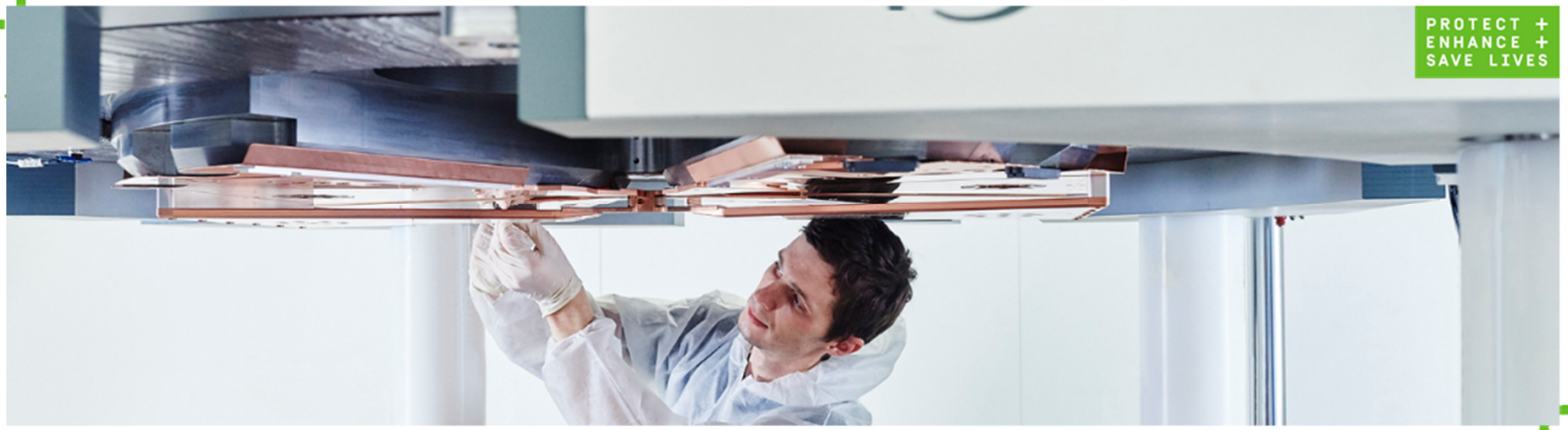


Cyclotrons for radioisotopes production

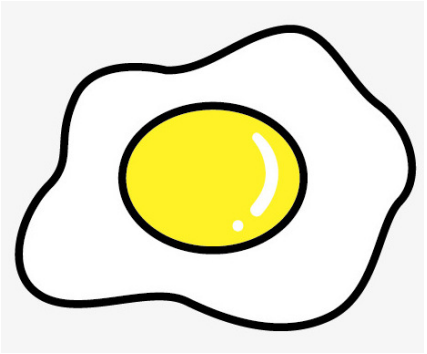
Geets Jean-Michel

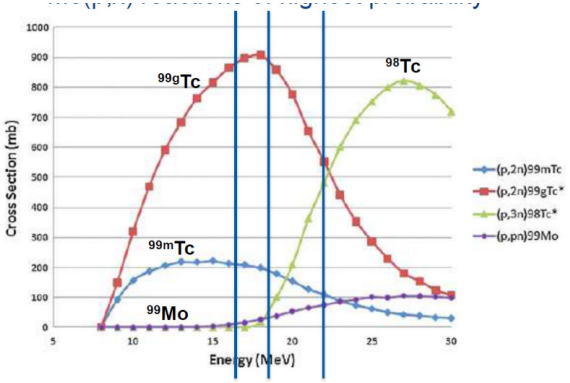
IBA Fellow & Domain Expert IBA RadioPharma Solutions

geets@iba-group.com

RADIO
PHARMA
SOLUTIONS

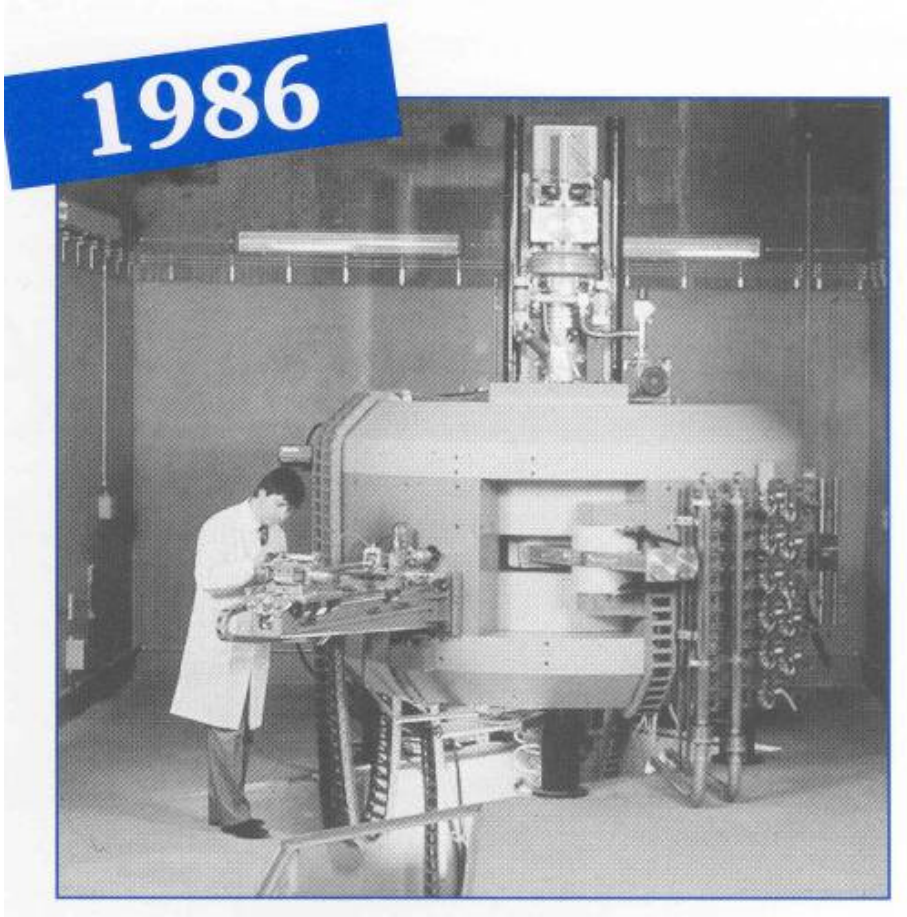
Production of RI => human injectable drugs





- Pharmacopea – spec
- GMP production
- Safety
- Cost, distribution,..

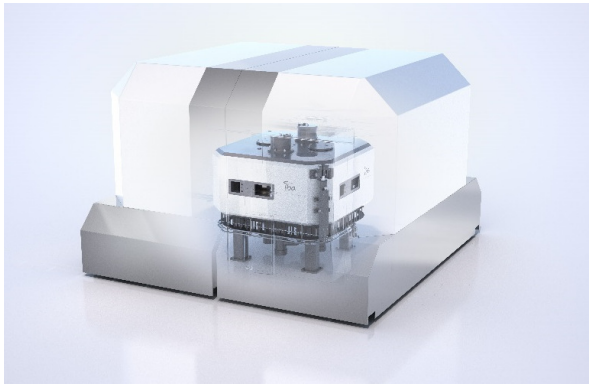
Once upon a time… in a Belgium physics research center



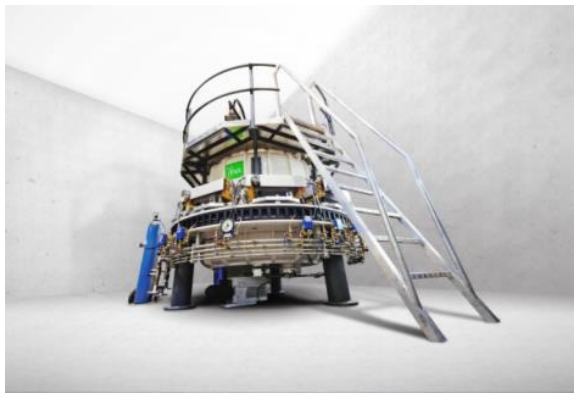
- A young researcher who had imagined a new cyclotron…
- Producing 5x more output
- Consuming 3x Less energy than any existing cyclotrons…
- A revolutionary cyclotron ***Cyclone 30*** *was invented*

