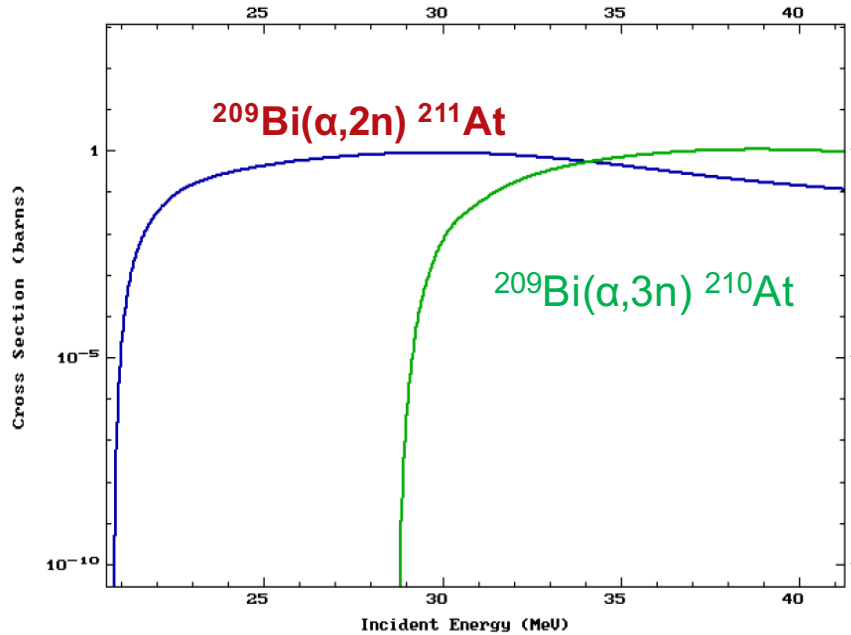
Shielding of chemistry modules

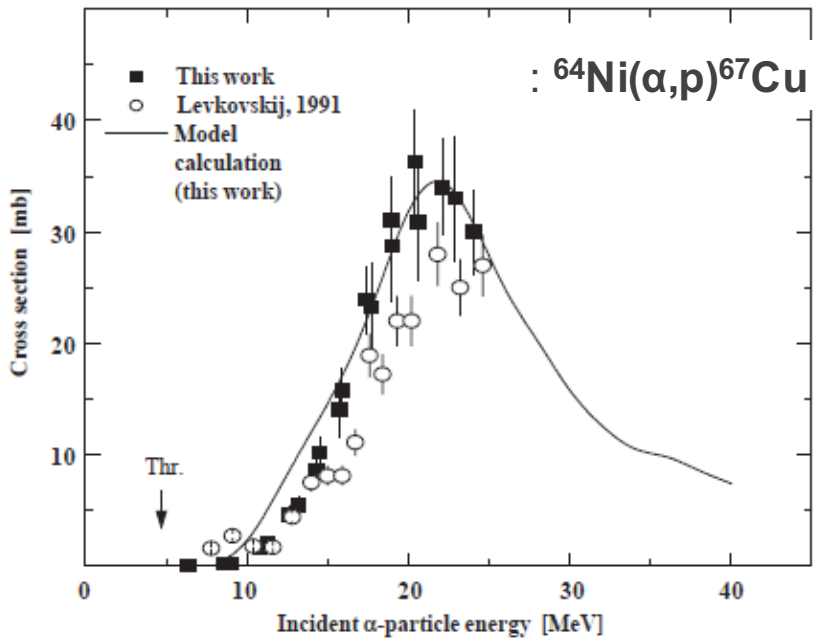
- Module dimensions & access & process (acid coating)
- Manipulator + shield thickness + utilities



Extended family: Cyclone 30 XP (now in Julich, Germany)

- Cyclone 15- 30 MeV proton + 15 MeV deuteron
- Addition: 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.

