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Production of new radioisotopes for theranostics using a medical cyclotron

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Outline

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- > Compact medical PET cyclotrons: *tools for medicine and science*
- > SWAN project in Bern: *production and research under the same roof*
- > Positron Emission Tomography: *conventional and novel radioisotopes*
  - > *Liquid vs solid targets*
- > Production of new radioisotopes for theranostics
  - > *Tools and methods from high-energy physics*
  - > *Some achievements with the Bern cyclotron*

Medical cyclotrons

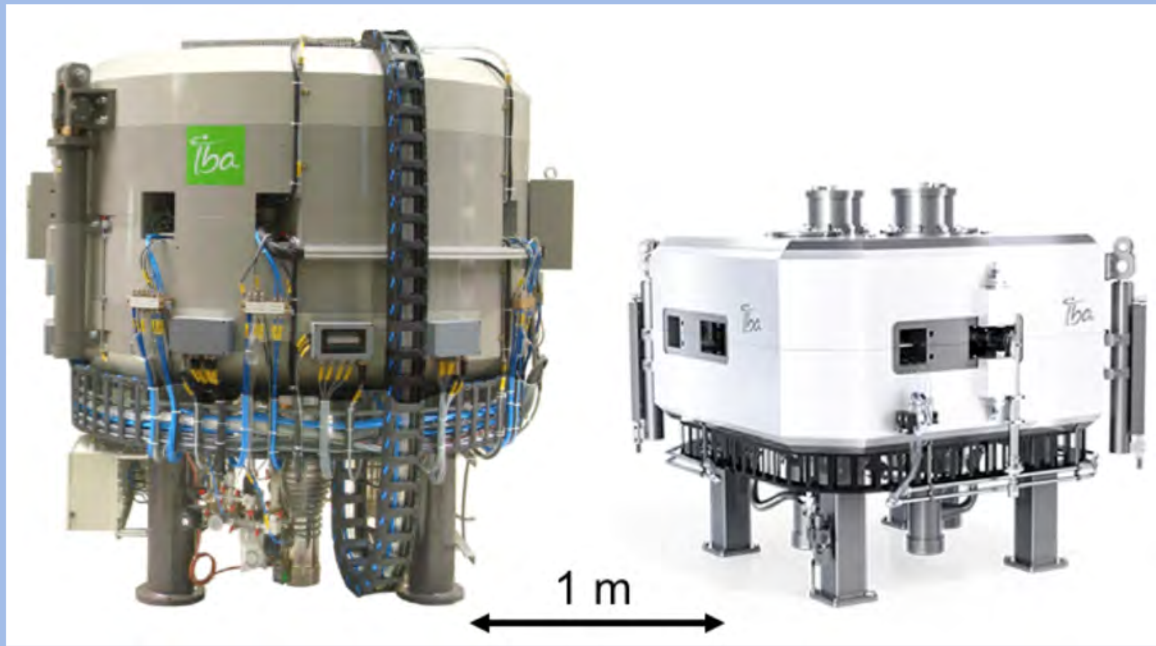
	Main Use	Typical User	Max. Proton Energy (MeV)	Max. Beam Current (μA)
A	Proton therapy	Hospital	200-250	10^{-3}
B	Radioisotope production / research	Research laboratory	70	500-700
C	SPECT radioisotope production	Research lab. / industry	30	500-1000
D	**PET radioisotope production**	**Hospital / industry**	**15-25**	**100-400**
E	PET radioisotope production	Hospital	10-12	50

A) Varian Comet (250 MeV)

B) Best 70p (70 MeV)

C) ACSI TR30 (30 MeV)

Compact medical PET cyclotrons



- Commercial accelerators: ~20 MeV protons, ~100 μA
- Designed for: hospital based facilities + radiopharmaceutical industry
- > 500 in operation in the world (number continuously growing)

Compact medical PET cyclotrons
Physics must answer to medicine

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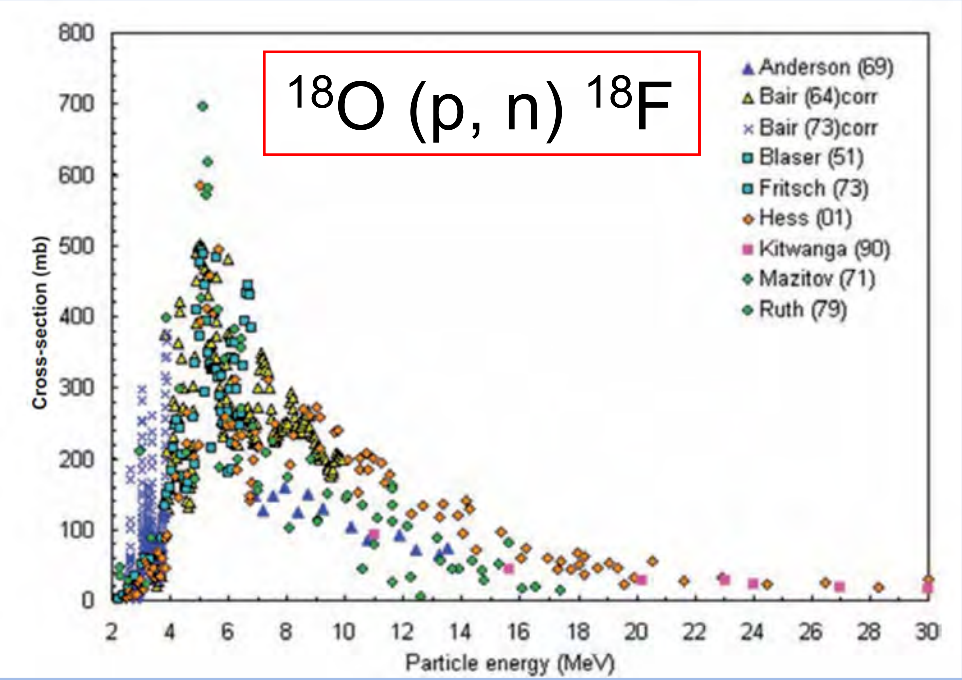
- FDG most common PET radiotracer ➔ ^{18}F (1 dose ~400 MBq)



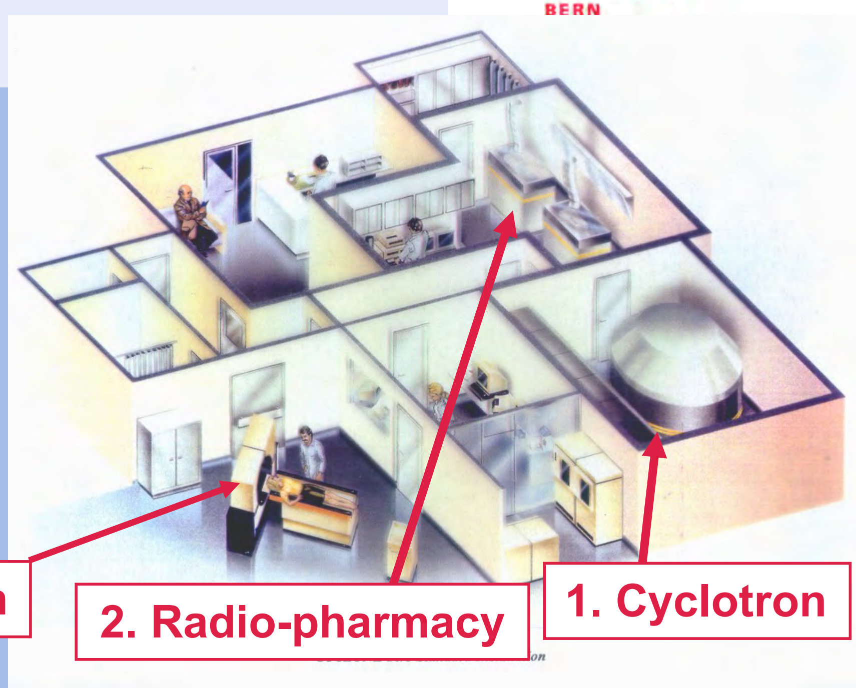
Liquid targets:
- ~ 3 g, ~ 3 cm^3
- Beam: 1 cm FWHM

- Beam energy: 15-25 MeV
- 150 μA in 120 min. ➔ 500 GBq of ^{18}F ➔ 250 GBq of FDG
- $T_{1/2}$ = 110 min. ➔ Production(s) every night

… and during the day ?

Positron Emission Tomography (PET)

- Radioisotope: ^{18}F ($T_{1/2}$=110 min.)
- Radioactive sugar (FDG)
- Glucose metabolism