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

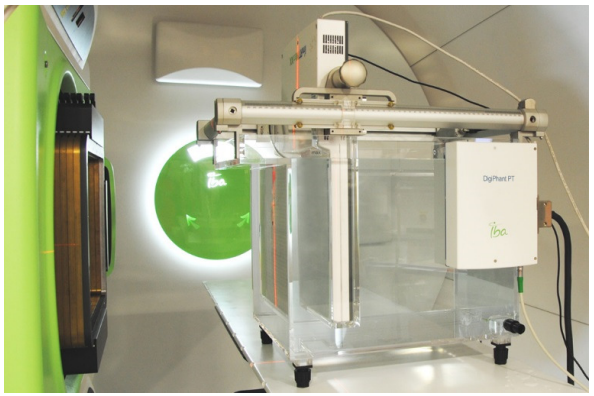
PROTON THERAPY



RADIOPHARMA SOLUTIONS



INDUSTRIAL SOLUTIONS



DOSIMETRY

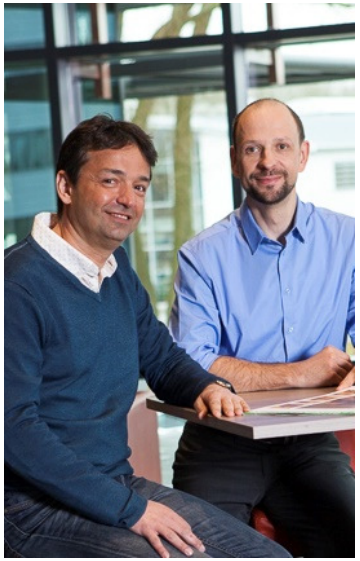
Protect, Enhance and Save Lives

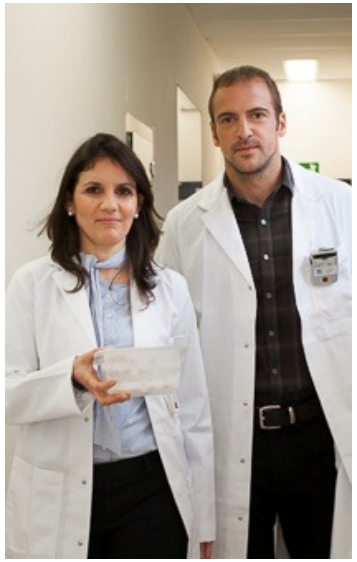
38+

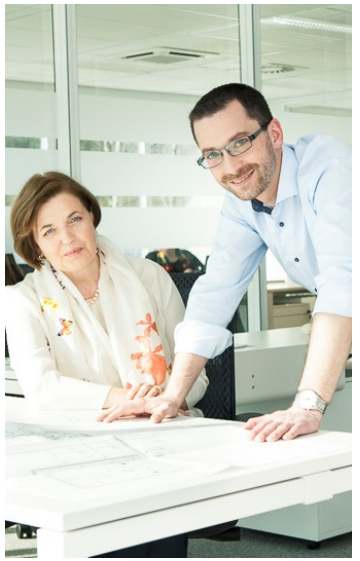
years of experience

Global Solutions provided by **EXPERTS**

for a **SUCCESSFUL** project

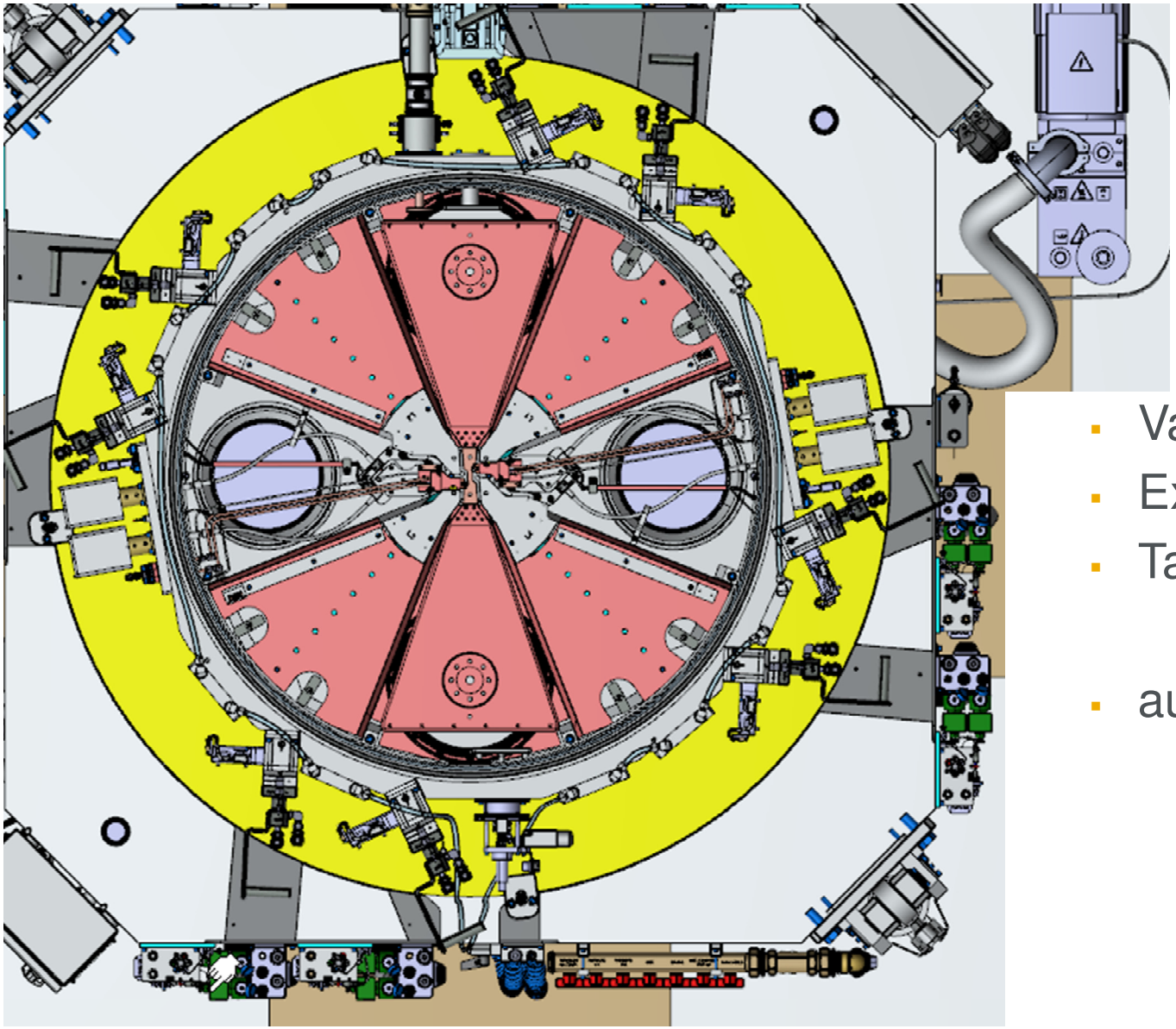




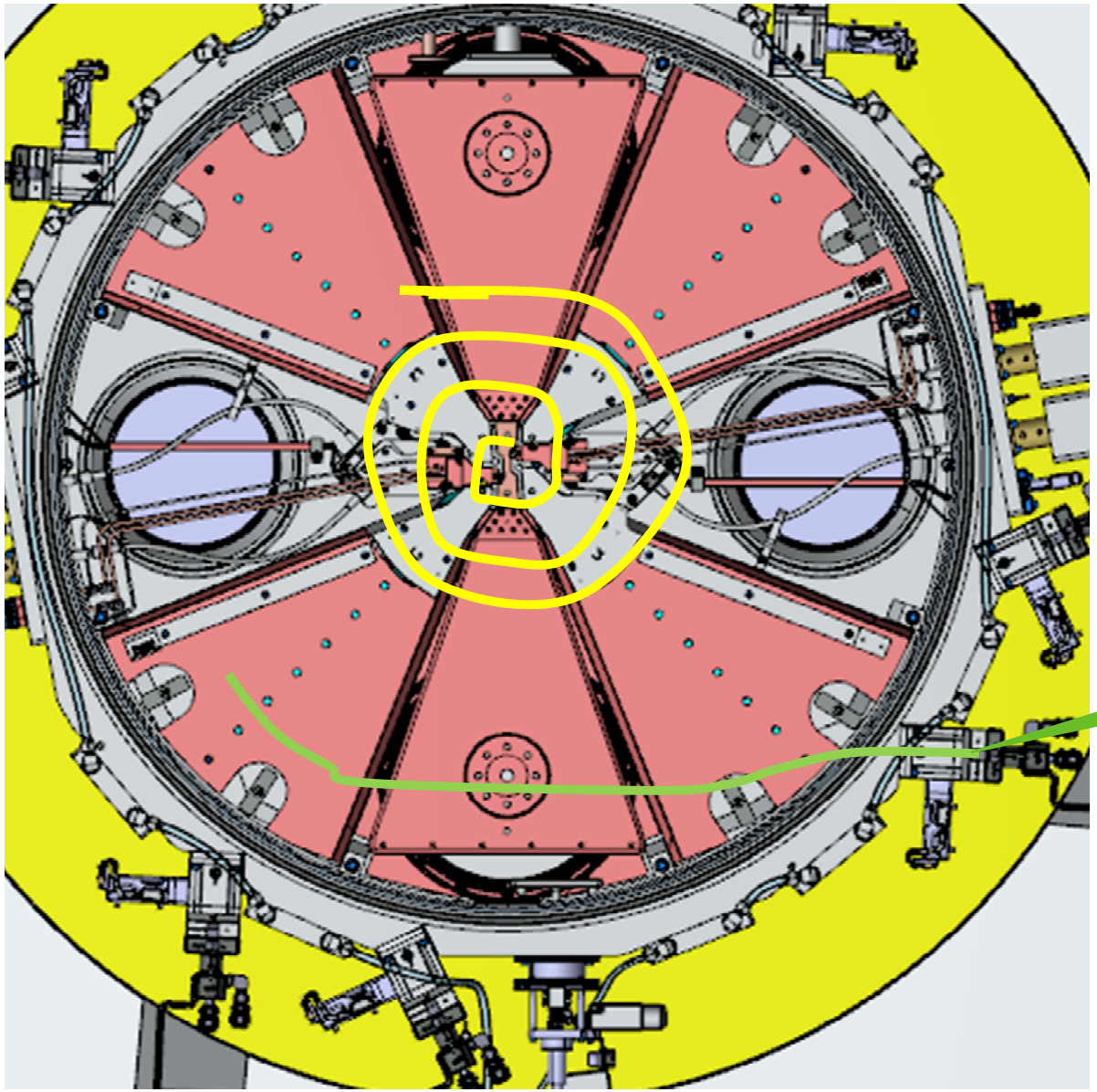


Cyclotron ?

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



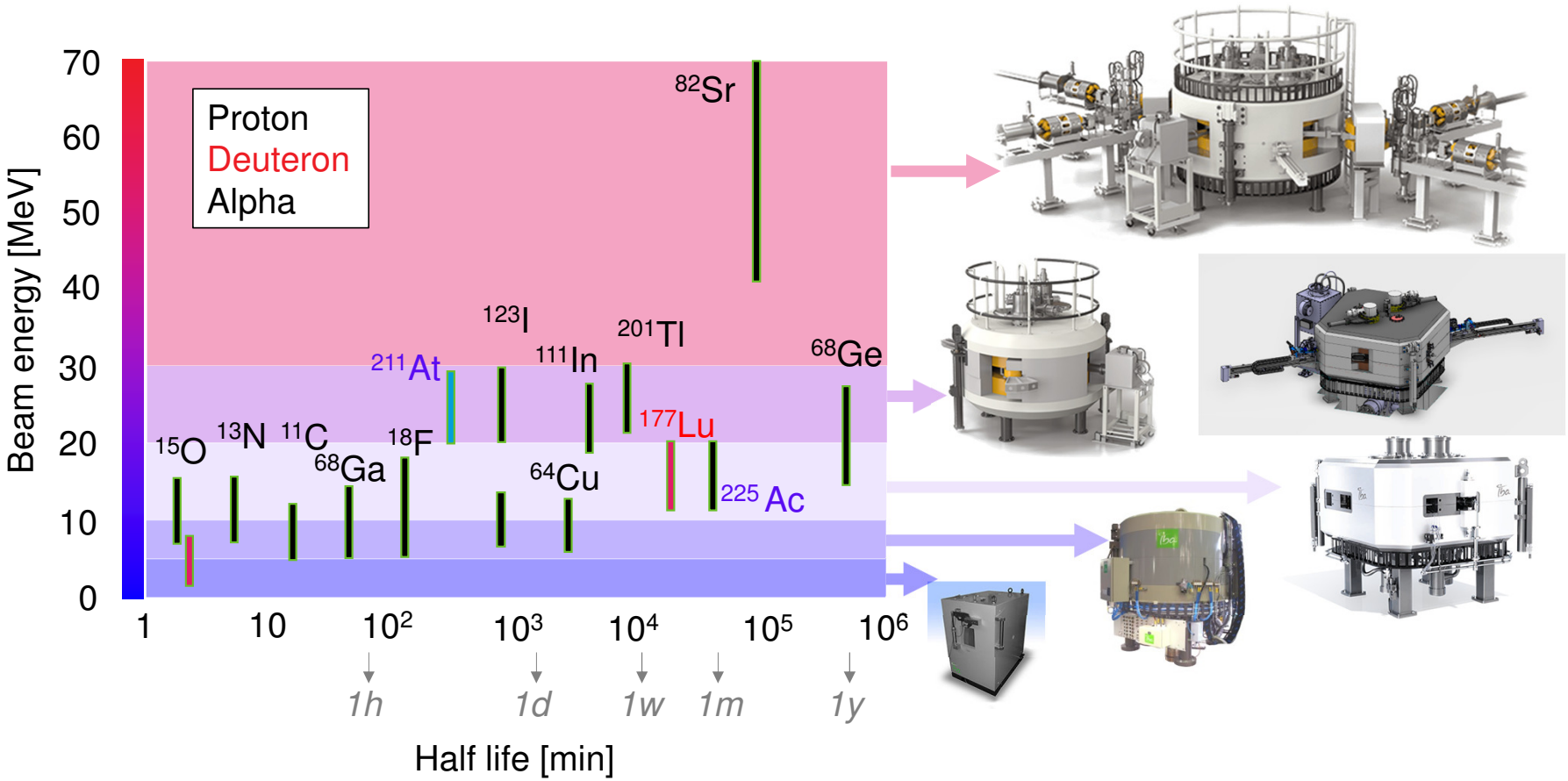
- Vacuum
- Extraction
- Targets
- auxiliaries



