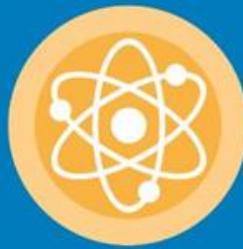


From the Production of Radioisotopes to the Precision Dispensing of Radiopharmaceutical Injections: the Complete Spectrum



RADIOPHARMA

Mario Malinconico

Product Manager & Senior Radiochemist

 **COMECKER**
AN  **ATS COMPANY**



WHO IS COMECER



We develop and manufacture high-tech systems necessary for Aseptic Processing and Containment.



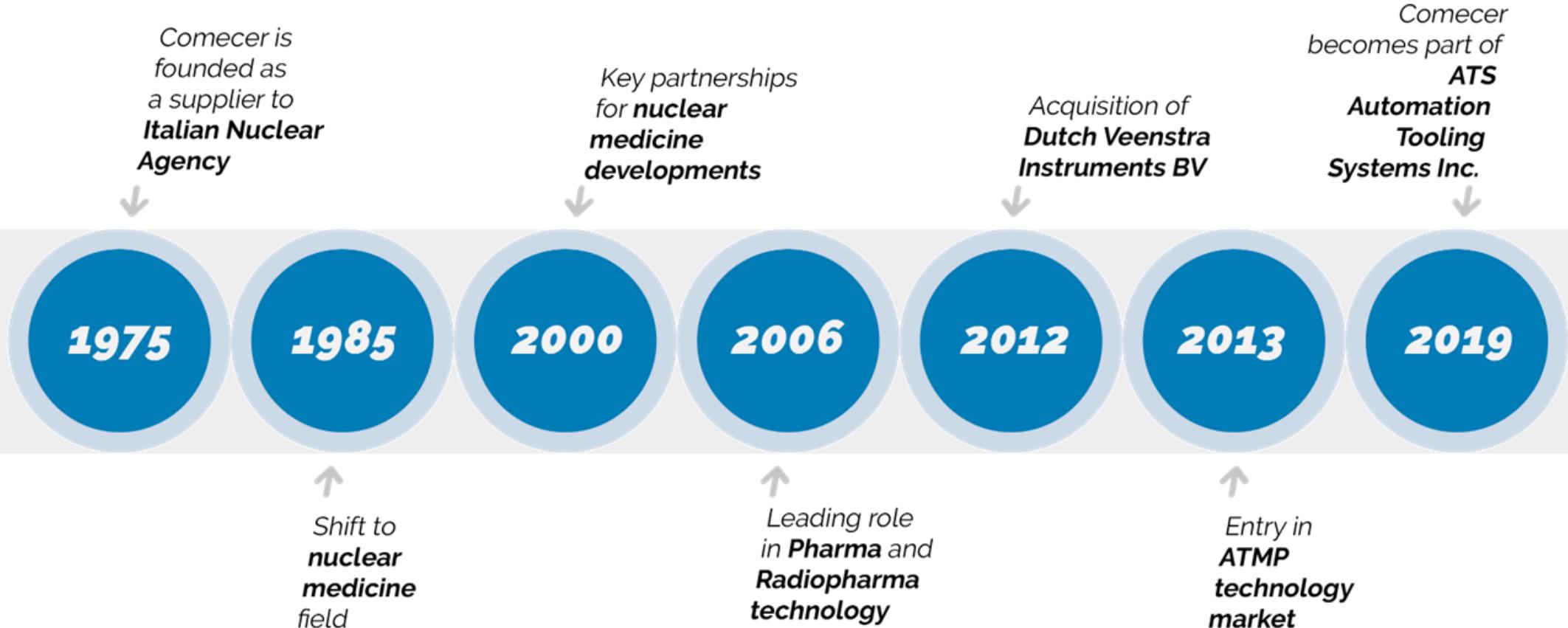
Our equipment is used by pharmaceutical companies, radiopharmacy departments, regenerative medicine and tissue engineering organizations worldwide.