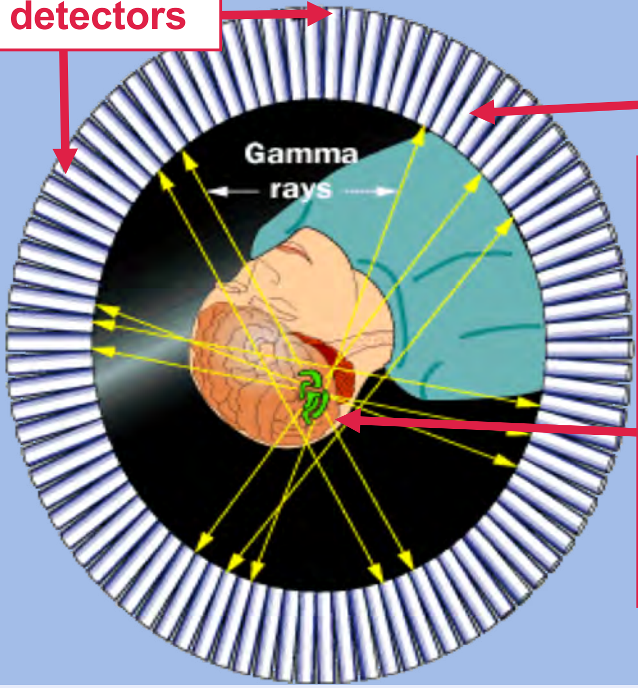


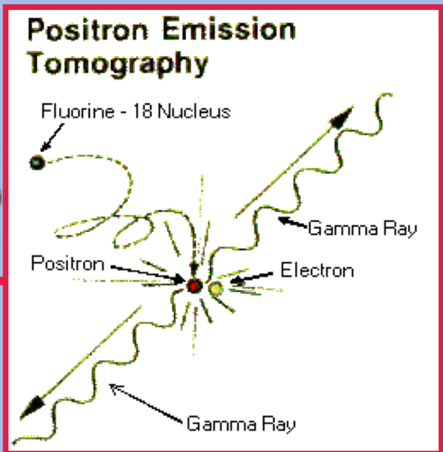
1. Cyclotron

2. Radio-pharmacy

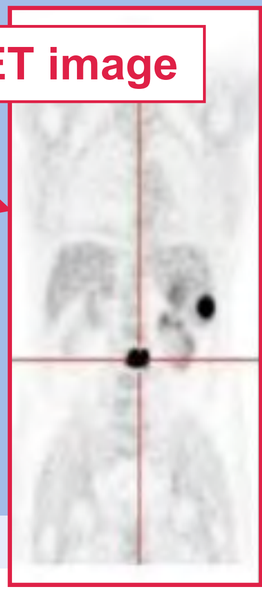
3. PET tomograph

Particle detectors



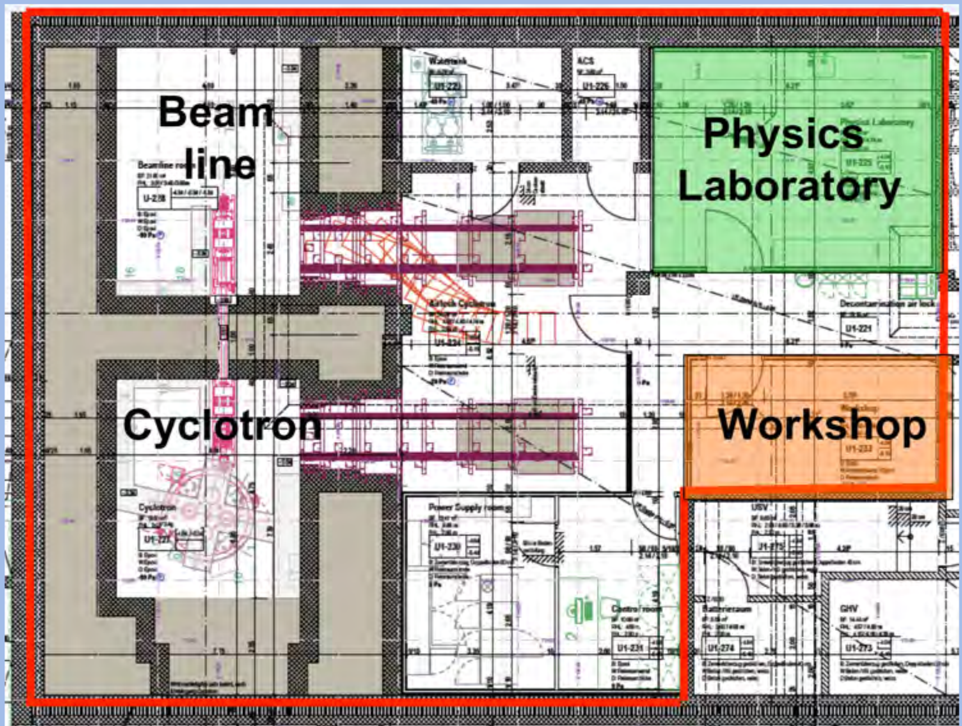


4. PET image



CT-PET image:
morphology
+
metabolism

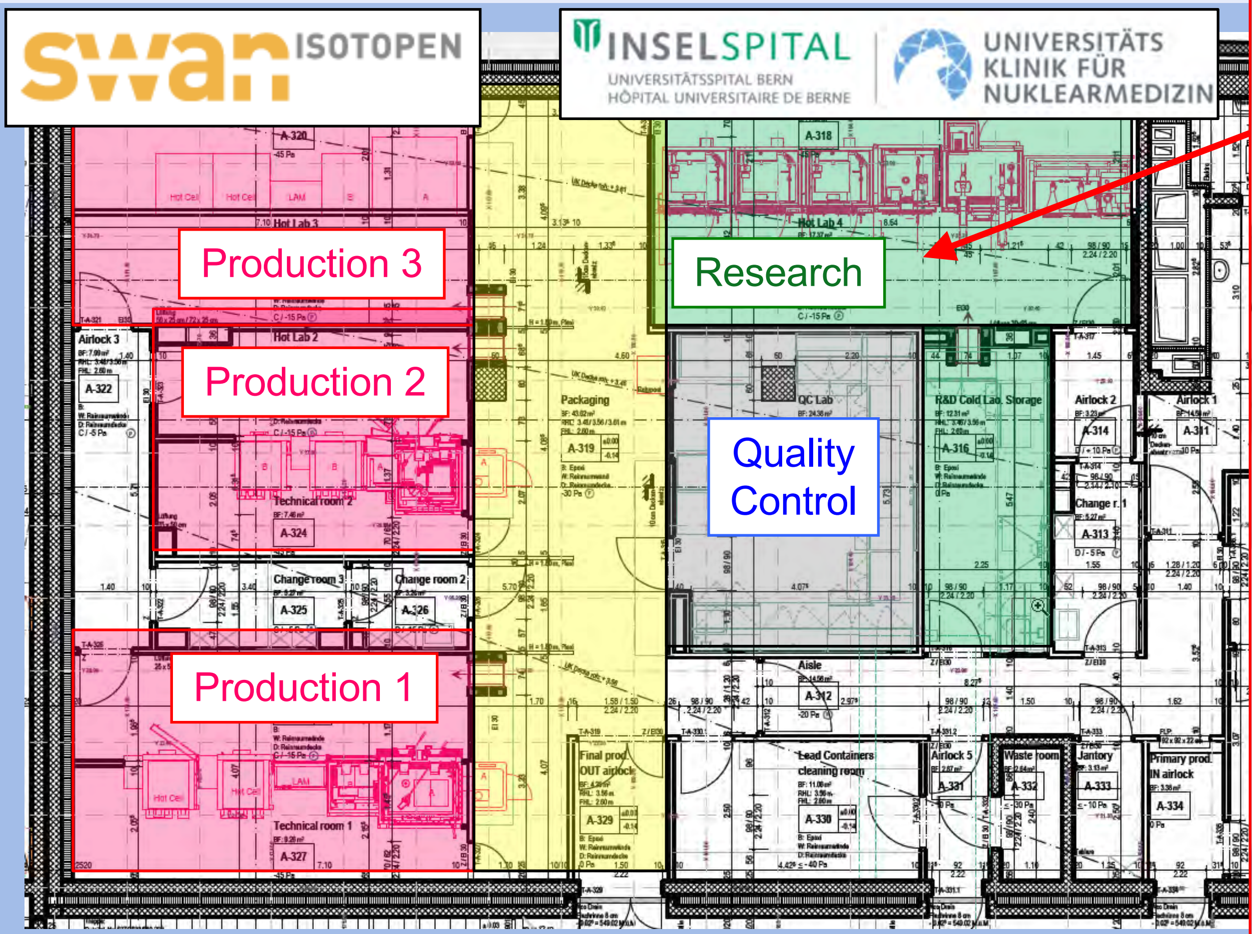
The Bern medical cyclotron and its Beam Transport Line (BTL)



- IBA 18 MeV high current cyclotron (up to 150 μA) – 2 H^- ion sources
- **6 ^{18}F liquid targets: daily production**
- **External beam line in a separate bunker: research**
- Specific method to produce currents down to 1 pA

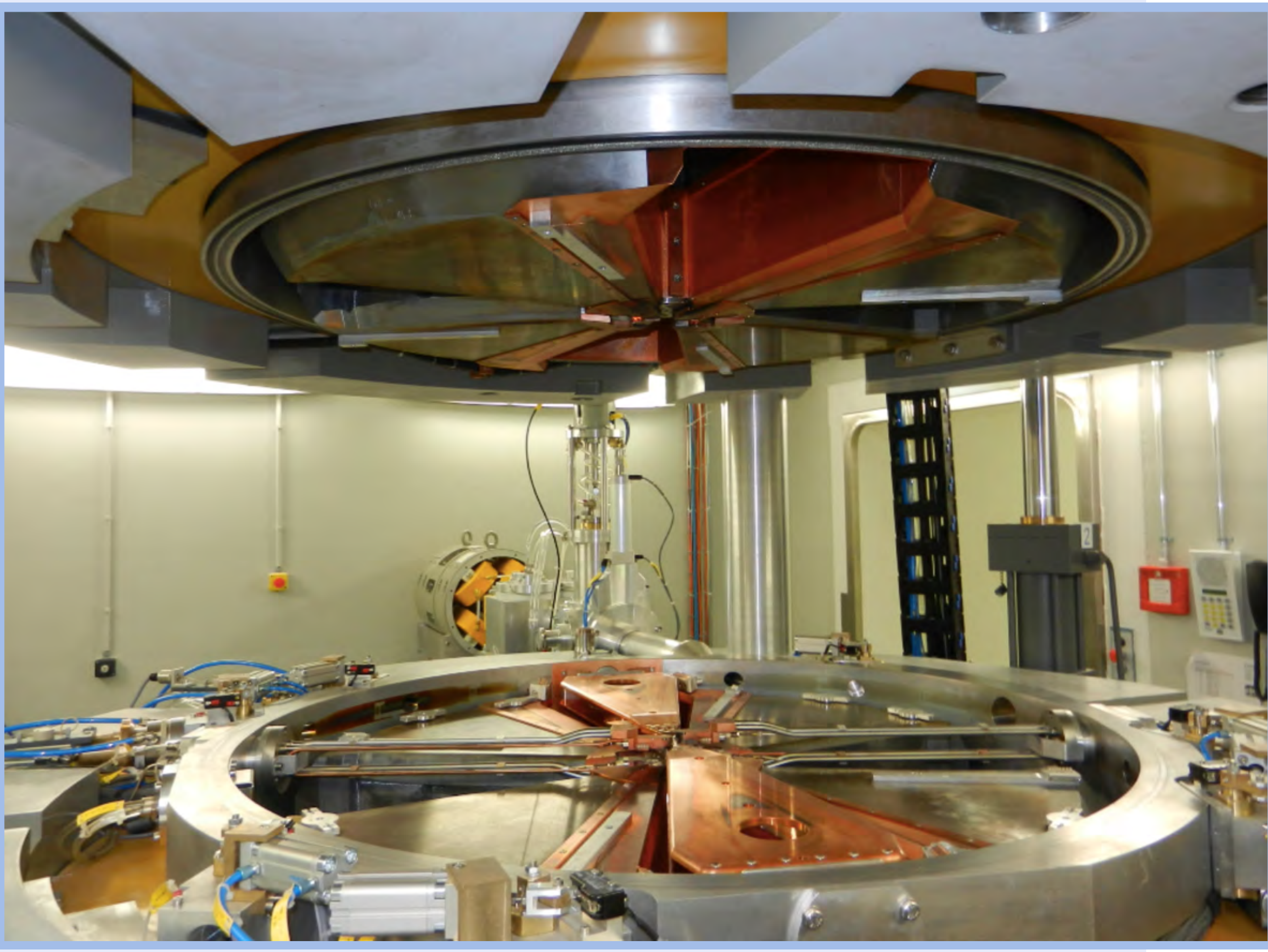
M. Auger et al., Meas. Sci. Technol. 26 (2015) 094006