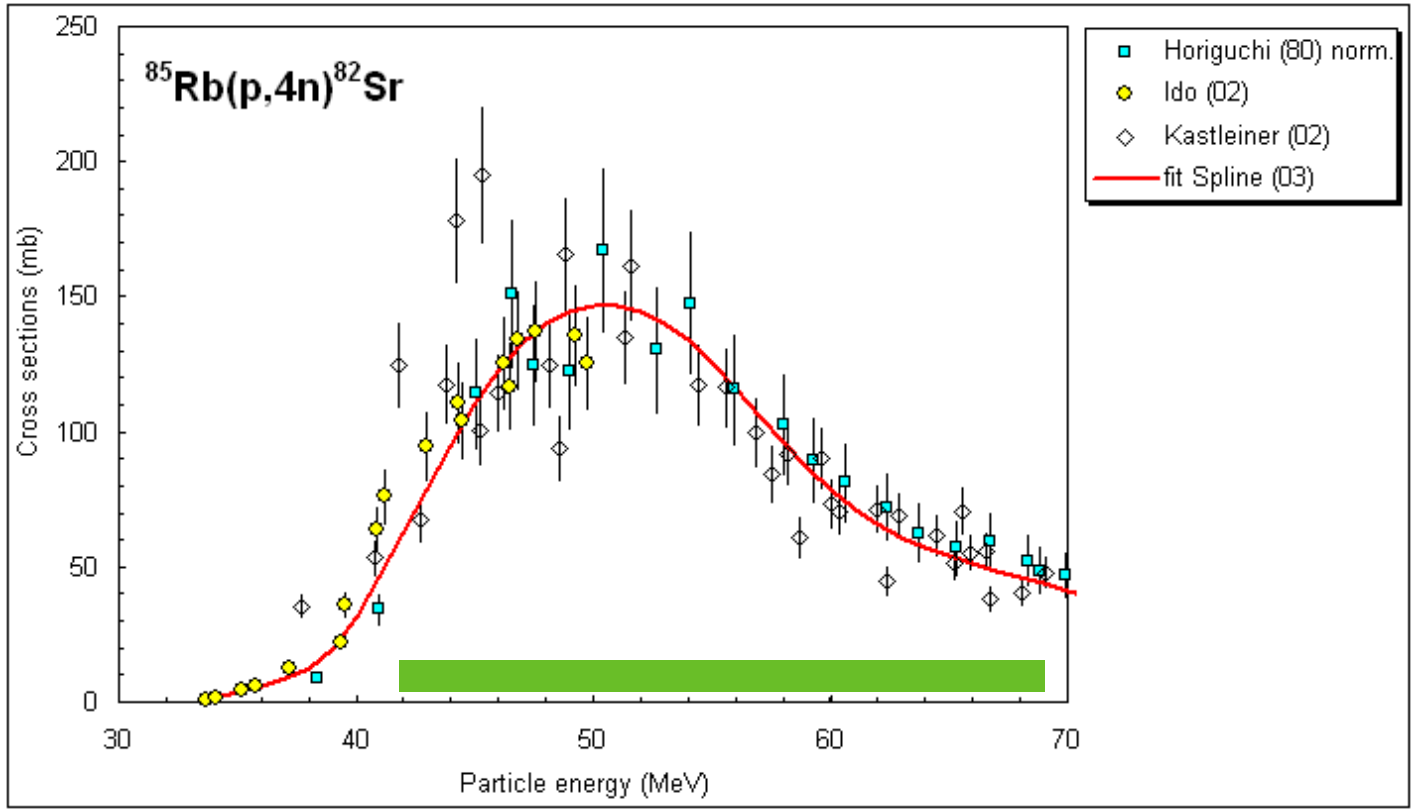
PROTECT +
ENHANCE +
SAVE LIVES

Generators for PET :

^{82}Sr (25d)/ Rb (1.2 min)
^{68}Ge (270d) /Ga (68 min)

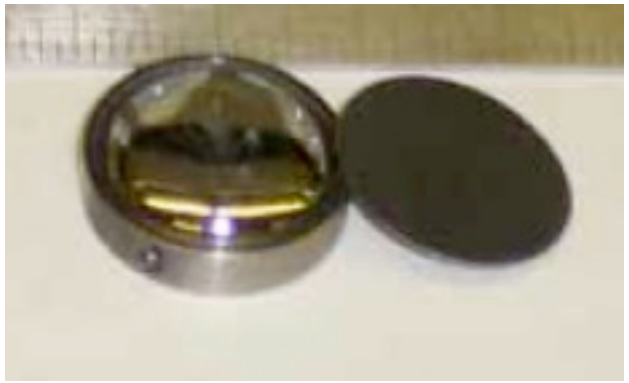
Sr/Rb : generator from cyclotron (or Linac..)