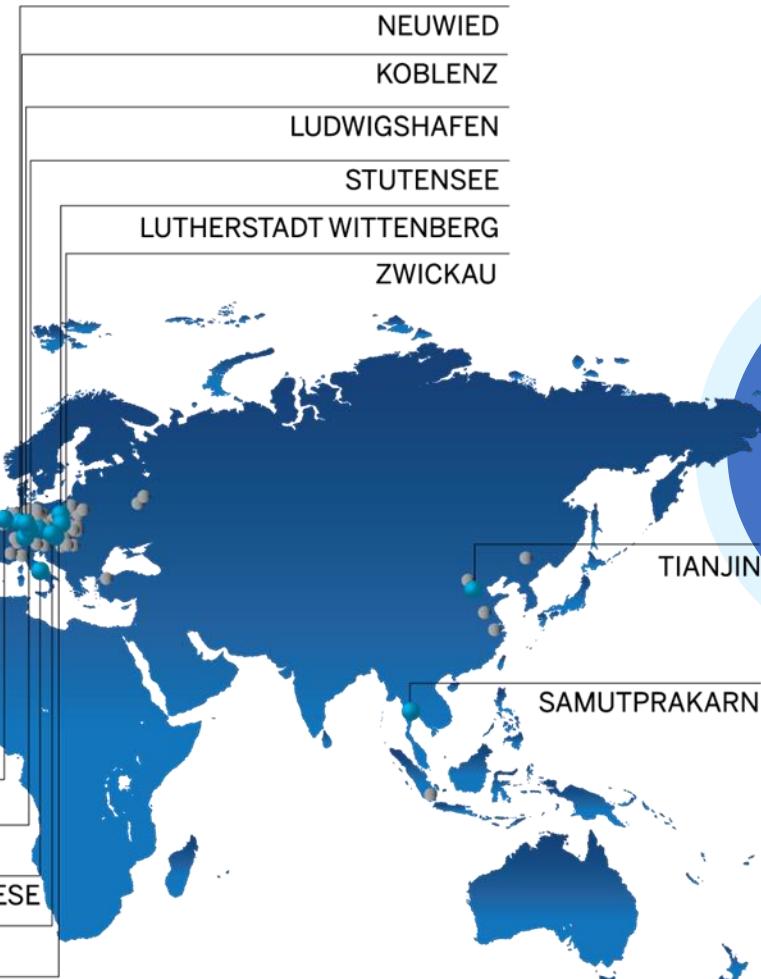
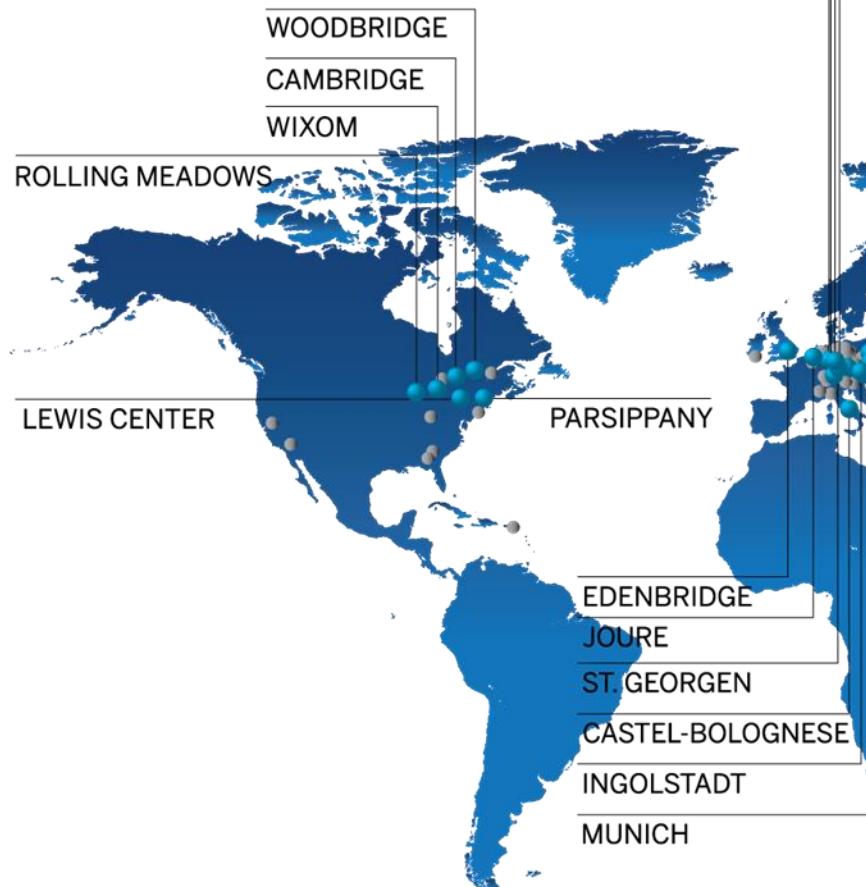
We believe in Safety first for operators, patients and products.