The hot labs

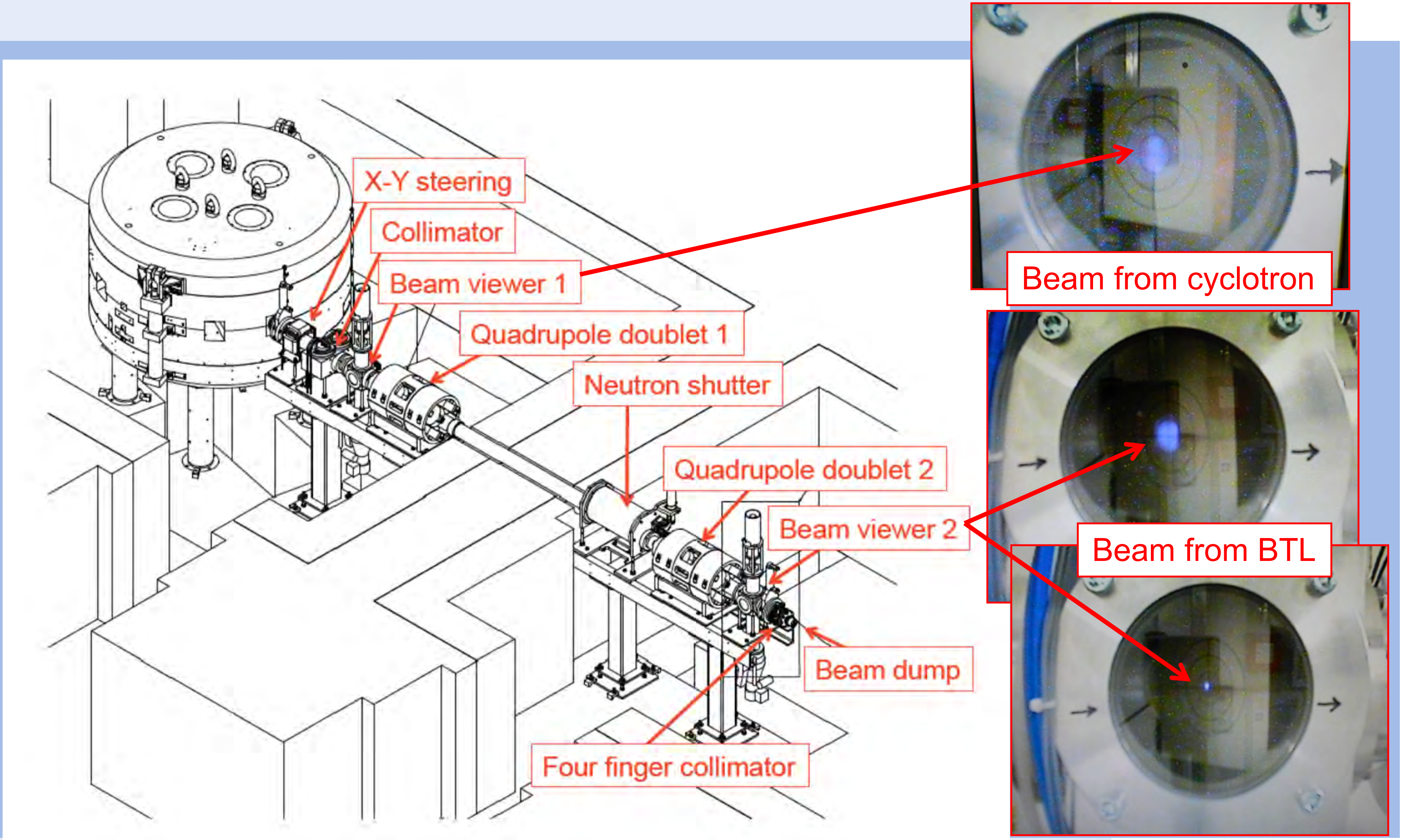


- 3 GMP production labs (SWAN Isotopen AG – ^{18}F, ^{68}Ga, ^{177}Lu radiopharmaceuticals)
- 1 GMP clinical research lab (Nuclear Medicne, Inselspital)