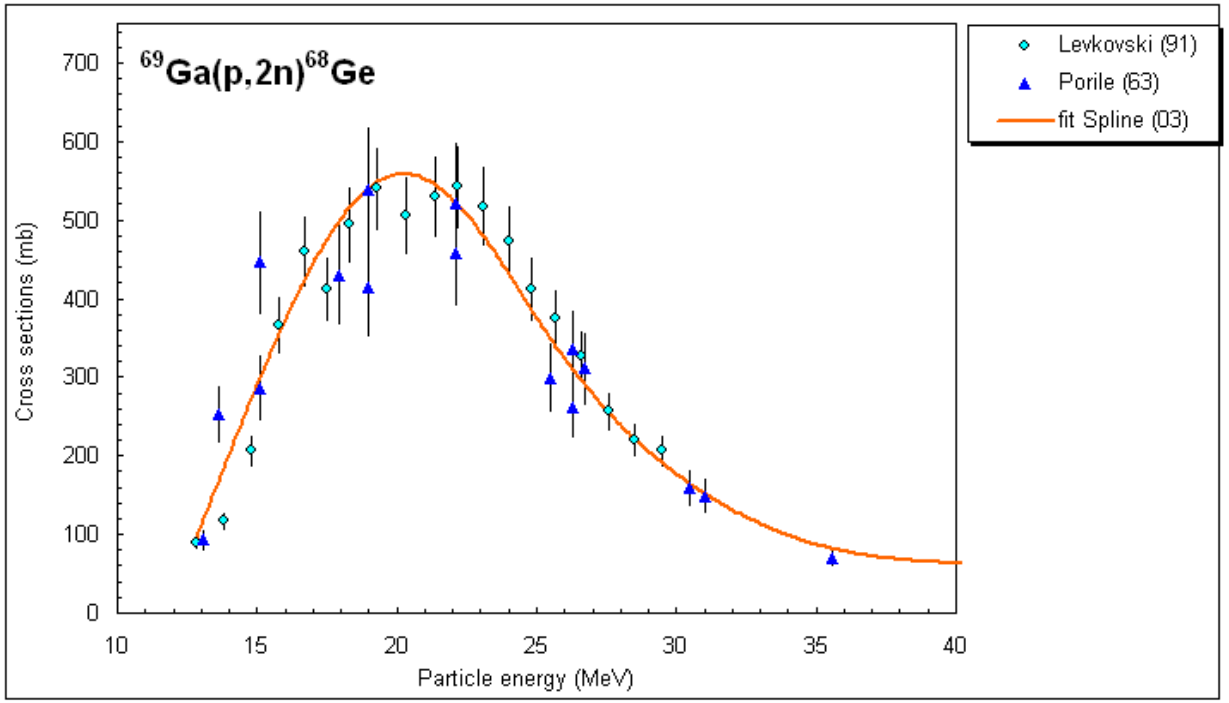
- ^{82}Sr (25d)/ Rb (1.2 min)
  - **^{85}Rb(p,4n) ^{82}Sr** 42-65 MeV
  - Avoid (p,3n).. (< 41 MeV, proton energy lost)



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





Cyclone® 70 P / XP

IBA Cyclone® 70 breaks world record performances at ARRONAX in Nantes, France

IBA Cyclotron Solutions reach world record performances for ARRONAX in Nantes, successfully producing 750µA in proton beam intensity with its Cyclone® 70 triple particle high energy cyclotron.