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

ance and Save Lives

Energy ranges & example of IBA cyclotrons



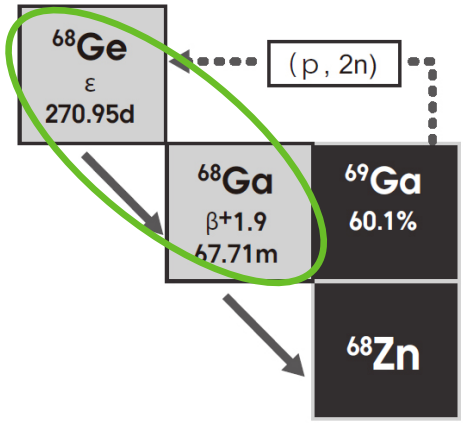
Cyclotron for PET : Cyclone® KIUBE

PET isotopes production

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

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

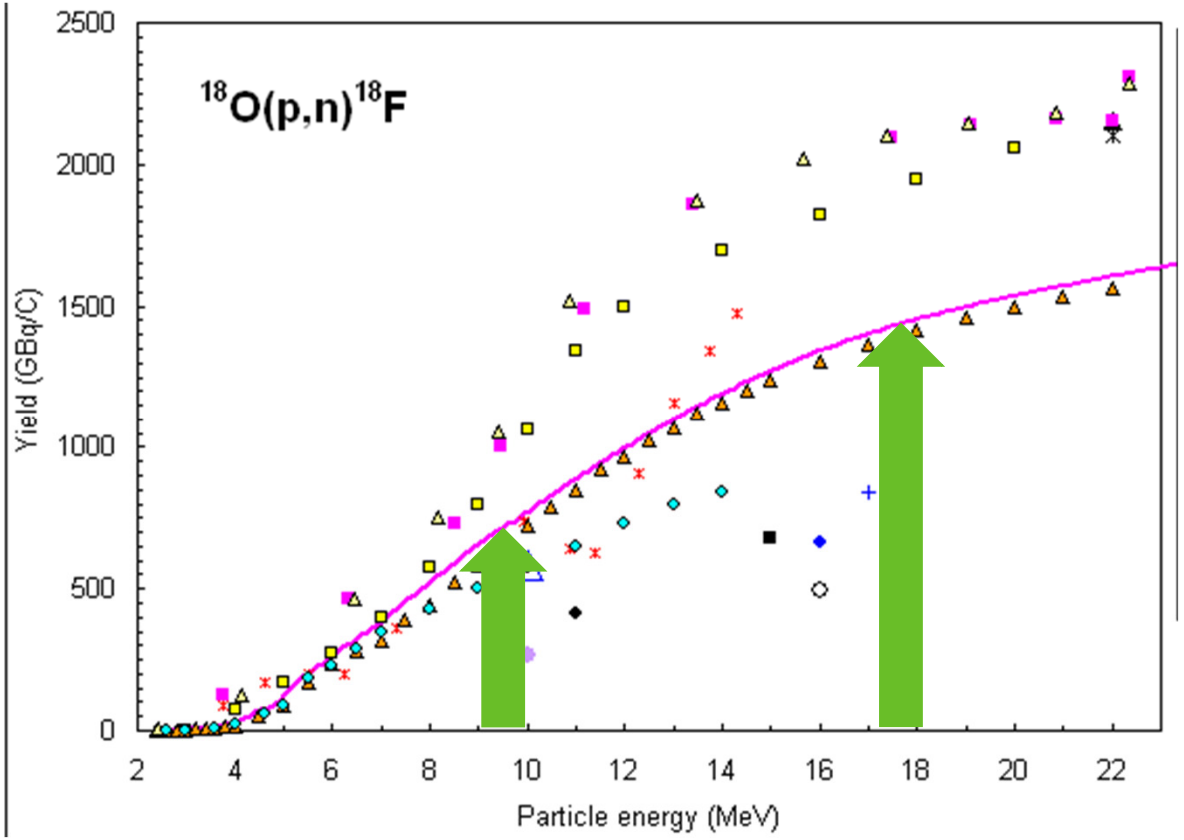
- ✓ Or Generator concept !



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	$^{63}Cu(p,2n)^{62}Zn(9.1\ hr) \rightarrow {}^{62}Cu$
^{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	$^{85}Rb(p,4n)^{82}Sr(25\ d) \rightarrow {}^{82}Rb$
^{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

Ep on 18O(p,n)18F



Factor 2 by choosing the right energy !

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
EP1568082

2005
HIGH CURRENT MACHINE 150µA
FOR INCREASED PRODUCTION
CAPACITY

2006
SHIELDED TARGET DOORS SHIELDING
CLOSURE FOR EASY DECOMMISIONING
EP200199

2008
TWIN PROTON SOURCES
TO MAXIMIZE UPTIME
EP2196073

2011
NIRTA® FLUOR CONICAL TARGET
FOR REDUCED ENRICHED WATER USE
WO 2012/055970

2012
ZEPHIROS® CYCLOTRON
CONTROL SYSTEM
FOR EASE OF USE
EP2581914

2016
CYCLONE® KIUBE
EP16169489, EP16169490
EP16169494, EP16169497
EP16171282

Targets
~ 150 µA

80 µA

100 µA

150 µA

300 µA

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

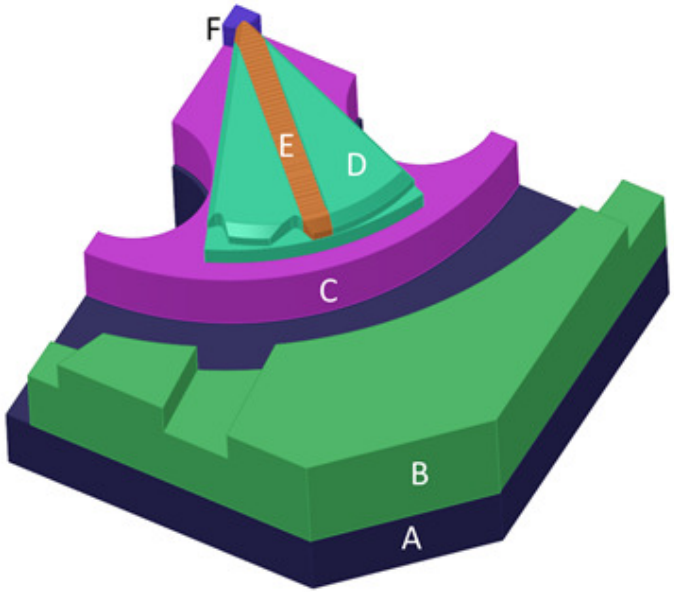
Optimization of "conventional cyclotrons" still possible and driven by new simulation tools !

24 Tons

16 Tons

what to learn from it (1/6)

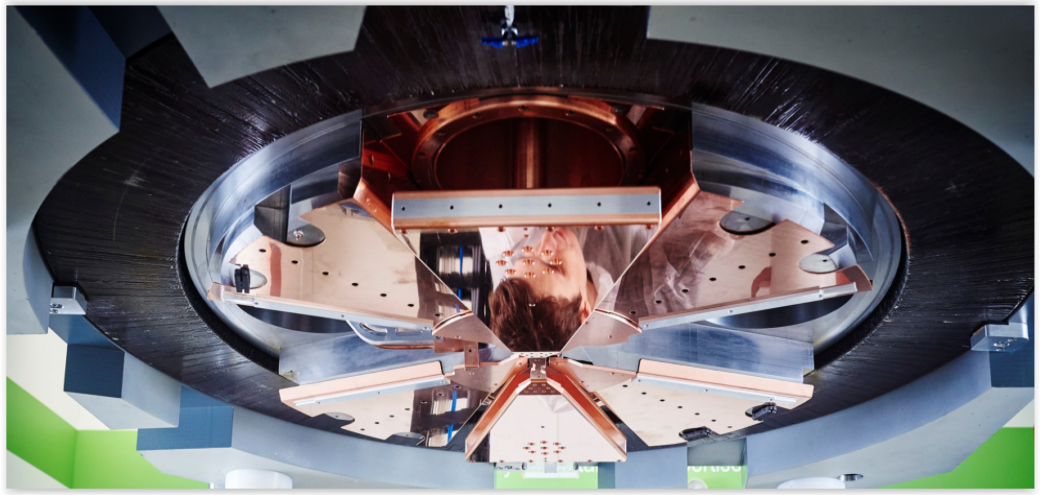
90's → 21st century tools
- Improved magnet design (OPERA3D)

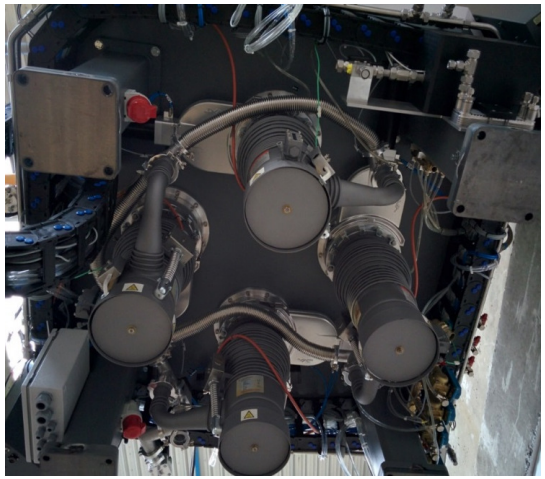


what to learn from it (2/6)

90's → 21st century tools

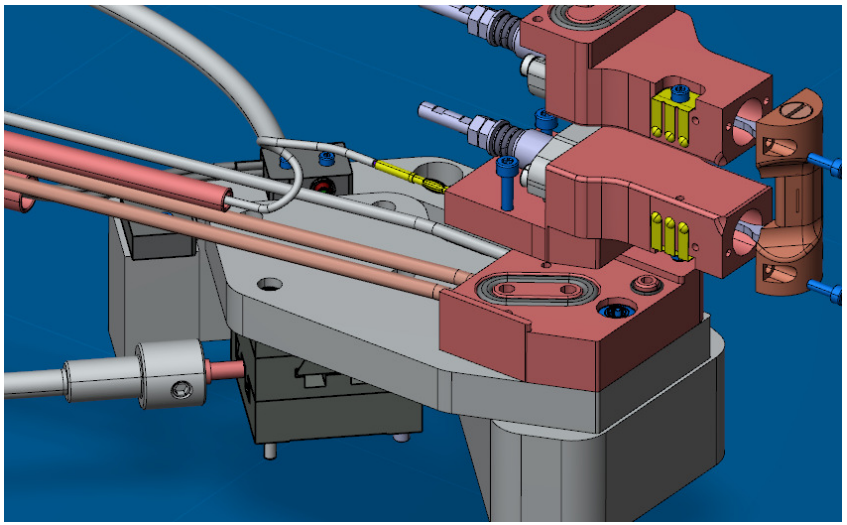
- Improved magnet design (OPERA3D)
- Improved vacuum design (Comsol) : **H-** (transmission 50% -> 70%)

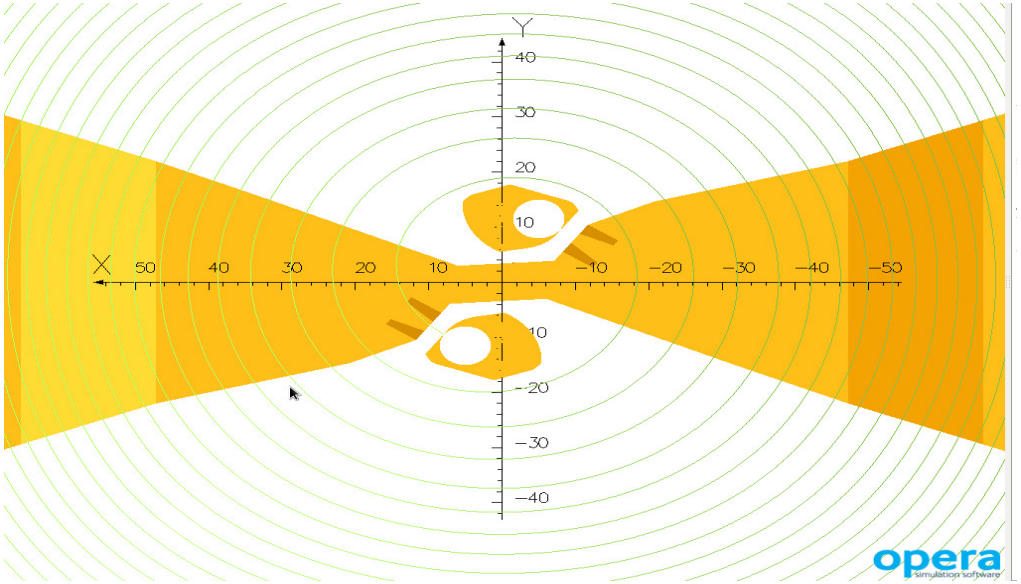




what to learn from it (3/6)