The Bern cyclotron

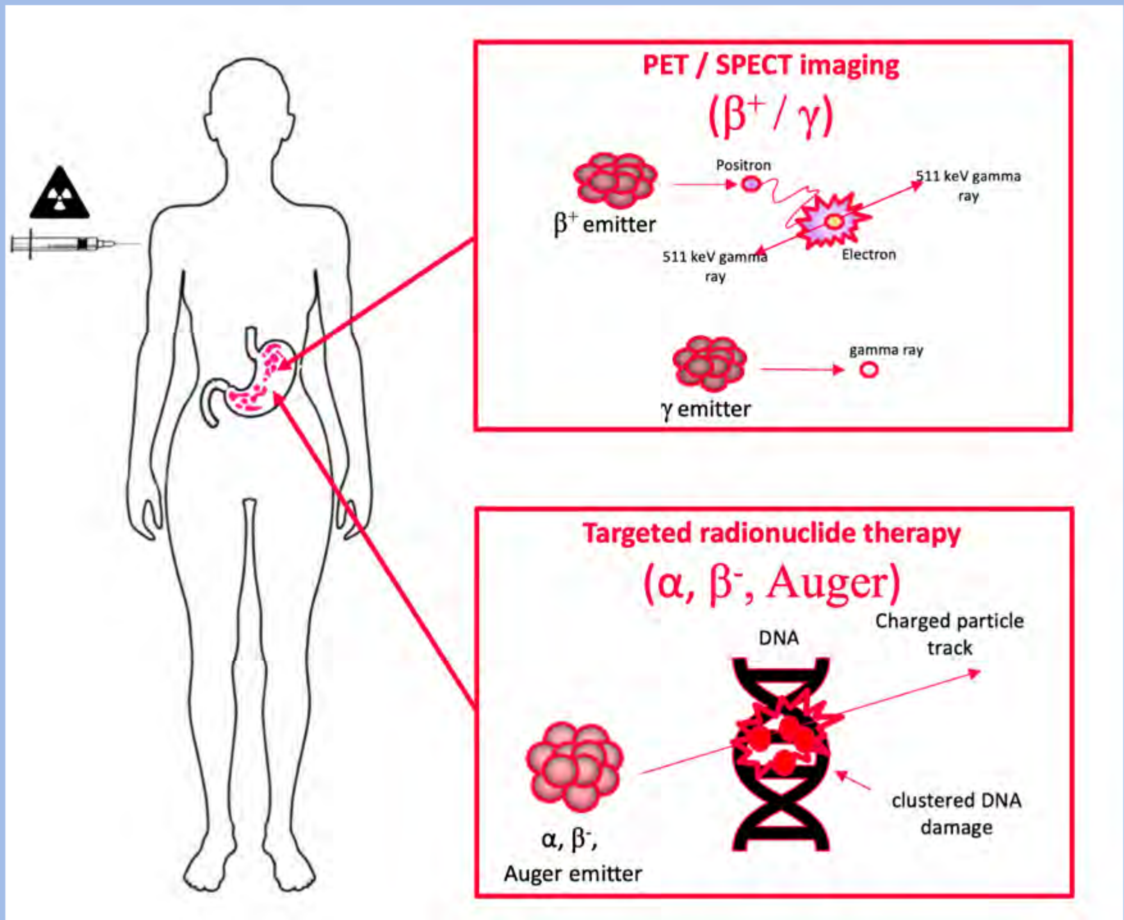


Multi-disciplinary research activities with the BTL



S. Braccini, *AIP Conf. Proc.* vol. 1525, p. 144, 2013

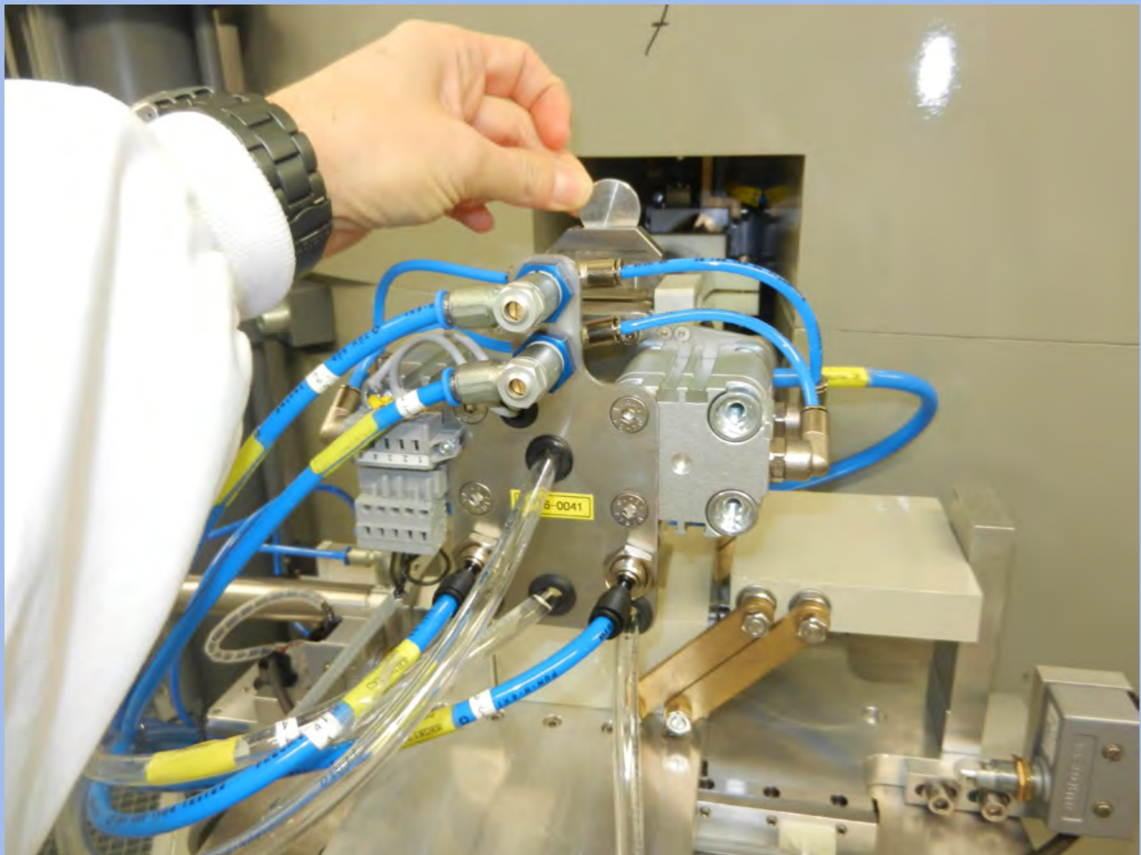
Radionuclides for theranostics in nuclear medicine



- Promising pairs:
  - **^{68}Ga**/^{177}Lu and **^{68}Ga/^{225}Ac**
  - **^{43}Sc/^{47}Sc** and **^{44}Sc/^{47}Sc**
  - **^{61}Cu/^{67}Cu** and **^{64}Cu/^{67}Cu**
  - **^{155}Tb**/^{149}Tb and **^{155}Tb**/^{161}Tb
- Radiometals

Solid targets:
- ~10 mg
- ~ 5 mm diameter
- Material: powder
- Beam: ?

Commercial solid target station



> IBA Nirta "COSTIS"

>Target:

- > 24 mm diameter 2 mm thick disk
- > electro-plated materials

> Manual insertion and recovery of the disk

> Cooling: water in the back, helium in the front

Our strategy for the production of radioisotopes for theranostics

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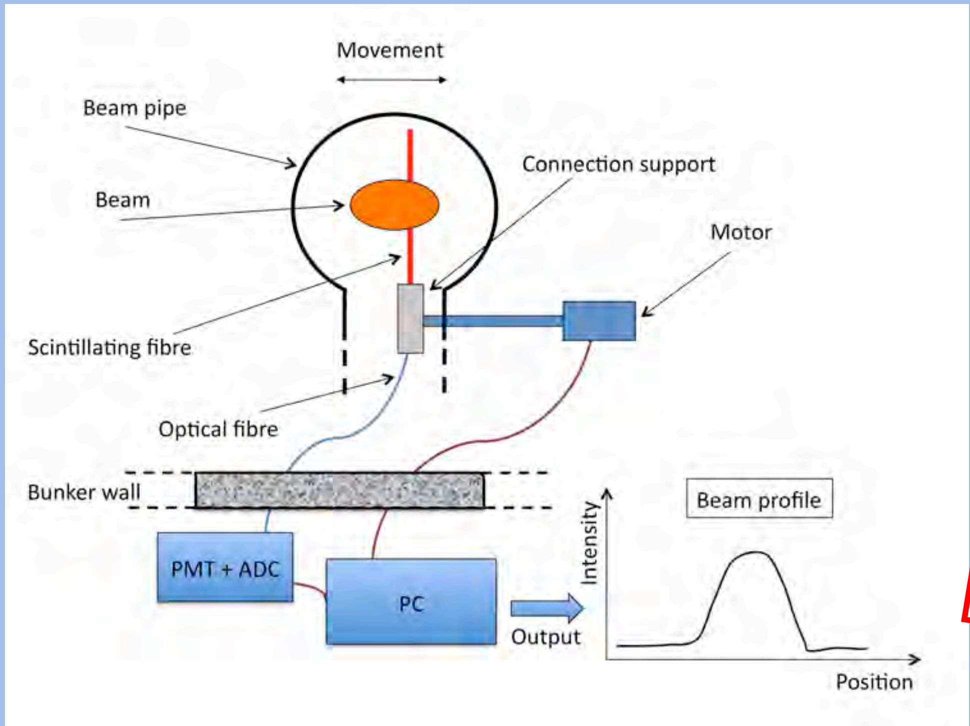
> Accurate knowledge of the beam (position, shape, energy)
  - Beam monitoring detectors

> Novel target + transfer system

> Accurate knowledge of the production cross sections (impurities!)

> Active system to focus the beam

The UniBEaM detector

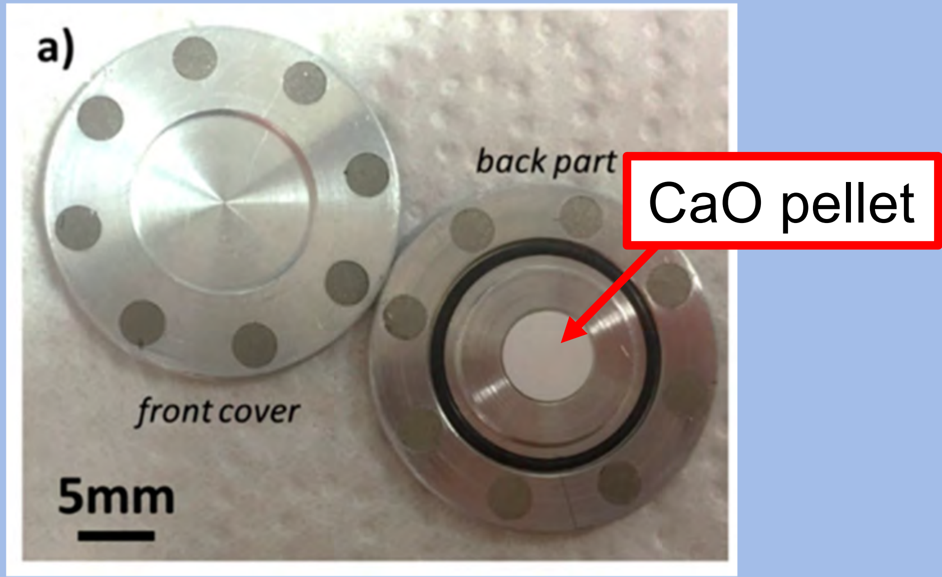


- 1D beam profiler based on (doped) optical fibres passed through the beam
- On-line, minimal interference with the beam
- Developed by LHEP and commercialized by D-Pace (Canada)

S. Braccini et al., 2012 JINST 7 T02001

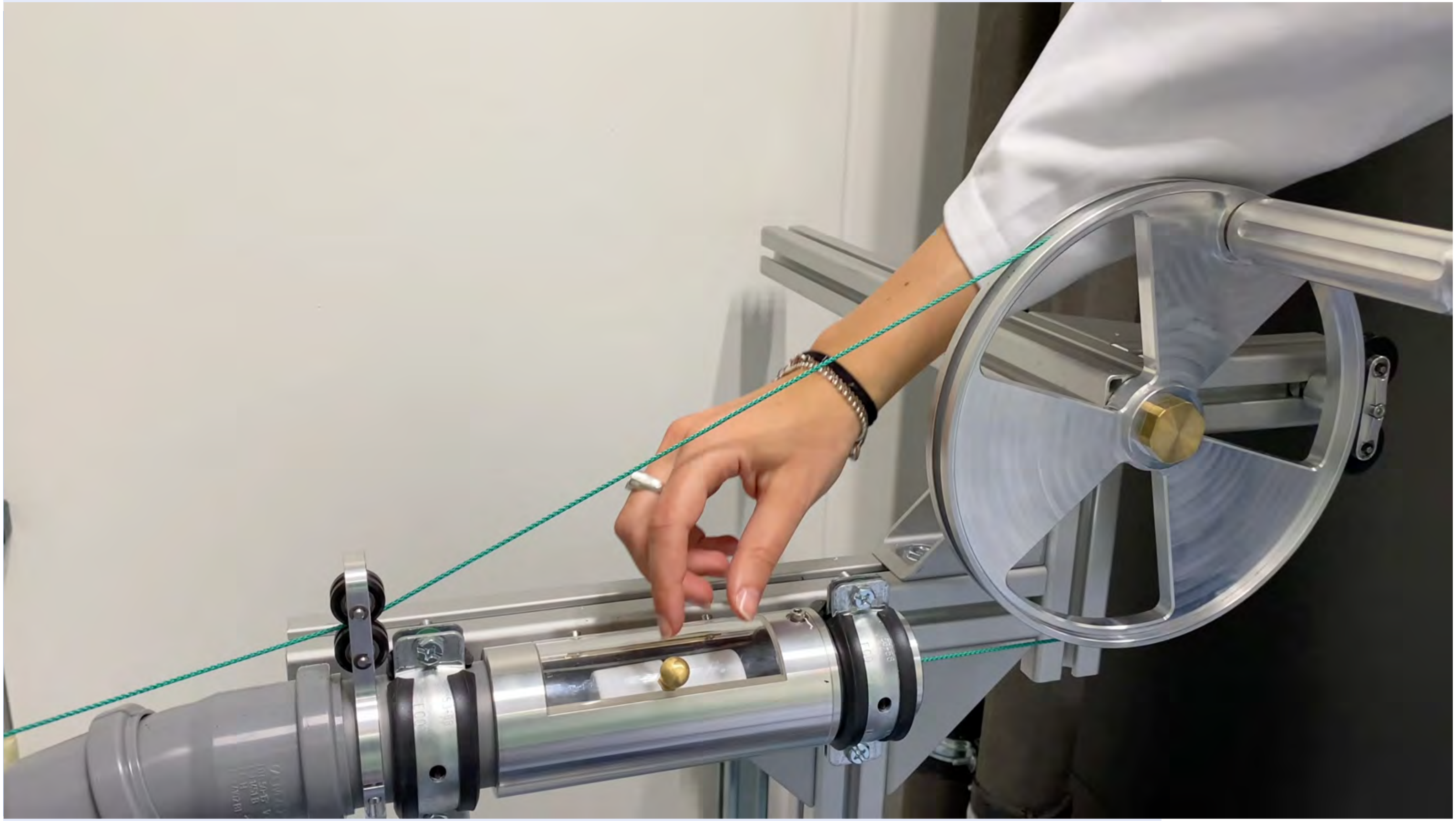
On-line monitoring with UniBEaM

The target “coin”