Louvain-la-Neuve, November 18, 2010

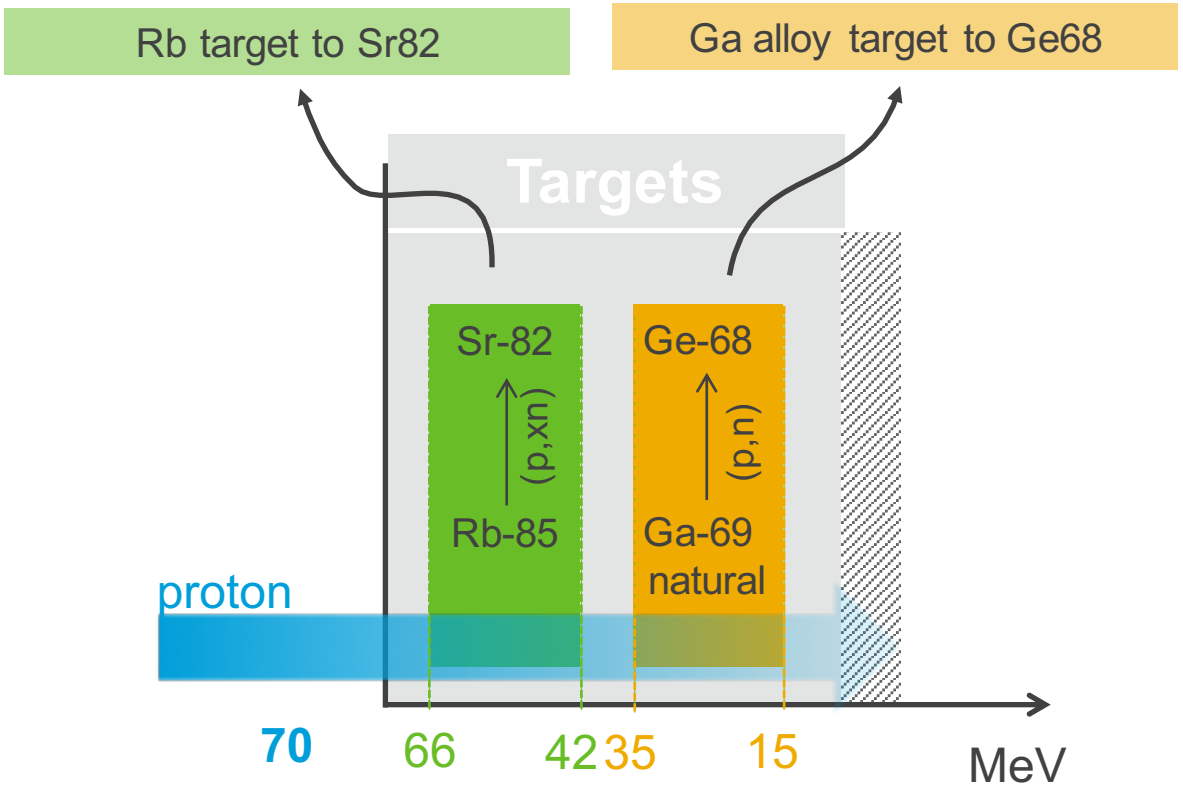
The primary focus of the 70 MeV Cyclotron will be the commercial manufacture of Strontium-82 to ensure an ample, stable U.S.-based supply of Strontium-82/Rubidium-82 generators for use in the diagnosis of cardiovascular disease. It will also produce a wide variety of other radionuclides for both research and clinical applications.

zevacor MOLECULAR

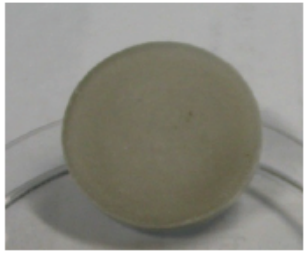
Particule	Energy	Current
Proton	30- 70 MeV (stripper)	750 µA
Deuteron	15- 35 MeV (stripper)	50 µA
Alpha	70 MeV (ESD)	70 µAe
HH+	35 MeV (ESD)	50 µA

Cyclone 70 & interesting PET generators

- **Strontium-82 and Germanium-68 Production at the ARRONAX Facility**
- **Now converted to Metal Rb**