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

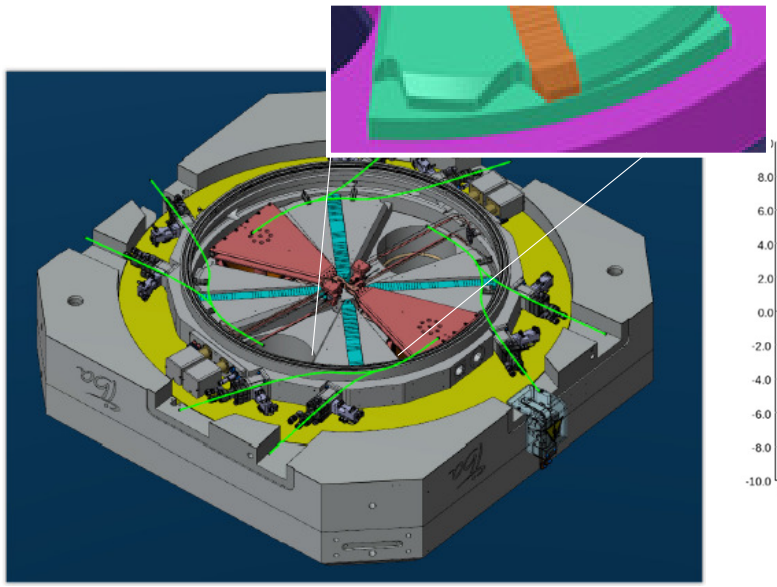




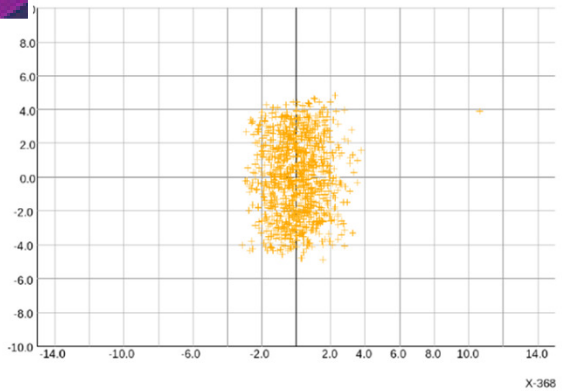
- *Motorized source positioning for better orbit centering & ease of maintenance*

what to learn from it (4/6)

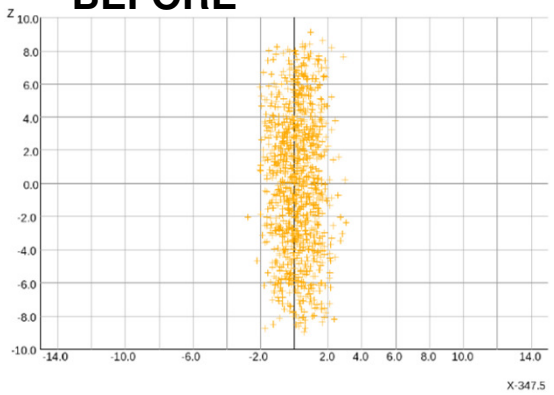
90's → 21st century tools
- Improved magnet design
- Improved vacuum design
- Optimized central region
- Optimized extraction optics



AFTER

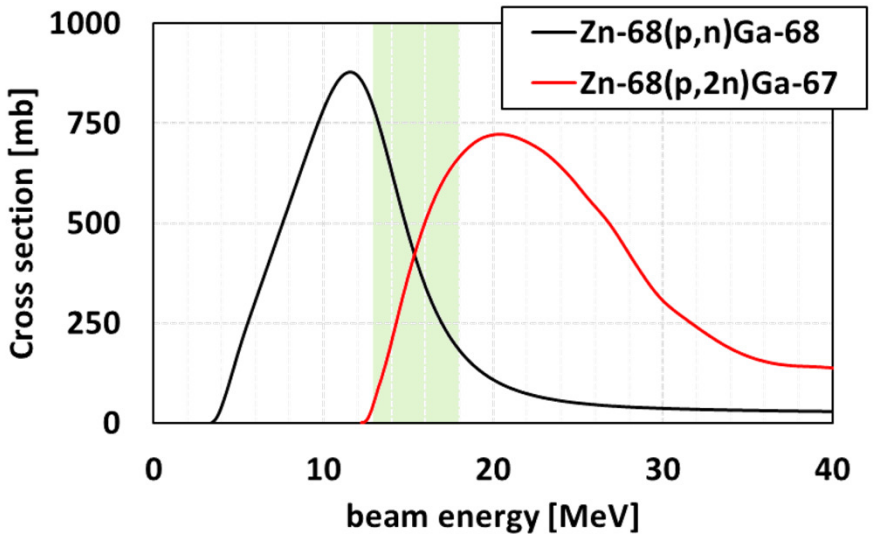


BEFORE



what to learn from it (5/6)

Isotope	Energy on target [MeV]
Zr-89	14-15
Cu-64	11-14
Y-86	15
Ga-68	13

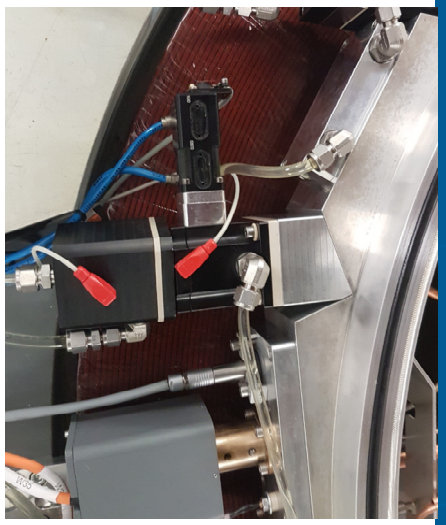


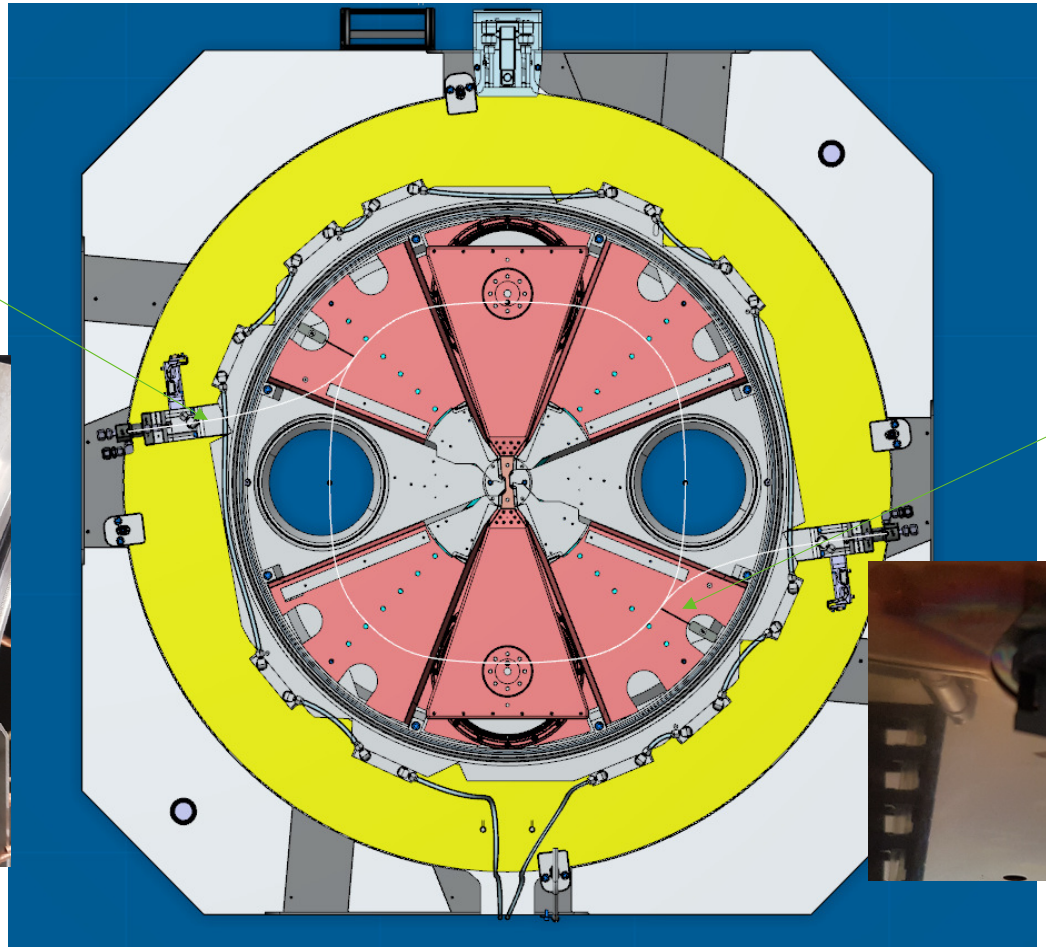
- ✓ H- stripping enables (fixed) variable energy extraction (13 - 18 MeV)
- ✓ Avoid energy degraders in “plug-in” target assembly
- ✓ Avoid ‘radial stripper’ & external dipole
- ✓ Avoid ‘radial stripper’ & target mechanical position

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

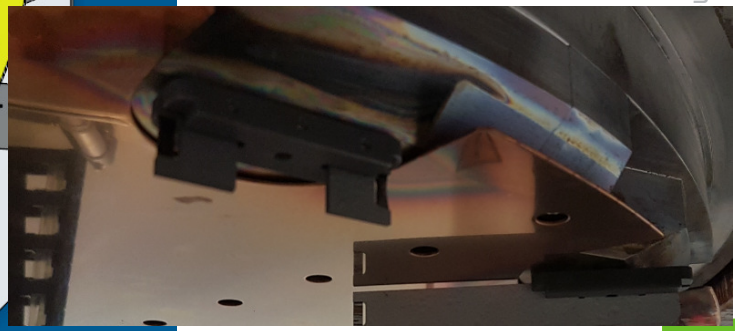
IBA Cyclone KIUBE Custom Energy (6/6)