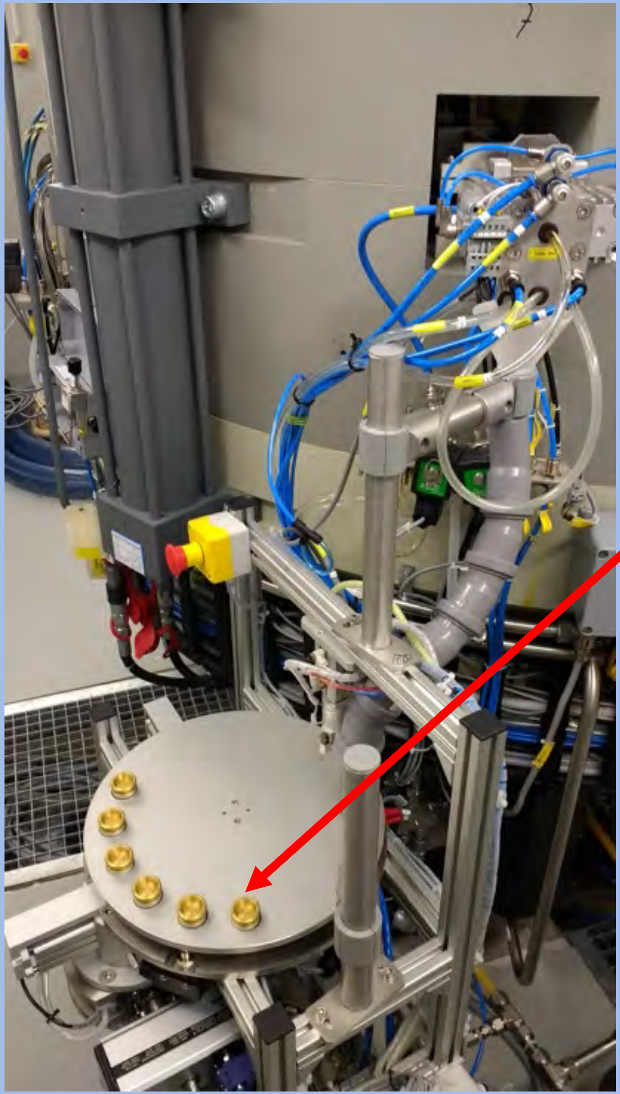


- High-purity aluminum
- Two halves kept together by permanent magnets
  - SmCo, 350°C Curie temperature
- O-ring (viton) to avoid radioactive degasing
- Variable thickness of the front (energy variation)

The Hyperloop by LHEP

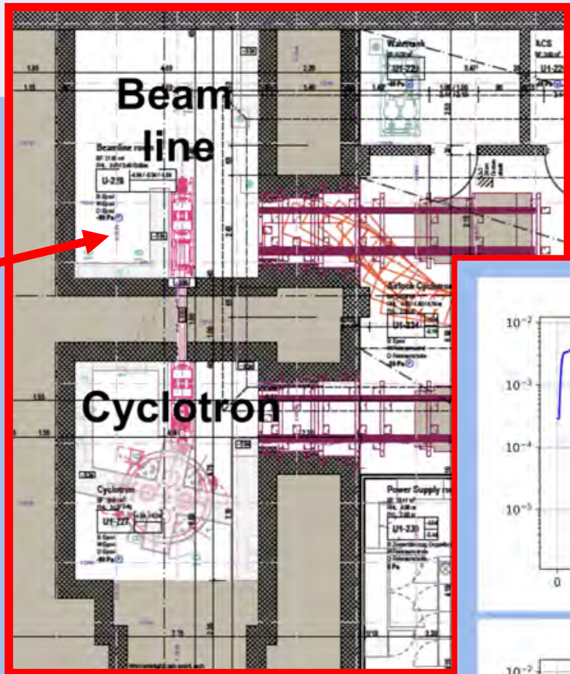


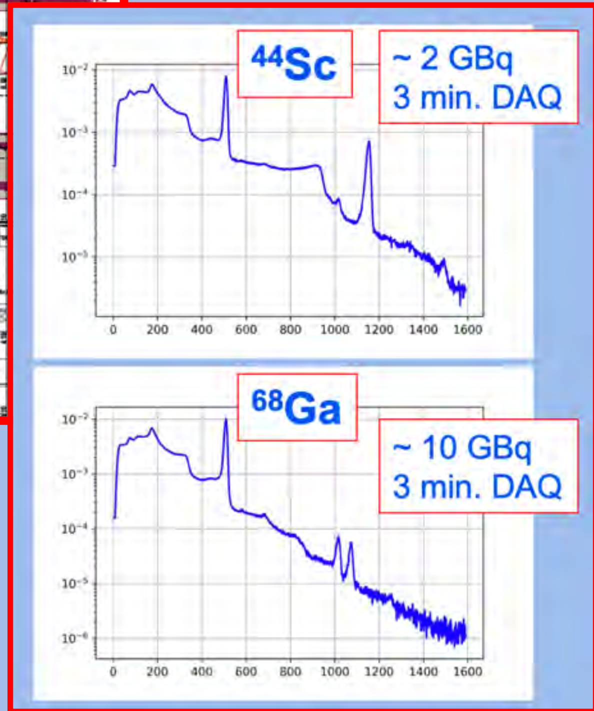
The solid target station and the pneumatic transfer system (by TEMA)



- 6 shuttles
- 2 delivery pathways
  - Hot-cell + BTL bunker

The receiving station in the BTL and the CZT detector





- ~ 1 cm^3 CdZnTe (CZT) crystal
- ~ 40 cm from target
- Gamma spectroscopy

Beam energy measurement (1): magnetic deflection in the BTL

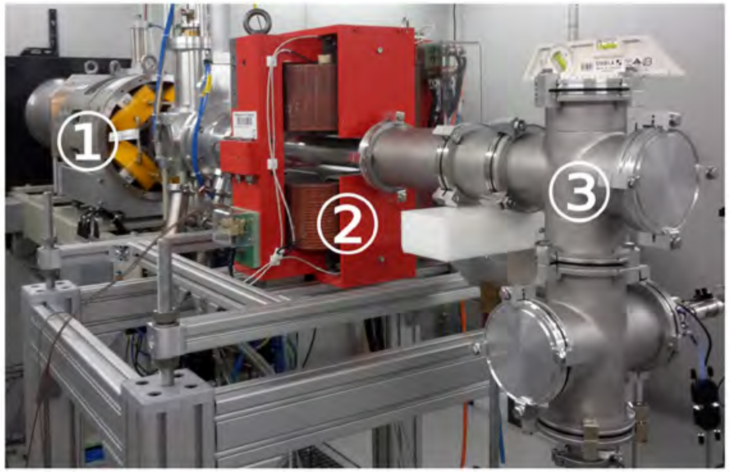
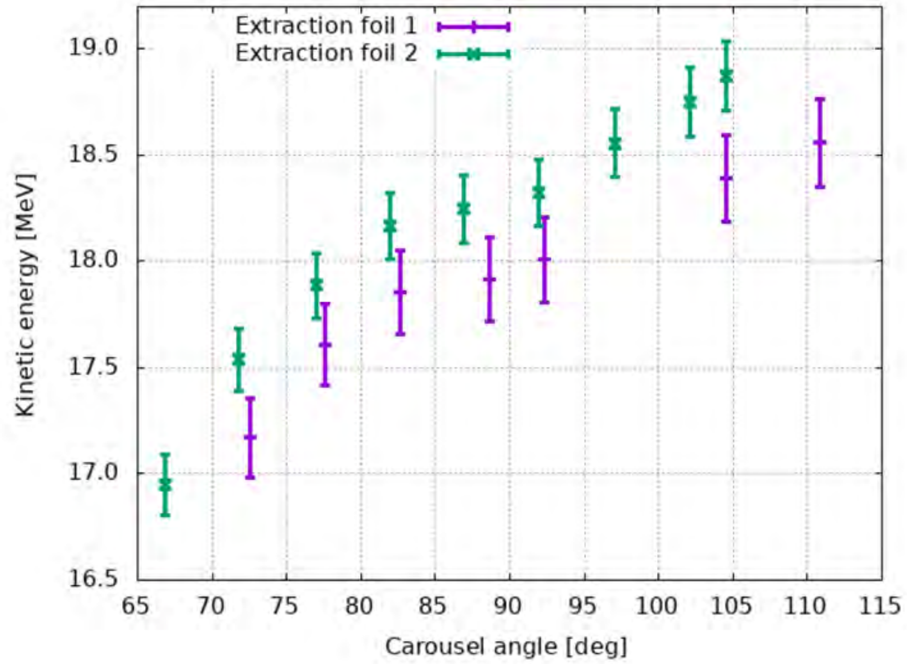


Figure 2. Experimental set-up: the Beam Transfer Line (BTL) quadrupole doublet (**1**), the dipole bending magnet (**2**), and the UniBEaM detector (**3**).



<u>WARNING</u>

The beam energy changes with the cyclotron operational parameters!