Pressed pellet of RbCl

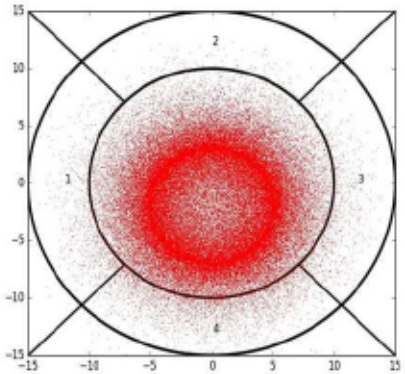


Encapsulated RbCl

Routine production 2*100μA on RbCl targets for a week (24/24)

Nuclear Data Sheets 119 (2014) 261–266

Thermal model of rubidium target



Calculated optimal beam position (Calculations performed at INR RAN)

Beam parameters:

σ = 3.1 mm

Diameter of beam rotation: 10 mm

Shift of beam spot center: 2 mm down

Target parameters:

Liquid (during irradiation) metallic Rubidium

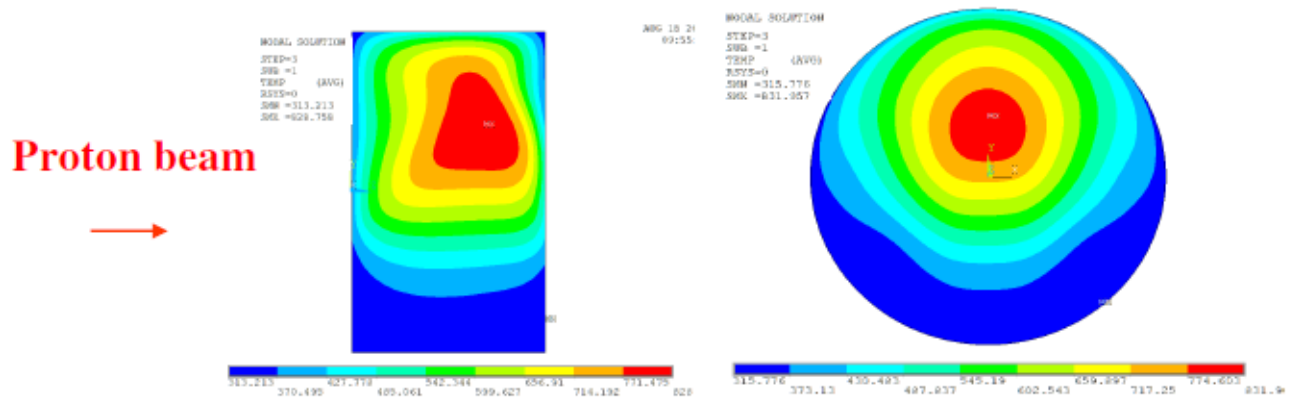
Water cooled on all sides

Initial design goal 150 uA

Actually achieved >200 uA

14 kW of proton beam

Calculated temperature distribution in Rb-metal (T_{max} =400°C at 200 μA)



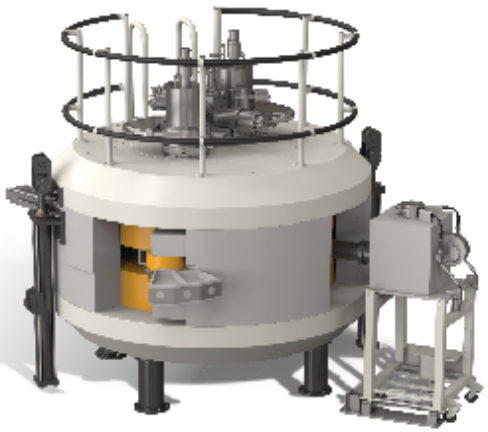
Kiselev et al (Zevacor), 13th Topical meeting on Nuclear Applications of Accelerators, Quebec; 2017