Trajectory adaptation flange 13 MeV



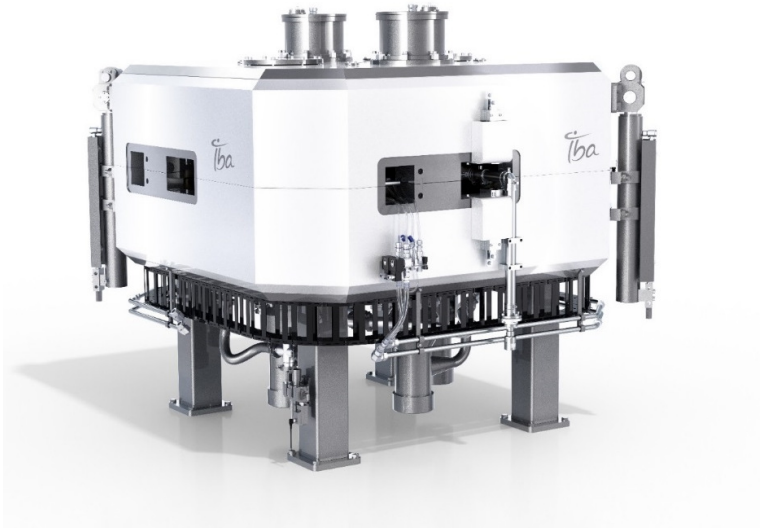


Long stripper fork 13,14,15, 16 MeV



A compact, internal Twin source cyclotron 18 MeV

Performance
300 µA



Vacuum
40 min
4 pumps

Flexibility
13-18 MeV
8 ports

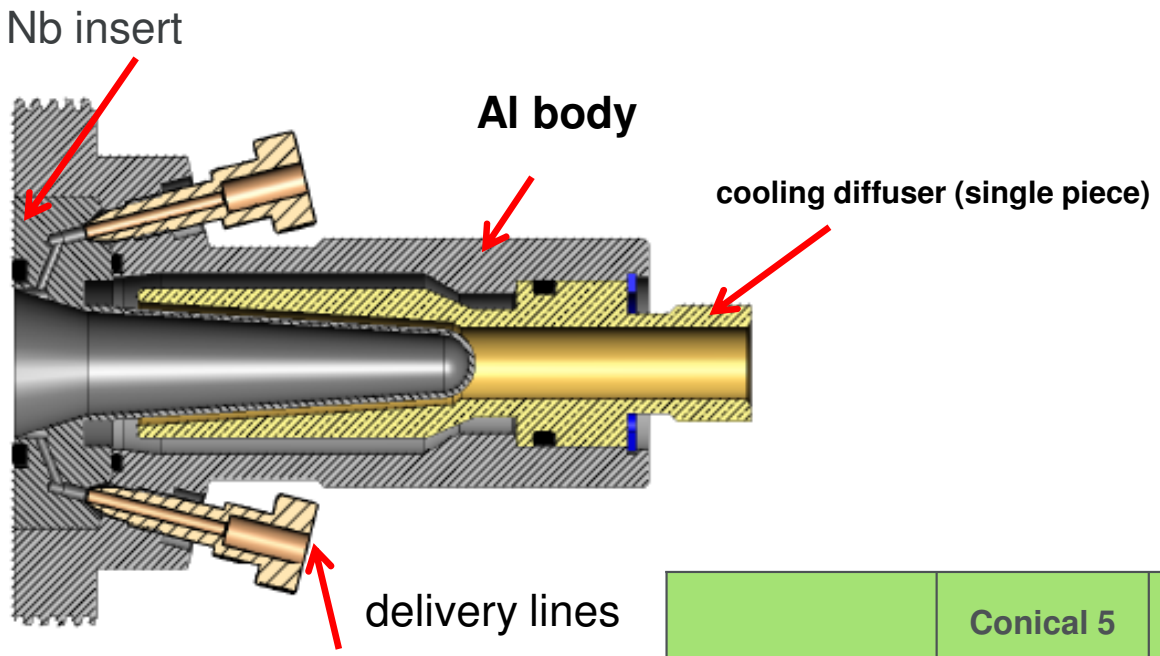
CYCLONE® KIUBE

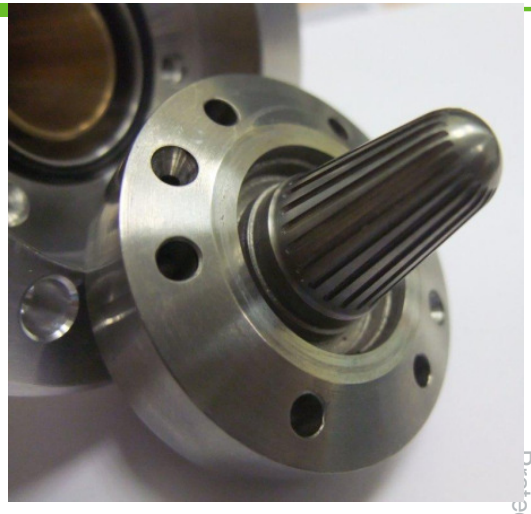
EP16169489, EP16169490
EP16169494, EP16169497
EP16171282

Reliability
2 ion sources
4 strippers /port

Protect, Enhance and Save Lives

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





	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

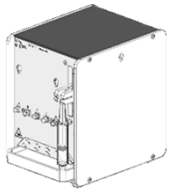
Novel routes of production: ^{68}Ga & ^{64}Cu

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

Cyclone® KIUBE

Ga-68 target

Cu-64/61 target

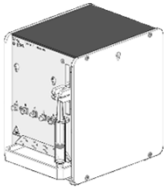


Purification:
Synthera ® Extension

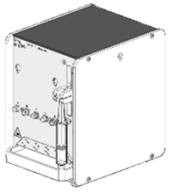
$^{68}GaCl_3$

Labelling: Synthera ®

^{68}Ga PSMA DOTATATE DOTANOC



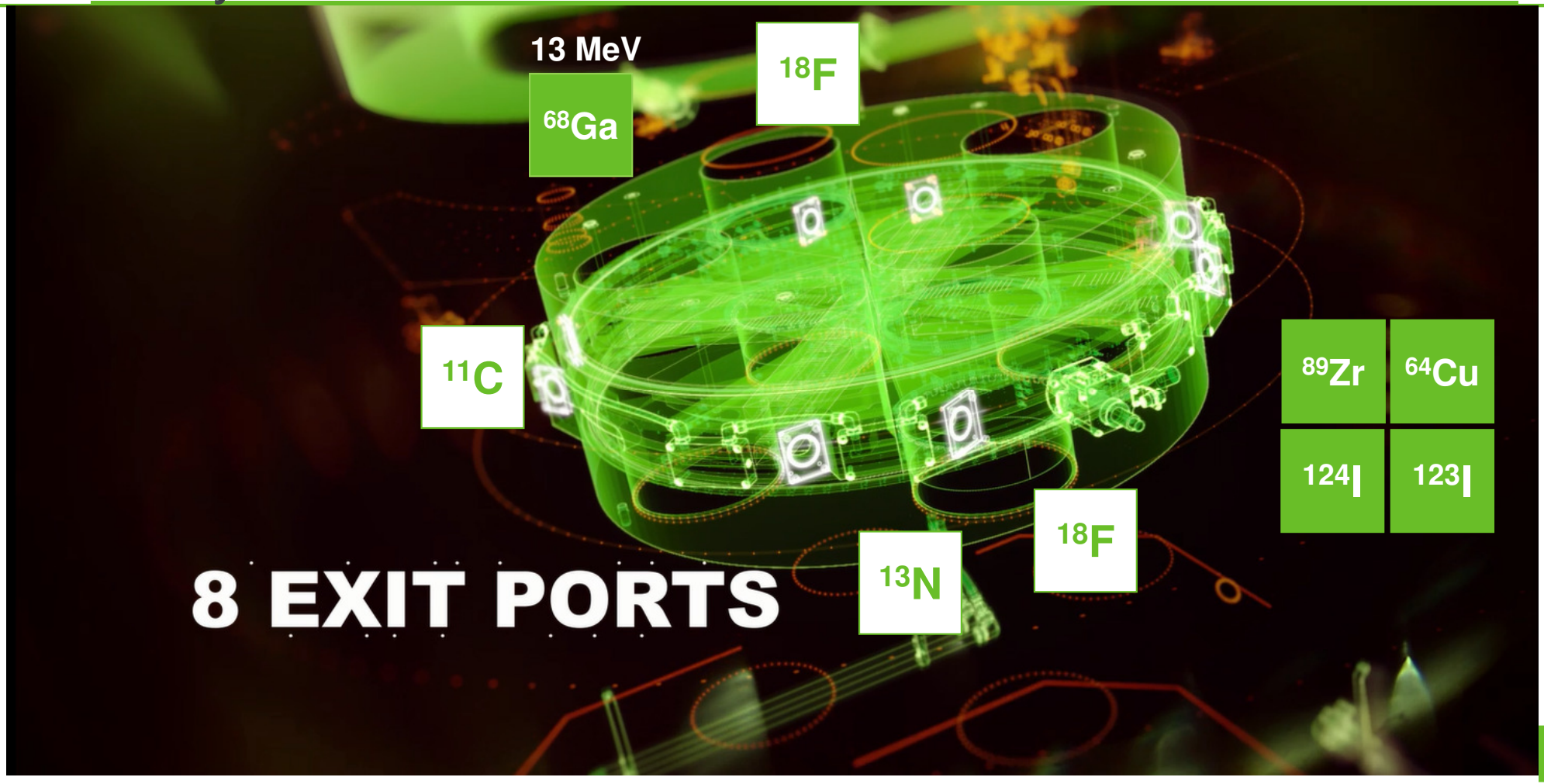
$^{64}CuCl_2$



^{64}Cu ATSM

Collaboration with the University of Coimbra

Flexibility



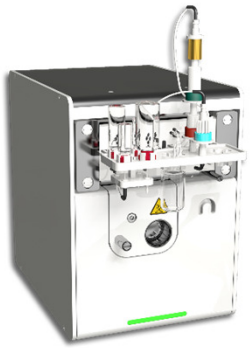
RadioChemistry- Synthera®+ Family for 18F-chemistry

+800 Synthera® worldwide

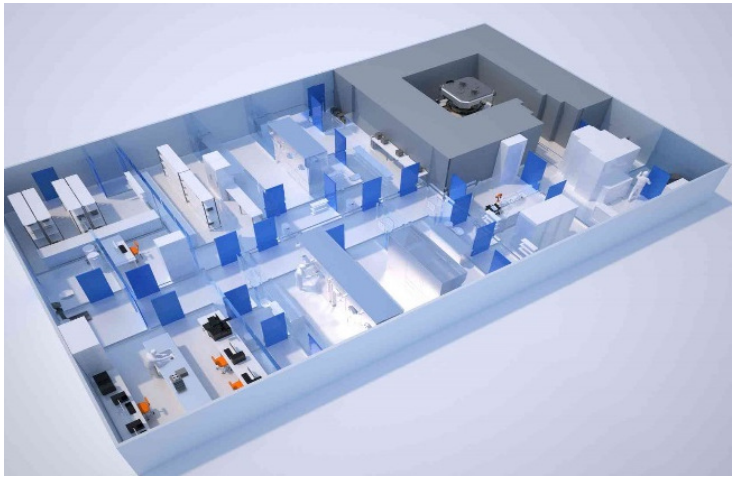
- **BETTER**
  Multiple runs of multiple tracers
- **SMARTER**
  Accessory-based ‘IFP’
- **STRONGER**
  Consistent yield and high uptime

RadioPharma Solutions : INTEGRALAB

CYCLONE®KIUBE

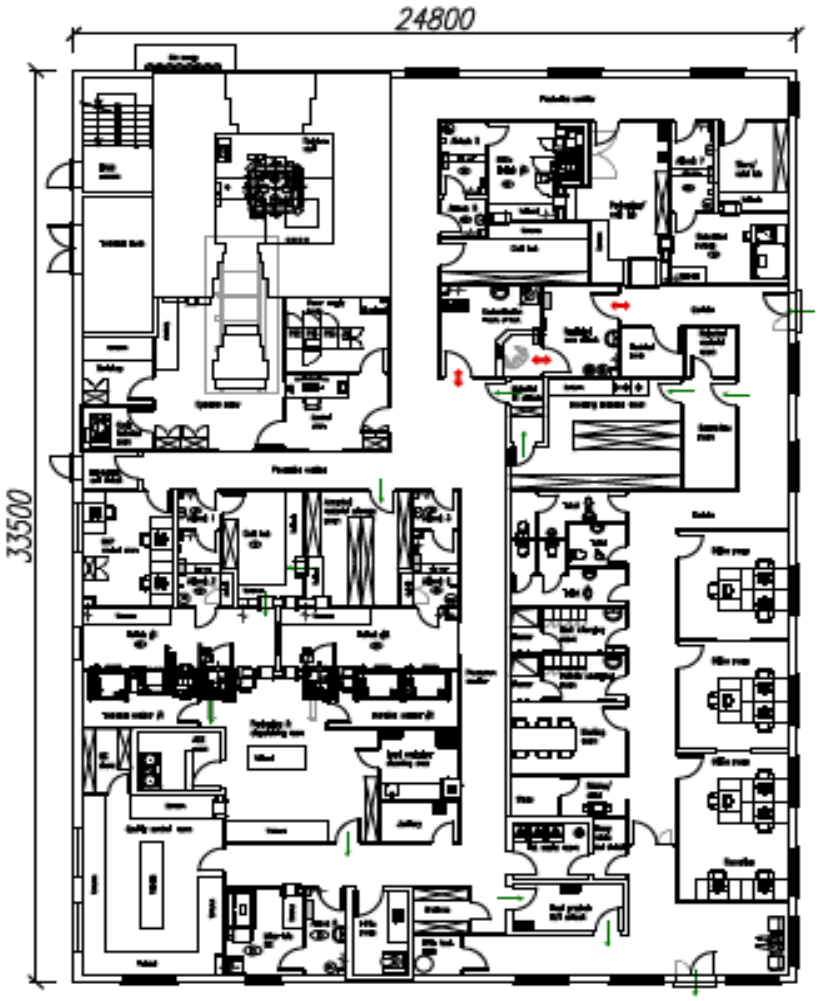


SYNTHERA®+

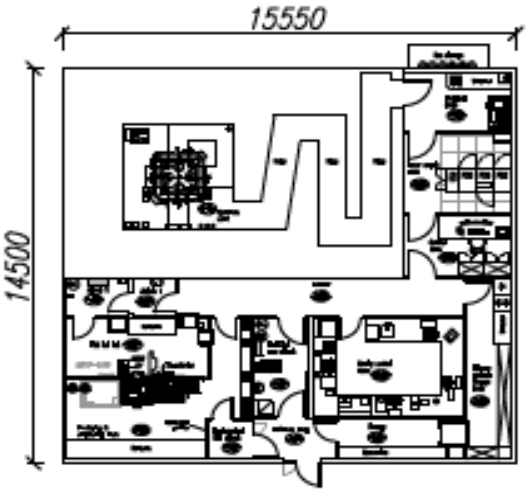


INTEGRALAB®

Protect, Enhance and Save Lives



Cyclone® KIUBE
830m²



Integralab® ONE
225m²

Protect, Enhance and Save Lives

Cyclone KIUBE extended option (beam line + solid target)