P. Häffner et al., Instruments 2019, 3(4), 63

Beam energy measurement (2): special “coin” for the STS

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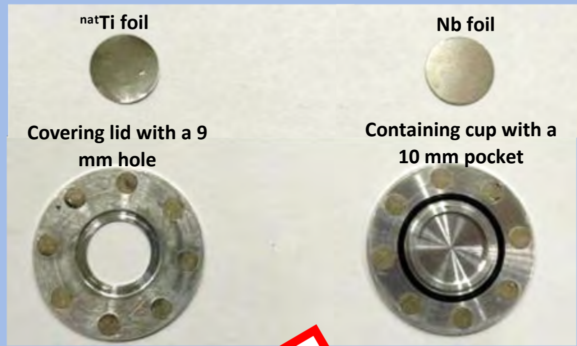
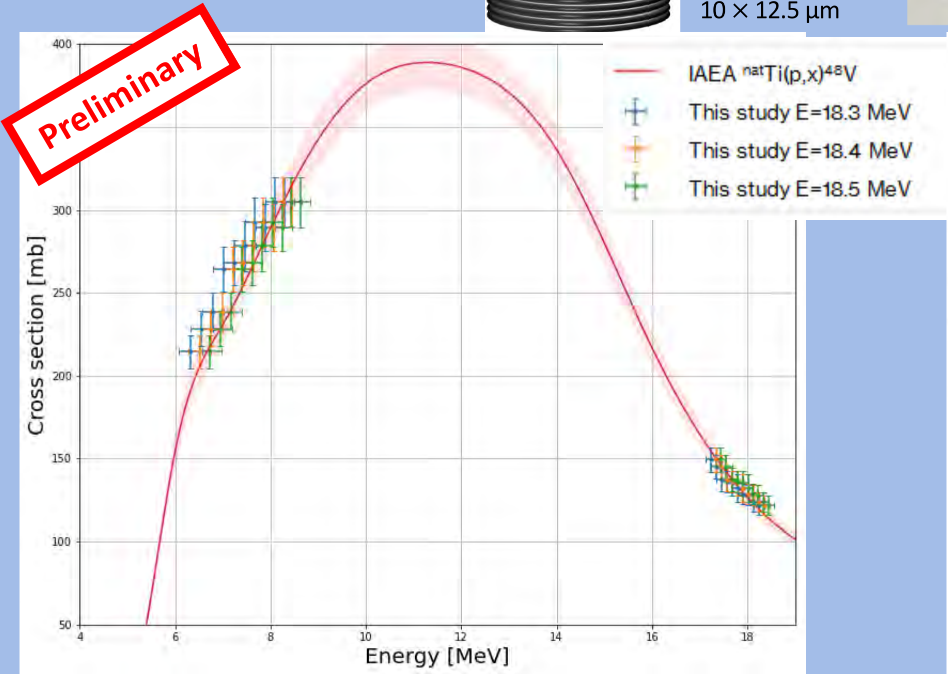
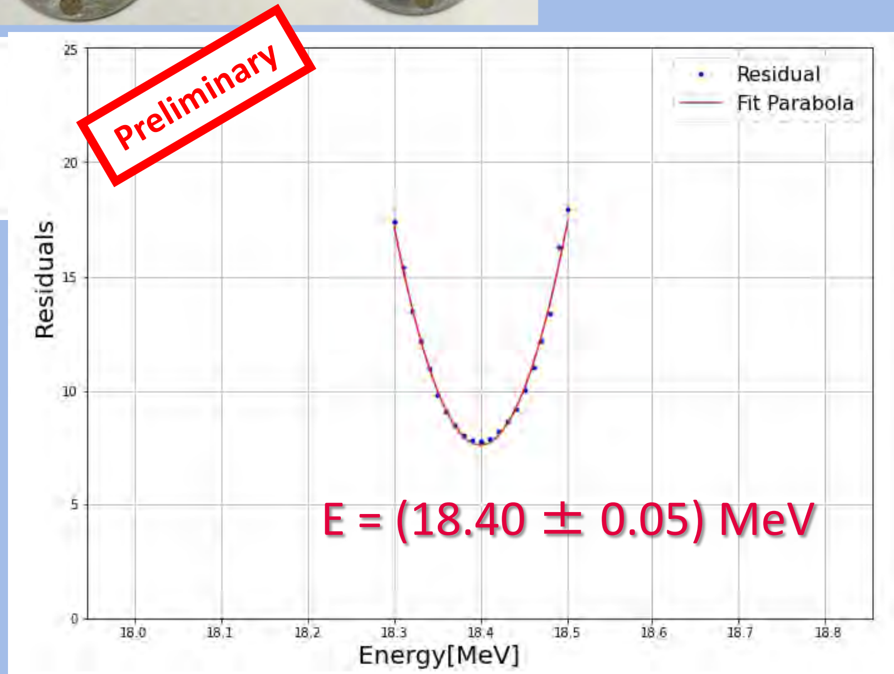
Monitor reaction

$^{nat}Ti(p,X)^{48}V$



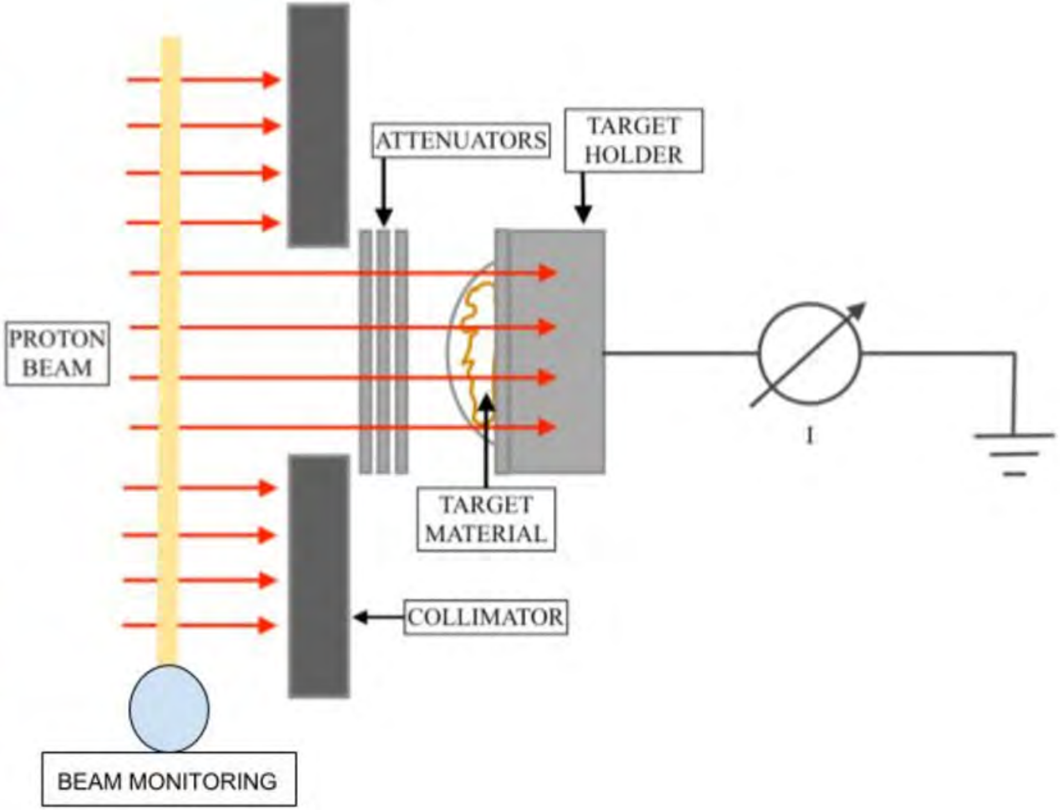
Closed target coin





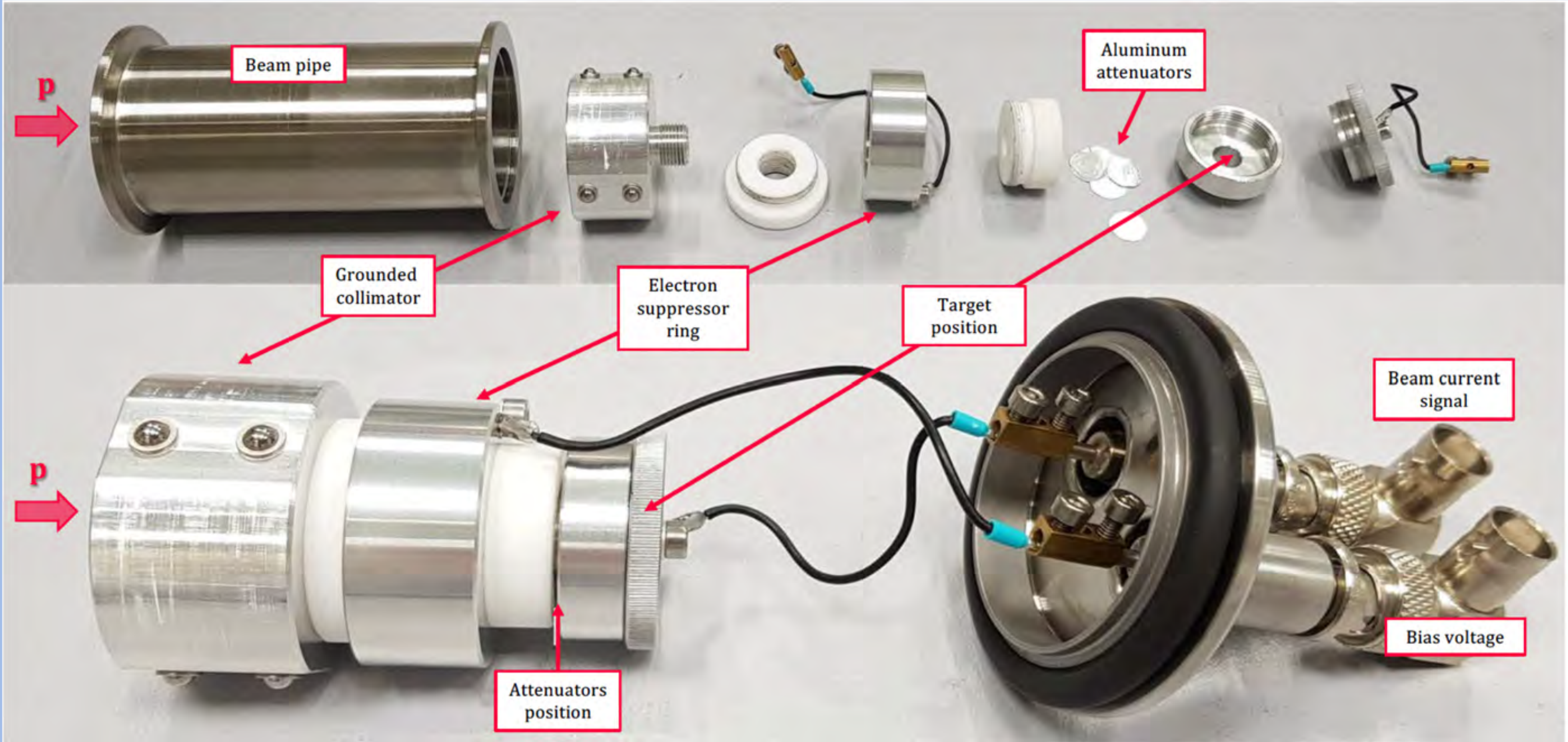
Elnaz Zyaee, Master Thesis, 2021; paper in preparation

Cross section measurements with a novel method



T. S. Carzaniga, M. Auger, S. Braccini, M. Bunka, A. Ereditato, K. P. Nesteruk, P. Scampoli, A. Türler, N. P. van der Meulen, *Measurement of Sc-43 and Sc-44 production cross-section with an 18 MeV medical PET cyclotron*, Appl Radiat Isot. 2017 Nov; 129:96-102.