HIGH CAPACITY CYCLOTRONS & targets

Cyclone® KIUBE [18 Mev]
Proton up to 300 µA

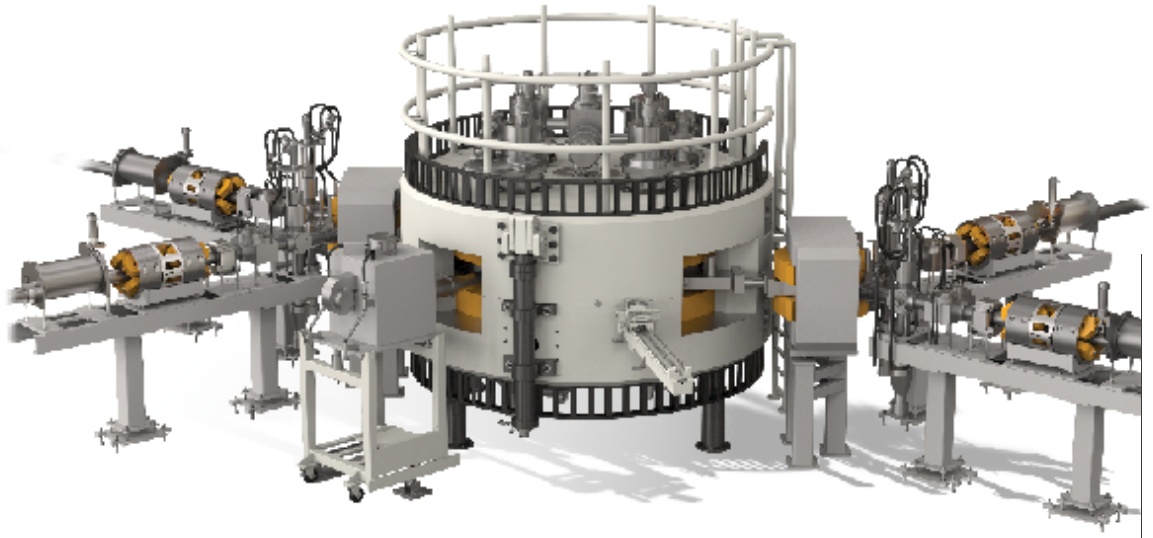
PET

Ga in target



Cyclone® 30 [MeV]
Proton, deuteron & alpha up to 1200 µA

PET & SPECT & Ac225, *At211*



Cyclone® 70 [MeV]
Proton, deuteron & alpha up to 750 µA

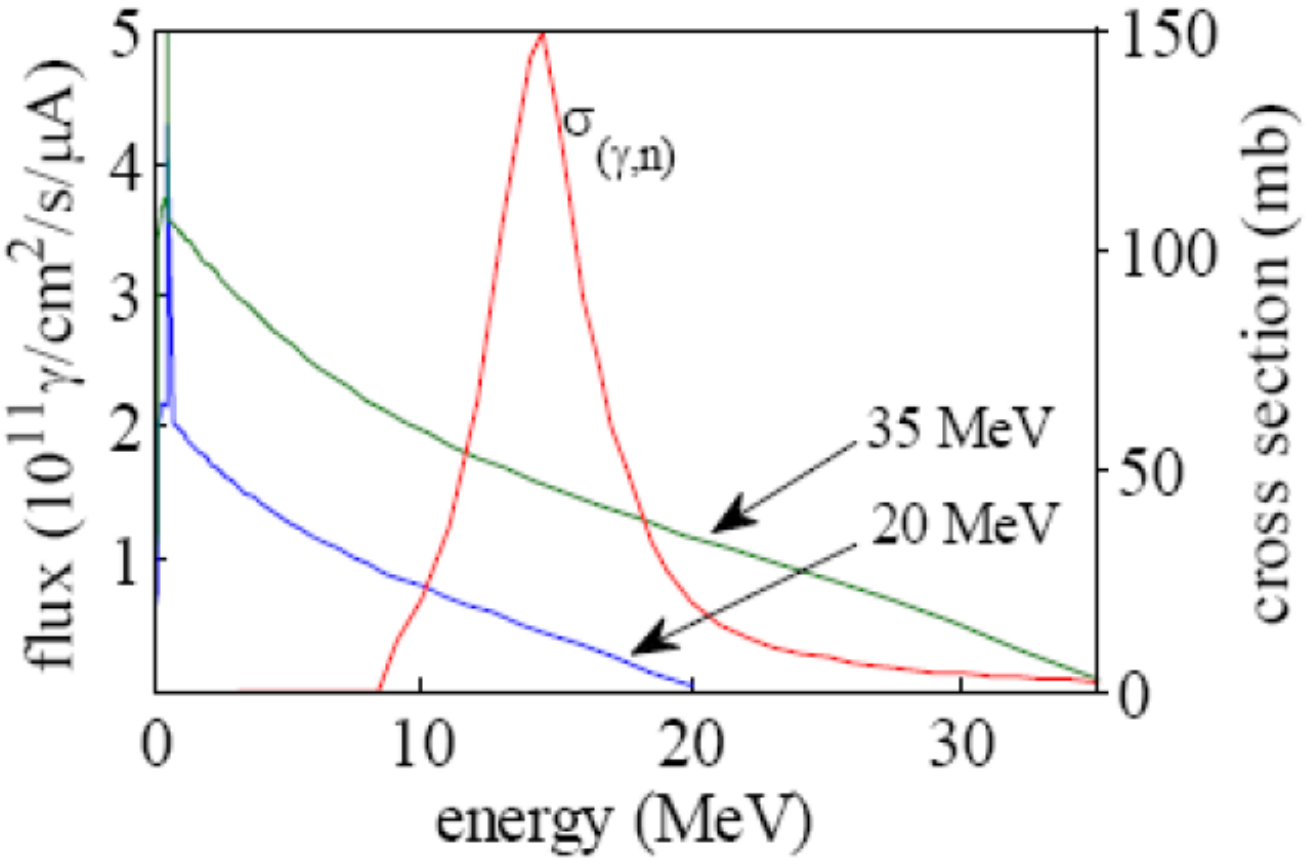
Sr82 for Sr/Rb generator & SPECT *& others*