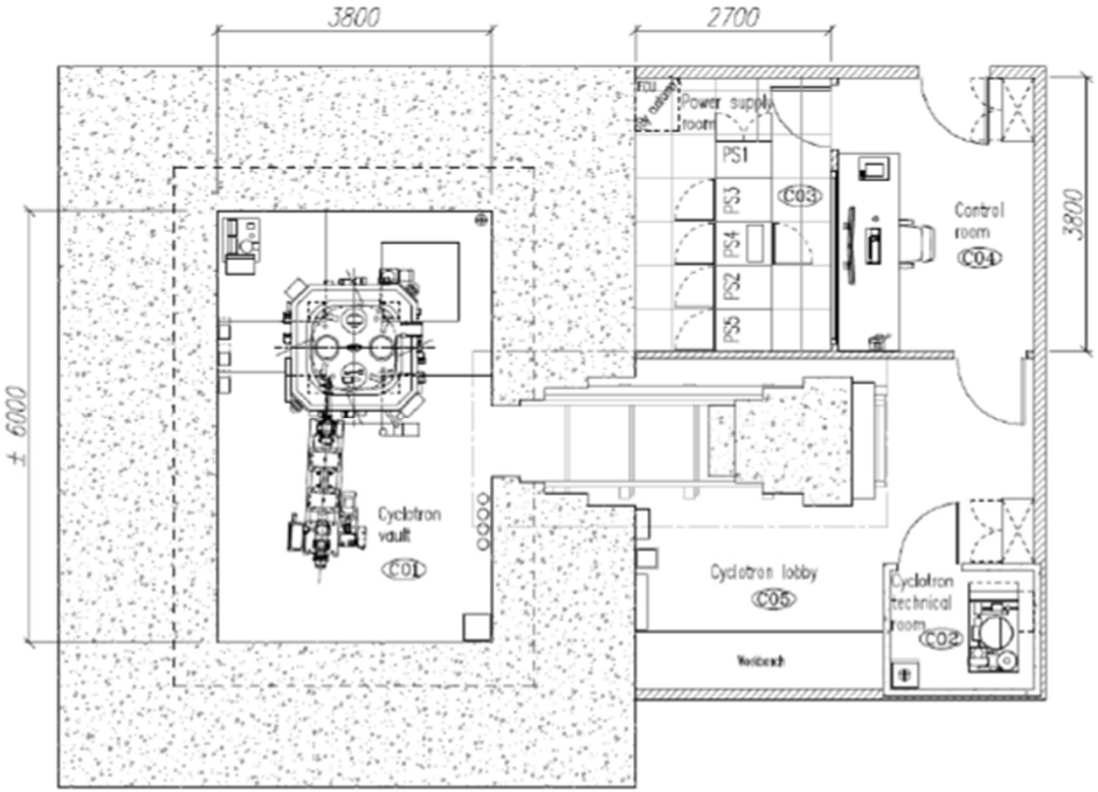


Figure 23: Cyclone® KIUBE with short beam line (vault)

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

OPEX for Cyclone KIUBE (ie 'PET cyclotron')

- **What is the power requirement (cyclotron & associated equipement)? (beam on and standby mode)**

Table 19: electrical power requirement and consumption

Total main power	Installed	Consumption
Cyclone® KIUBE 100	70 kVA	45 kW
Cyclone® KIUBE 150	85 kVA	55 kW
Cyclone® KIUBE 180	95 kVA	60 kW
Cyclone® KIUBE 300	100 kVA	65 kW
Vacuum stand-by (eco mode)	5 kVA	3 kW

Table 11: chilled water requirement and connection

The chiller minimum heat removal capability	55 kW (cyclotron)
Flow	100 l/min
Buyer water-cooling temperature INLET	between min 6° - 16°C max

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

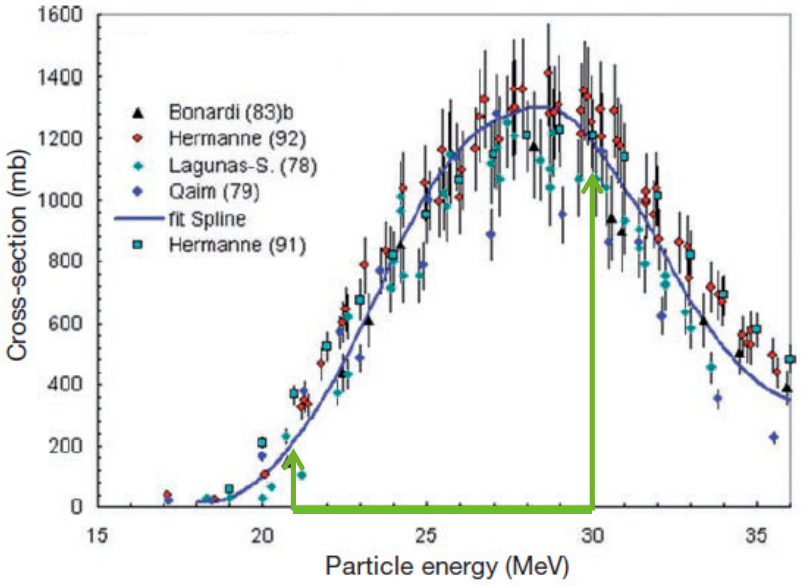


FIG. 2.40.1. Excitation function for the $^{203}Tl(p, 3n)^{201}Pb$ reaction.

- ✓ 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

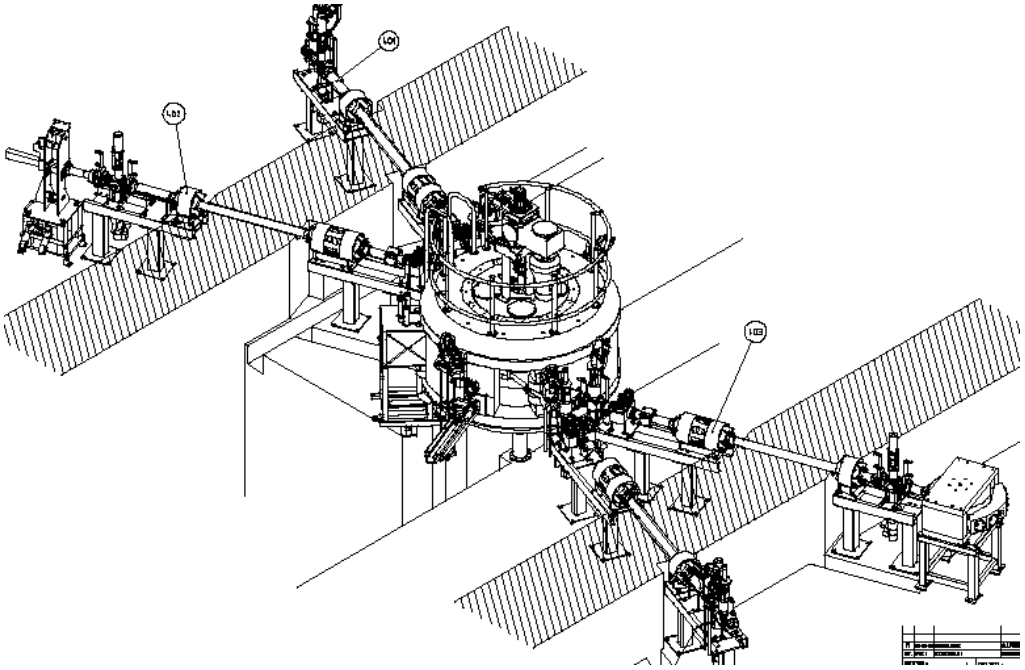
Table 4

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%

Cyclone 30 MeV proton for SPECT

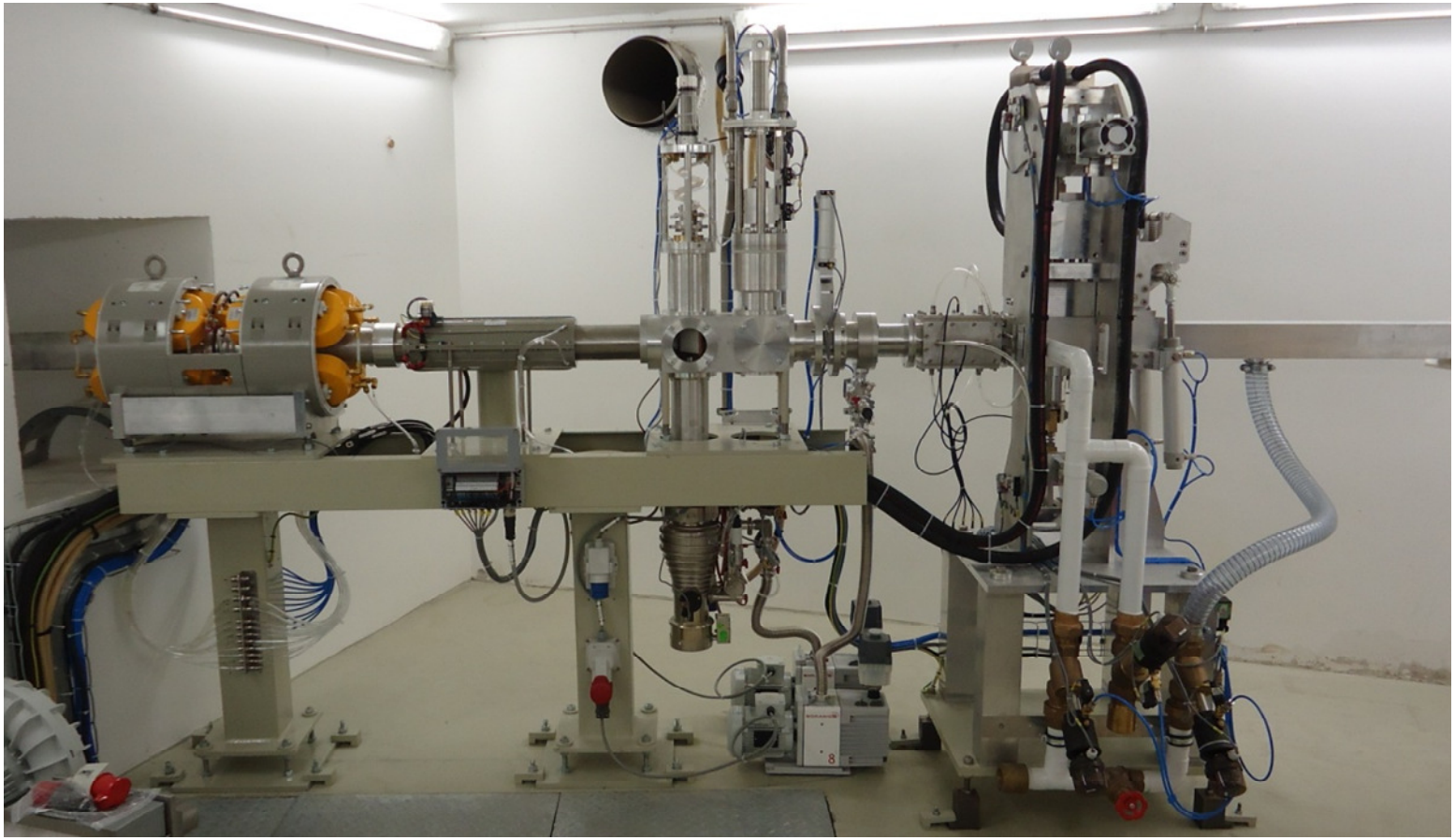
- 15- 30 MeV variable Energy proton
- Up to 1.2 mA proton (~ 36 kW)
- Mainly for SPECT isotopes (p,2n) (p,3n)
  - ~ Compact cyclotron (60 Tons)