The target station for cross section measurements



Measured cross-sections:

^{43}Sc, ^{44}Sc, ^{47}Sc, ^{48}V, ^{61}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{155}Tb, ^{165}Er, ^{165}Tm, ^{167}Tm

Cross sections and radio-nuclidic purity: the case of ^{68}Ga

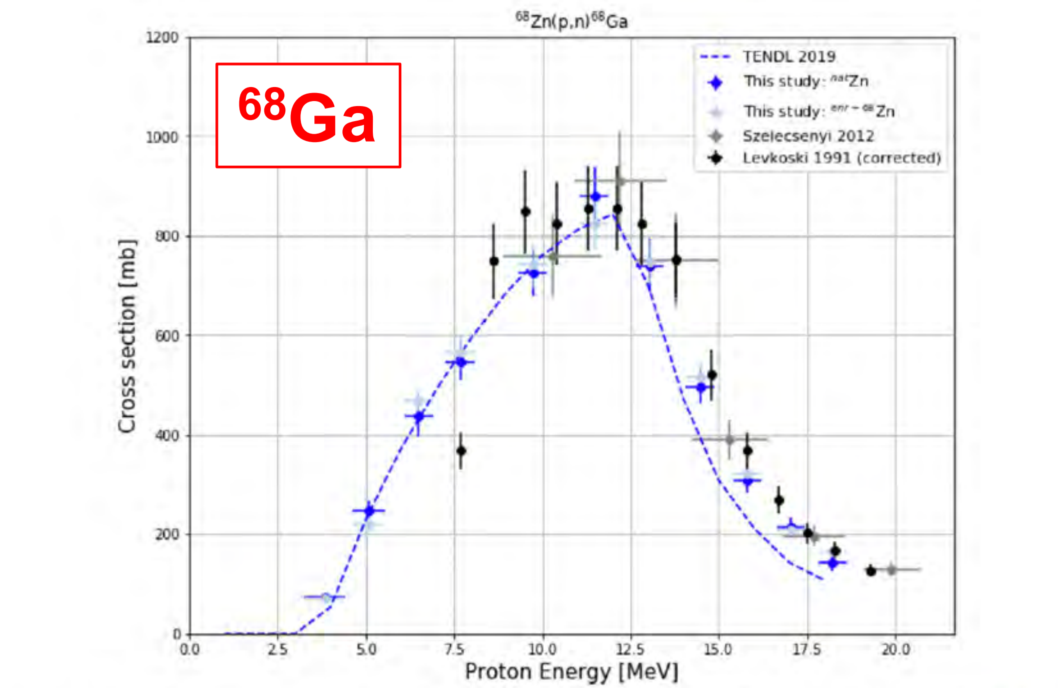


Fig. 4. ^{68}Zn(p,n)^{68}Ga cross section measured from natural and enriched ^{68}Zn targets with the isotopic composition marked as (A) in Table 1.

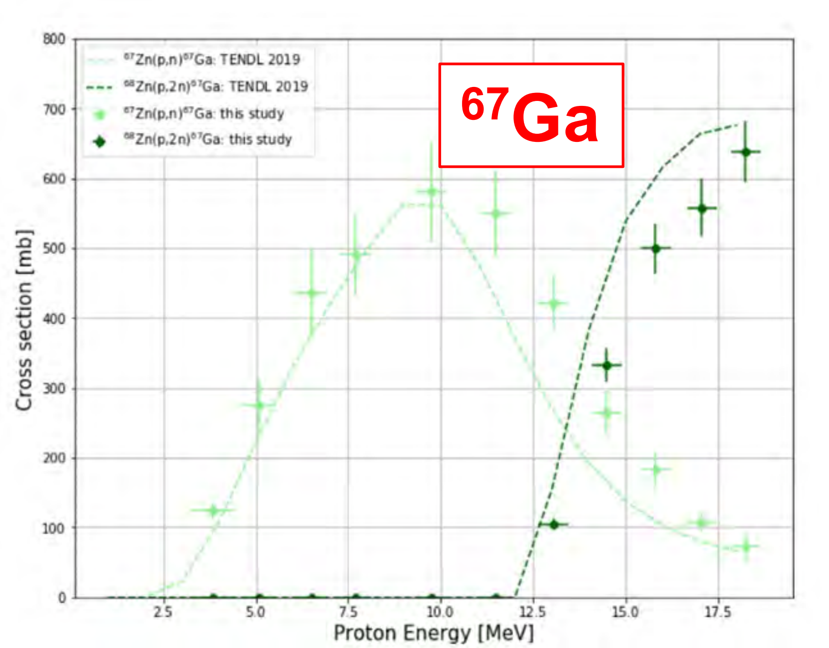
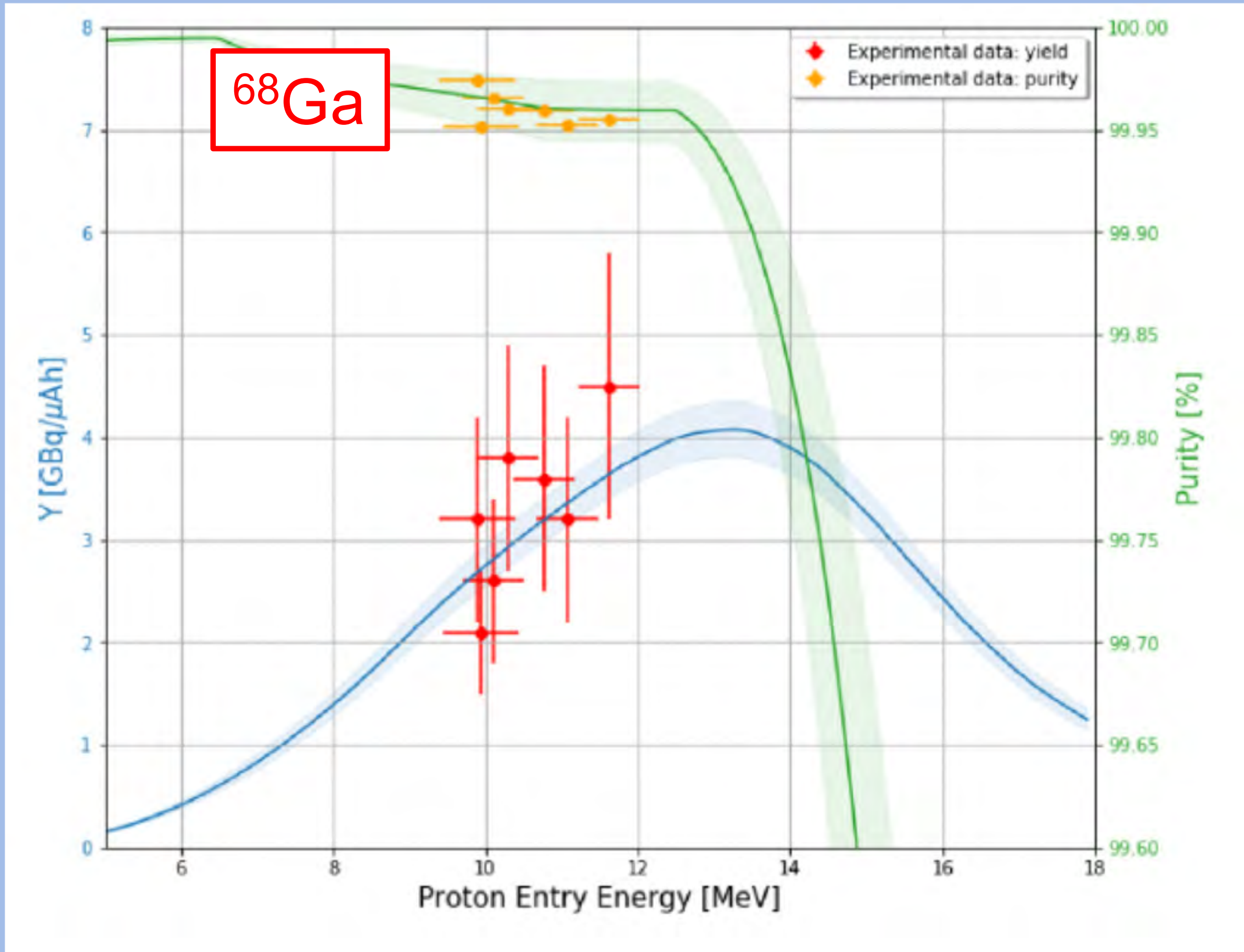


Fig. 6. ^{67}Zn(p,n)^{67}Ga and ^{68}Zn(p,2n)^{67}Ga reaction cross sections.

Use of two different enriched materials: the (p,n) and (p,2n) ^{67}Ga nuclear reactions can be measured!