Ge68 for Ge/Ga generator

Mo99 PRODUCTION WITH ELECTRON - ACCELERATORS

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

Photonuclear reaction (g,n) in Mo100 target to Mo99

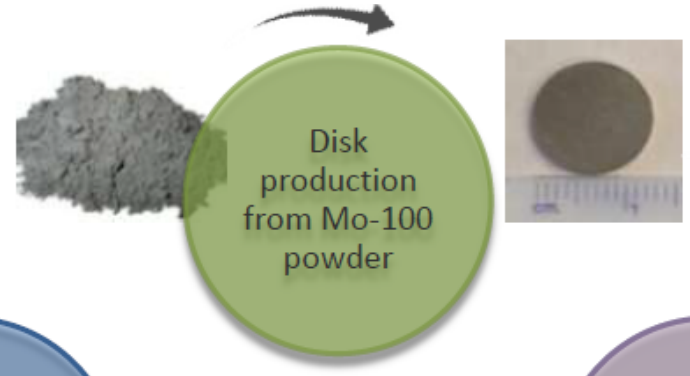


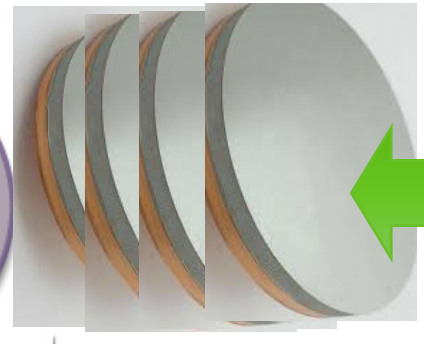
N_m – atom density of material m
E_{th} – threshold energy in m
$\Phi_{E0}(E)$ – photon fluence spectrum
$\sigma(\gamma,n)$ – cross section

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.