IBA Cyclone 30

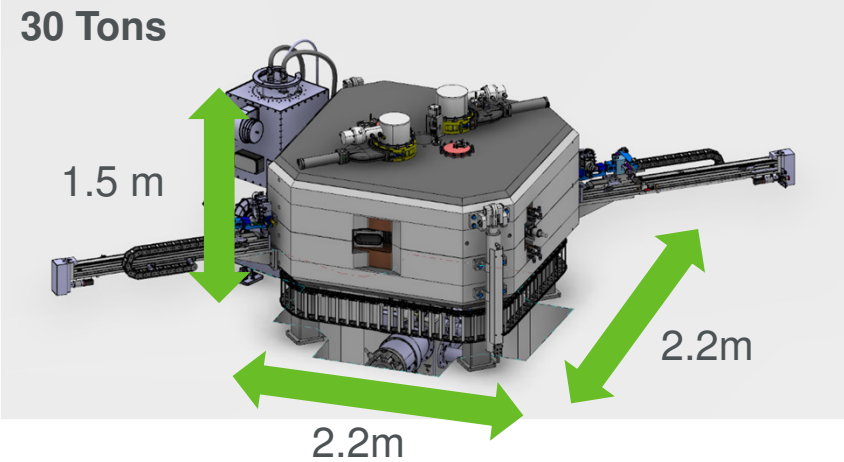
Solid target & beam line – target vault

Need to control the beam on target



Capitalizing on the Cyclone® KIUBE design

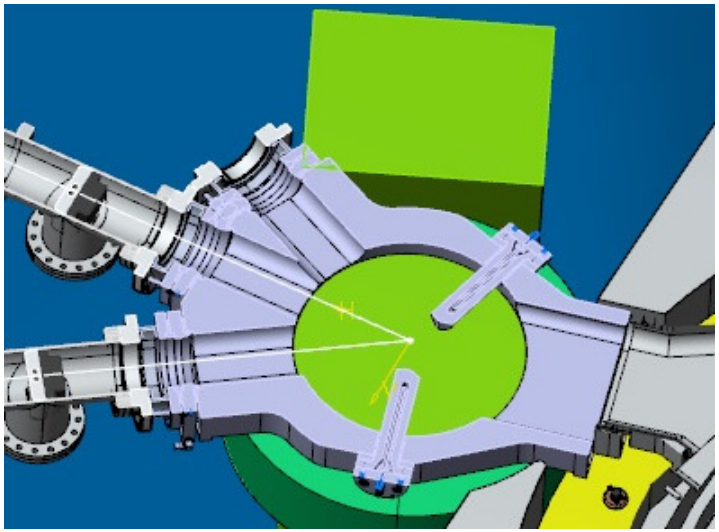
- to create a **compact, high-energy** and **high-current** Cyclotron

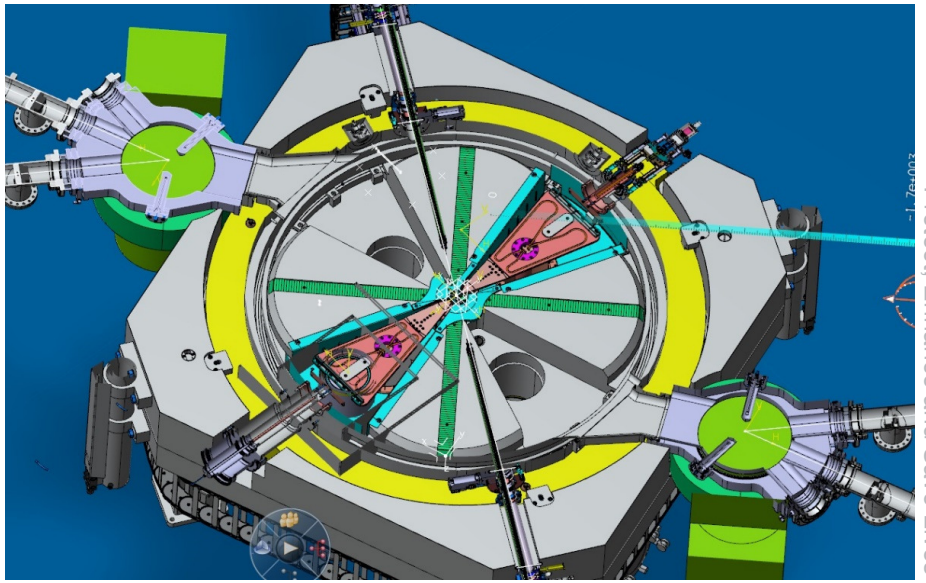


- Industrial cyclotron
  - >15% injection efficiency
  - >97% acceleration transmission
  - >99% extraction efficiency
  - >99% beam line transmission

Two exits – 3 ports each

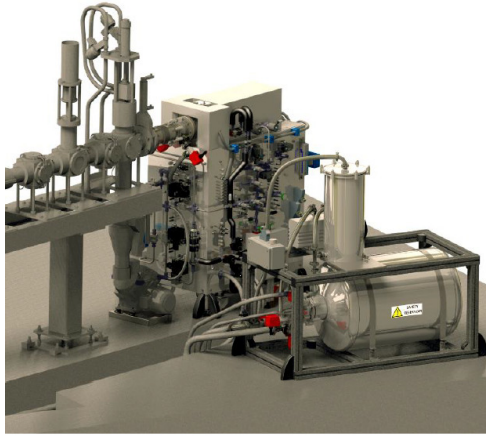
- Up to 2x 2 long beam line 13-30 MeV
- Up to 2x 1 target at 18 MeV



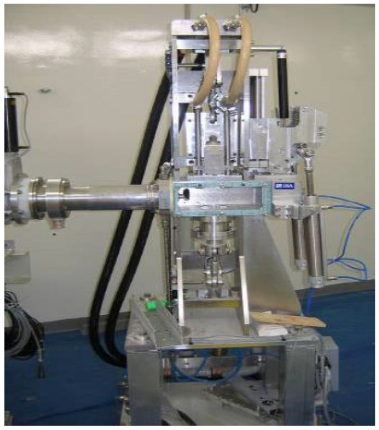


Machine with complete target range & IBA chemistry

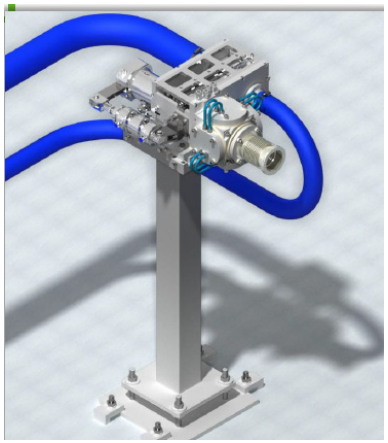
Xenon gas target for ^{123}I



High power 30 MeV solid target



High power PET solid target

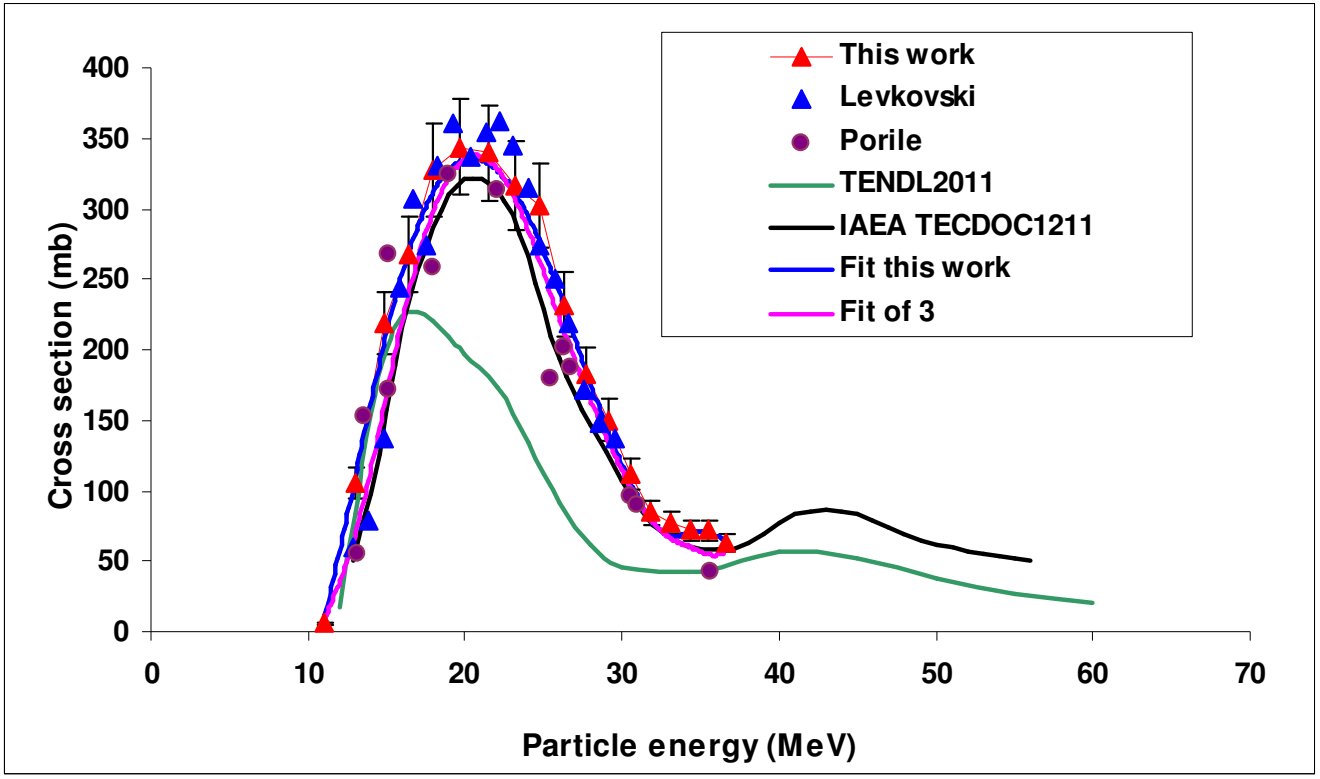


Nirta® PET liquid and gas targets

Installation first site ongoing (beam on tgt sept 2023)