S. Braccini at al., *Optimization of ^{68}Ga production at an 18 MeV medical cyclotron with solid targets by means of cross-section measurement of ^{66}Ga, ^{67}Ga and ^{68}Ga,* Appl. Radiation and Isotopes, Volume 186, August 2022

Yield, purity and production tests: example ^{68}Ga



Some produced radioisotopes

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Isotope	Reaction	Target	Current [μA]	Irr. Time [h]	A_{EOB} [GBq]
^{44}Sc	(p,n)	^{enr44}CaO pellet	5	5	$\sim$15
^{48}V *	(p,n)	^{nat}Ti metal foil	10	1	$\sim$0.15
^{61}Cu	(p,α)	^{enr64}Zn pellet	25	1.9	$\sim$1
^{64}Cu	(p,n)	^{enr64}Ni deposition	15	10	$\sim$20
^{68}Ga	(p,n)	^{enr68}Zn pellet	5	0.5	$\sim$15
^{X}Pm **	(p,X)	^{nat}Nd disc	5	3	$\sim 10^{-7}$
^{155}Tb	(p,n)	^{enr155}Gd pellet	2.5	1.15	$\sim$0.005
^{165}Er	(p,n)	^{nat}Ho metal disk	10	10	$\sim$1.5
^{165}Tm	(p,2n)	^{enr166}Er$_2$O$_3$	2.5	0.5	$\sim$1.5

> Other medical radioisotopes under study: ^{43}Sc, ^{47}Sc, ^{67}Cu and ^{167}Tm

> ^{48}V and Pm for fundamental physics

G. Dellepiane et al., Research on theranostic radioisotope production at the Bern medical Cyclotron, Il Nuovo Cimento, 2021

* High Efficiency Cyclotron Trap Assisted Positron Moderator, Instruments 2 (2018) 10.
** High-resolution laser resonance ionization spectroscopy of $^{143-147}$Pm, Eur. Phys. J. A (2020) 56:69

^{44}Sc is ready for clinical applications

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molecules — Molecules 2020, 25(20), 4706 — MDPI

Article

Developments toward the Implementation of ^{44}Sc Production at a Medical Cyclotron

Nicholas P. van der Meulen [1,2,*], Roger Hasler [2], Zeynep Talip [2], Pascal V. Grundler [2], Chiara Favaretto [2], Christoph A. Umbricht [2], Cristina Müller [2], Gaia Dellepiane [3], Tommaso S. Carzaniga [3] and Saverio Braccini [3]

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In collaboration with PSI

IBA Award 2020

IBA RadioPharma Solutions @IBA_RadioPharma

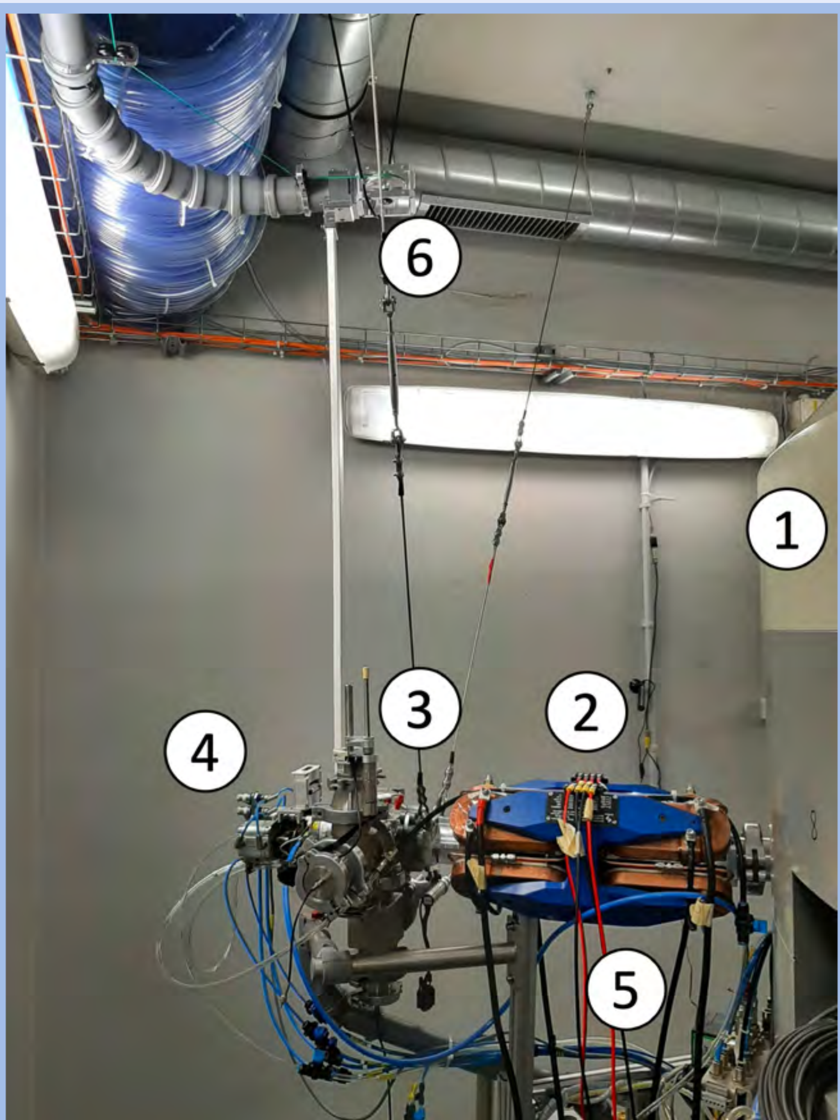
Congratulations to Saverio Braccini and the whole team of scientists for winning the #IBAaward 2020 with their publication on the production of 44 Sc on a #cyclotron. Read the paper 👉 iba-radiopharmasolutions.com/iba-award-2020

1:29 PM · Jan 18, 2021 · Twitter Web App

1 Retweet 1 Quote Tweet 2 Likes

Gilberto Colangelo @gilbertonvn · Feb 3
Replying to @IBA_RadioPharma
Congratulations!

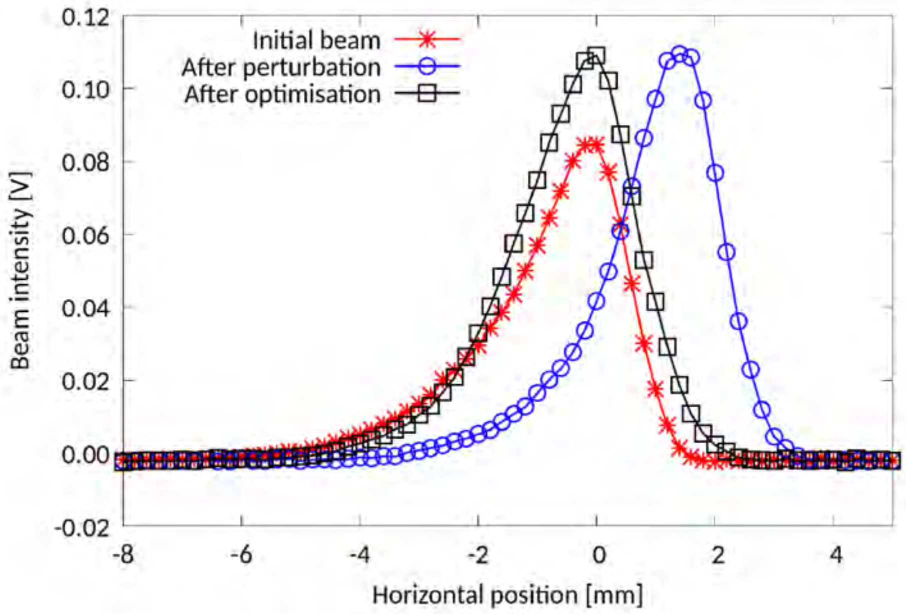
Work in progress :
Automatic Focusing System (AFS)

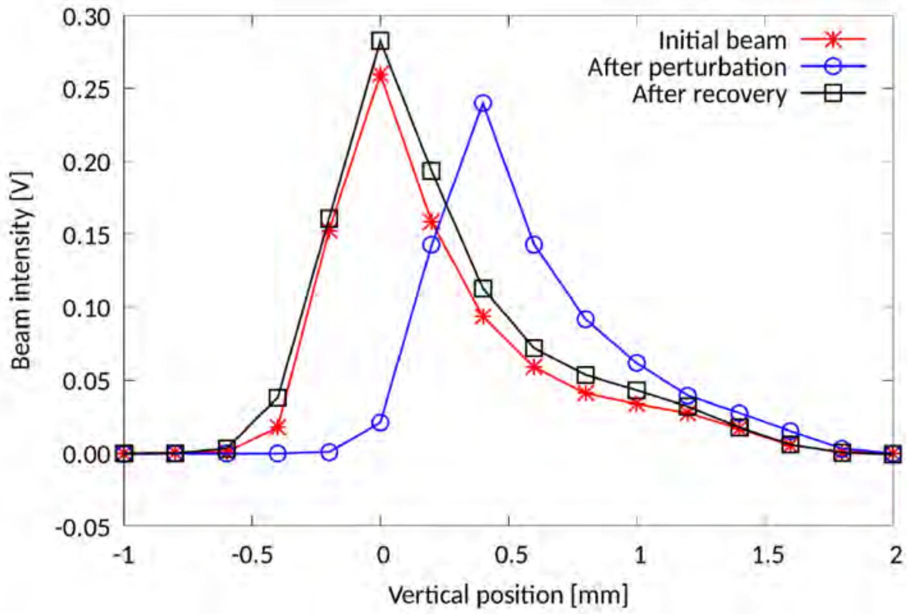


1. Cyclotron
2. Mini-PET Beamline (MBL)
3. Two-dimensional UniBEaM
4. Solid Target Station (STS)
5. Solid Target Transfer System (STTS)
6. Solid Target Loading System (STLS or Hyperloop)

Häffner, P. D. at al., An Active Irradiation System with Automatic Beam Positioning and Focusing for a Medical Cyclotron, Appl. Sci. 2021, 11(6), 2452; P. Häffner, PhD Thesis, 2021

Tests with the BTL:
Beam recovery with the AFS





Production yield improved by a factor 20
if compared to an unfocused beam

Conclusions and Outlook

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> Compact medical cyclotrons: tools of choice for PET radioisotope production in a hospital-based environment

> Production and research can run in parallel

> The Bern cyclotron laboratory
  - FDG industrial GMP production is running smoothly
  - Multi-disciplinary research activities: **radioisotopes for theranostics,** particle detectors, radiation hardness, …

> … we are open to collaborations!

Acknowledgements

- Seniors and PostDocs: P. Scampoli, I. Mateu, L. Mercolli, P. Casolaro, L. Franconi, C. Belver Aguilar
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- LHEP mechanics and electronics workshop

https://www.lhep.unibe.ch/research/medical_applications/index_eng.html