The Mo100- Mo99 cycle

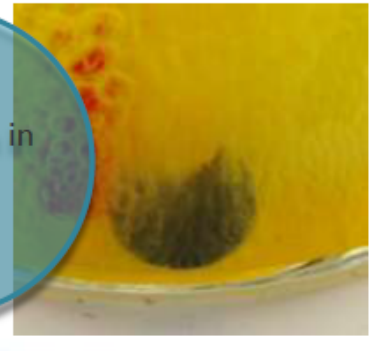
Need to adress recycling of the target material



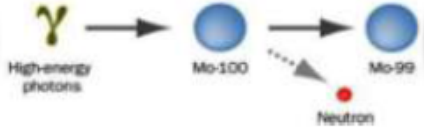


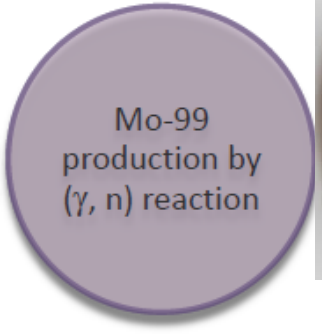
40 MeV ELECTRON

each target set ~2,500Ci of Mo99



Tc99m for labelling





RadioGenix Generating System - NorthStar

• High specific activity USP compliant Tc99m from low specific activity Mo99 sources

• Chemistry for Tc99m production is **unaffected by Mo99 production route:**

•Natural Mo or enriched Mo;

•neutron activated, *Mo98(n,g) Mo 99*

•photon activated, *Mo100(g,n) Mo99*

•fission Mo99

• **Keeps Mo99 logistics** (T1/2 : 66 h)

• FDA approval of the new extractor

40 MeV electron ‘rhodotron’ accelerator

- **Feasible & reliable**
  - More than 3MW of beam power installed
  - **running 24-7 with >99% availability**

- **Economical** alternative to Linac
  - Half the consumption of a Linac
  - Small footprint
  - Lower maintenance cost

Future is bright for accelerator production ;-)

- More output / products on existing PET cyclotrons
  - Decreasing price of FDG
  - New 18F tracers (& proprietary)
  - Instant production of Ga^{68}
- Production of therapeutic radionuclides (At^{211}, Cu^{67}, Ac^{225},..)
- New production needs for PET generators
  - Ge/Ga
  - Sr/Rb
- *Mo 99 by electron – photonuclear reaction*

https://iba-worldwide.com/

http://aipes-eeig.org/

geets@iba-group.com

The Mo-Tc crisis – perspectives and future for cyclotron ?

- Use of accelerators for direct production of Tc99m

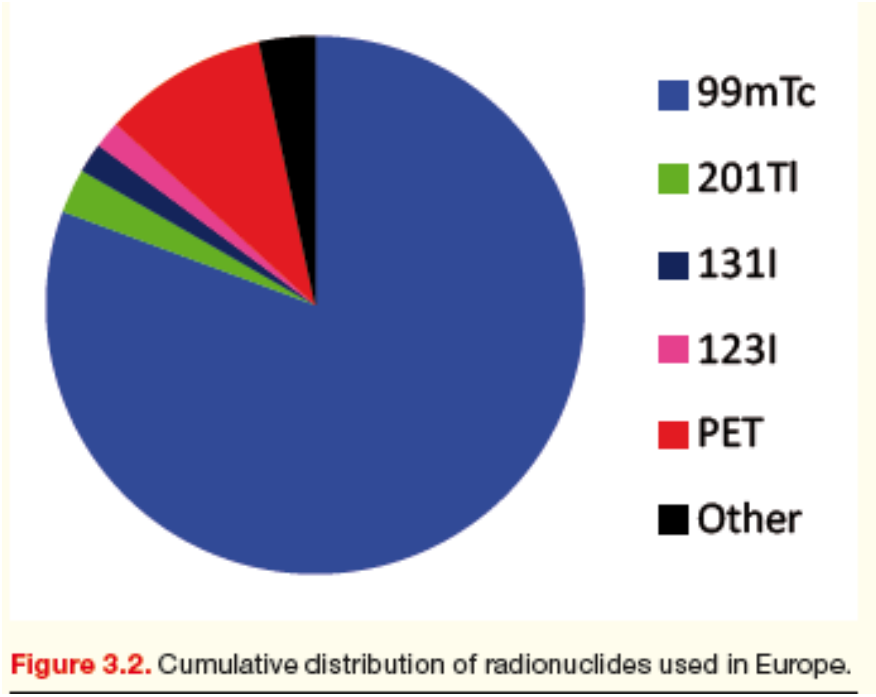


Figure 3.2. Cumulative distribution of radionuclides used in Europe.

NuPECC report 2014