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

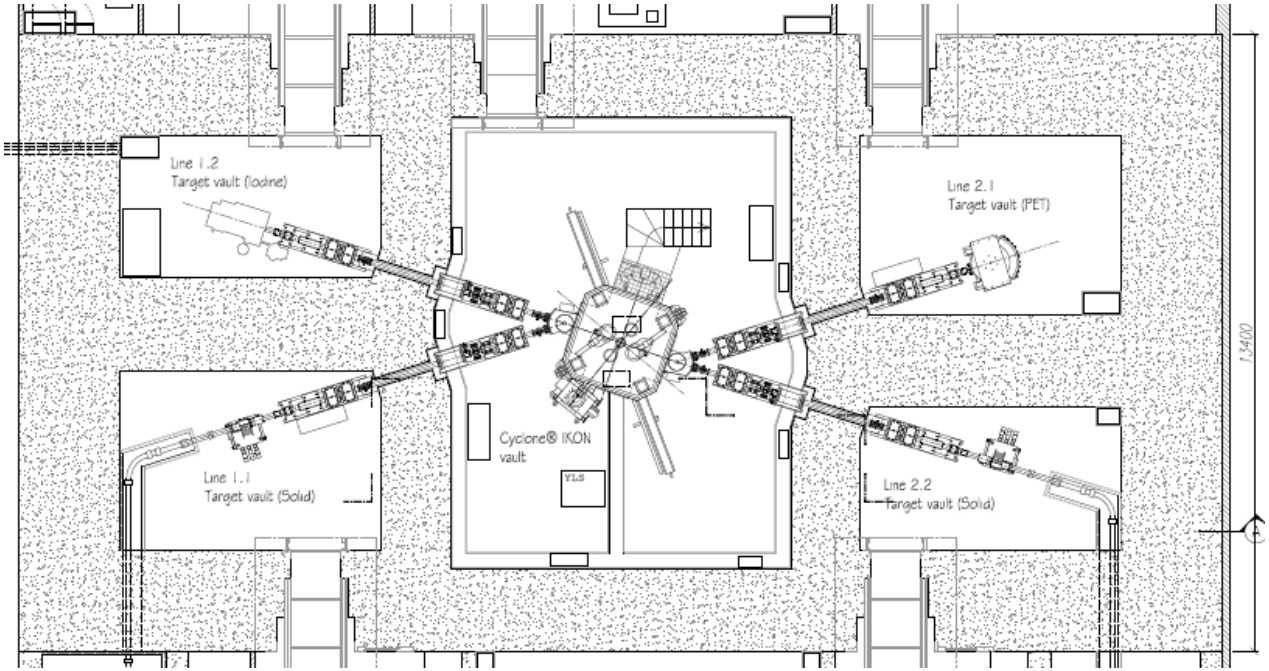
⇒ Long beam time ~4-5 days

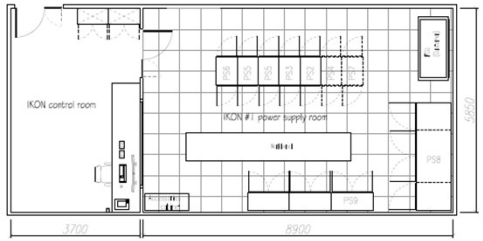
⇒ And low melting point of Ga !

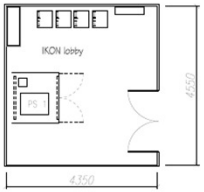
Protect, Enhance and Save Lives

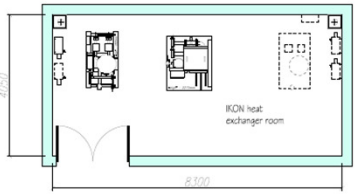
Cyclone IKON layout – fully redundant layout

- extended 26 m x 24m inc doors









Rooms to be placed o

OPEX Cyclotron IKON only

- ELEC: 350 kVA
- Chiller 200 kW heat load

3.4.1 **Electrical power for distribution cabinet (PS9)**

	value	Remark
Voltage	400Vac +/- 5%	
Frequency	50 /60 Hz +/- 2Hz	
Electrical supply Network type	3ph- 4 wires	4 wires / Star mandatory (3P+N+PE)
Electrical supply Earthing System	TN-S	
earth impedance	< 10 ohms	
hook-up to PS9	200 kVA	Power distribution

3.4.3 **Electrical power for anode power supply cabinet (PS8)**

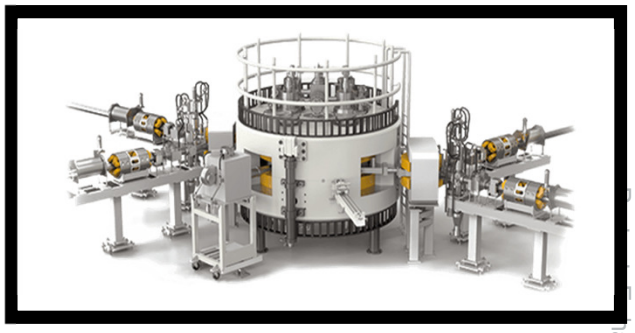
	Value	Remark
Voltage	400Vac / 480Vac +/- 5%	Either 400Vac 50Hz or 480Vac 60Hz
Frequency	50 / 60 Hz +/- 2Hz	Either 400Vac 50Hz or 480Vac 60Hz
Electrical supply Network type	3ph – 3 wires	(3P+PE)
Electrical supply Earthing System	TN-S	
earth impedance	< 10 ohms	
hook-up to PS8	150 kVA	Anode Power supply

he requirement in chilled water for the cyclotron water package interface are:

	value
Nominal flow	**350 l/ min**
Heat Load capacity	200 kW
Dissipated power	150 kW
Minimum load during standby	20 kW

Cyclone® 70P - specific use

Cyclotron High Energy segment 35- 70 MeV proton



^{68}Ge ^{82}Sr

Co production of interesting PET generators

Example: iThemba Labs target system

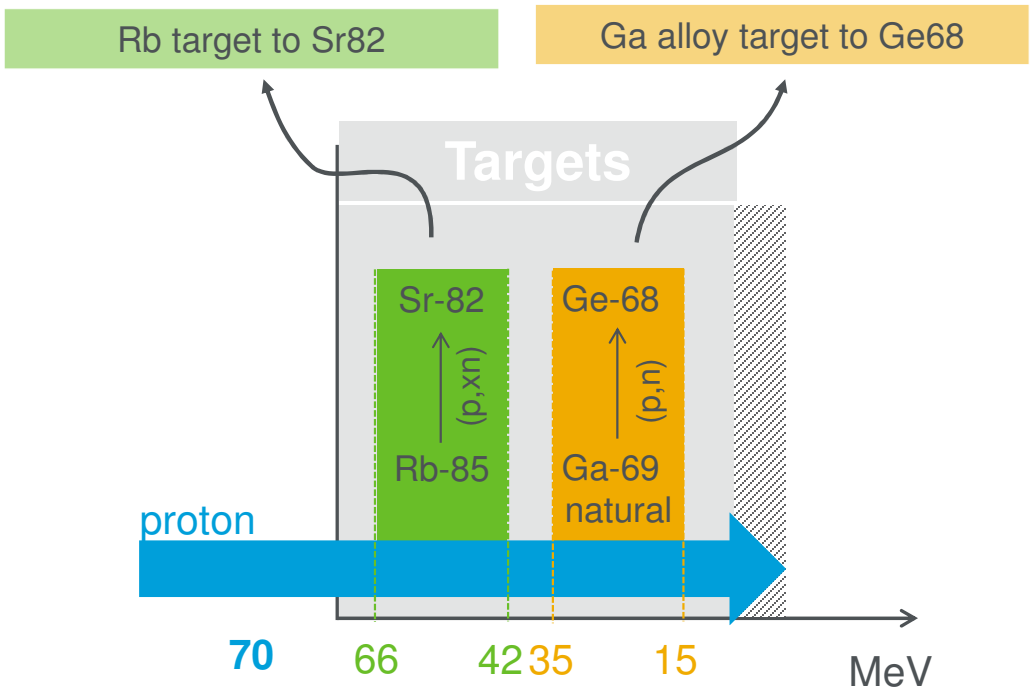


Figure 6. The tandem Rb/Ga targets mounted on a bayonet-mount plug.

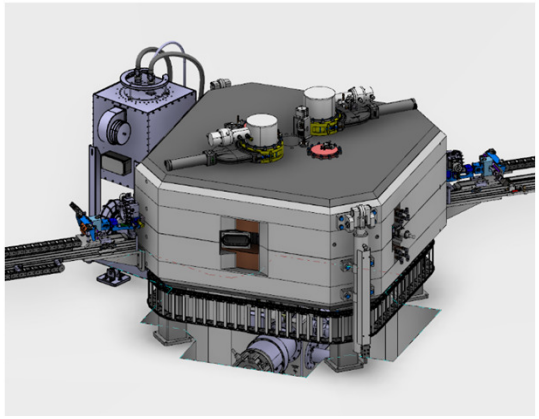
Instruments **2018**, *2*, 29; doi:10.3390/instruments2040029

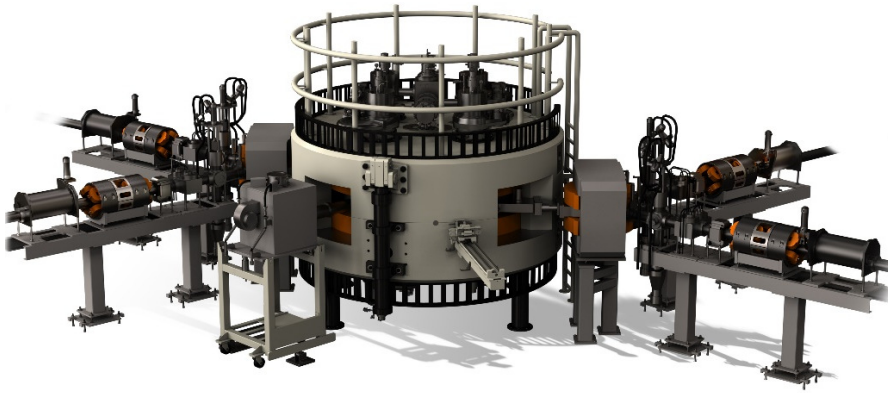
Conclusions

- Cyclotrons offer a robust and conventional technology for various radio-isotopes production PET & SPECT
- Optimization (‘State of the art’) of existing cyclotron technology still boosts production rates, reliability & flexibility
- Do not forget chemistry unit, QC system, GMP labs & process

The story of Cyclone KIUBE, Cyclone IKON and the 70P

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





(14) - **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

35 - 70 MeV

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

and Save Lives

Thank you

Geets Jean-Michel

Domain Expert

geets@iba-group.com

Moreno Ambrosio

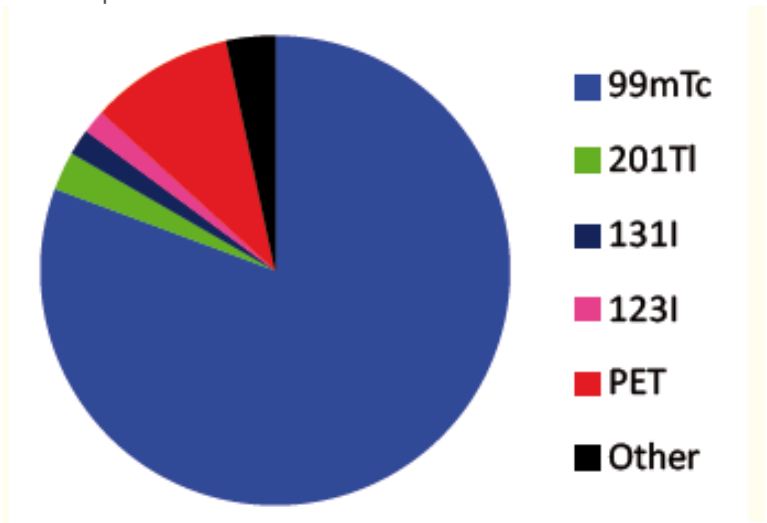
VP sales Africa

Ambrosio.moreno@iba-group.com

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

- Use of accelerators for direct production of Tc99m

NuPECC report 2014



IBA Rhodotron HE

IBA Cyclone's