MORE THAN 40 YEARS EXPERIENCE



PROUD TO BE PART OF ATS GROUP



4.400+
EMPLOYEES
WORLDWIDE

22
COUNTRIES

50+
OFFICES

20
FACILITIES



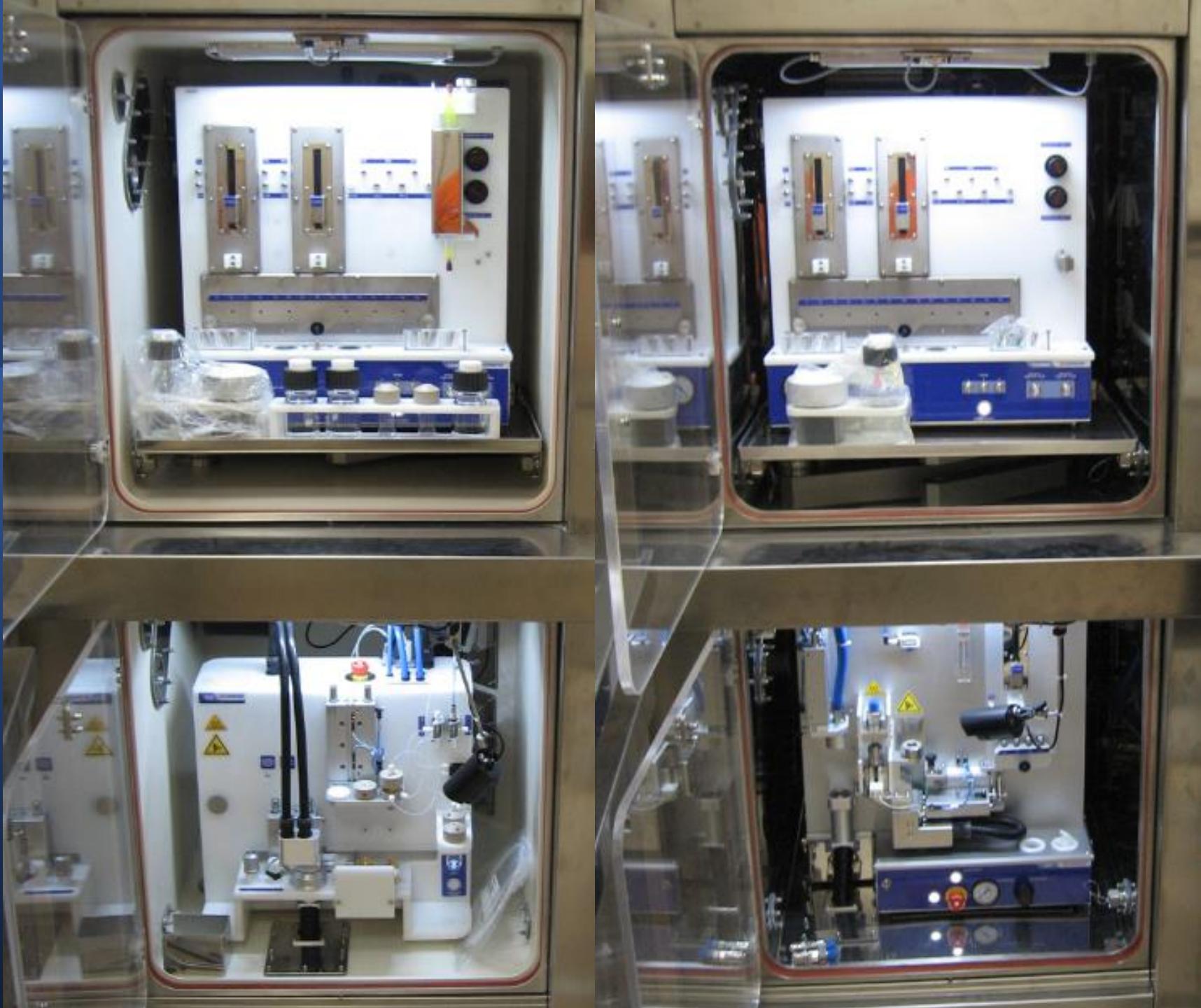
● MANUFACTURING FACILITIES

● OFFICES

Overview of ^{68}Ga life cycle: a case study

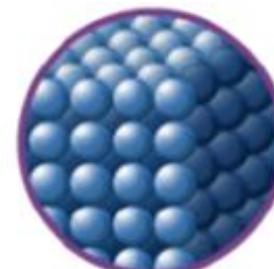


Radioisotope production

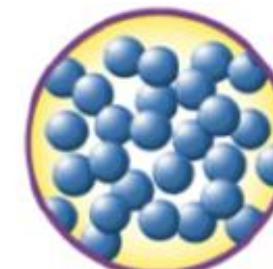


Why a solid target?

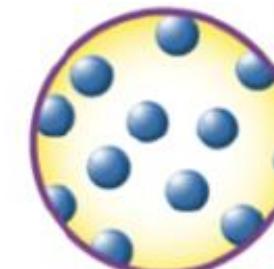
The atom density of the target species in the target material—e.g., a solid or liquid might provide higher atom densities than a gas and thus produce greater amounts of the desired product.



Solid

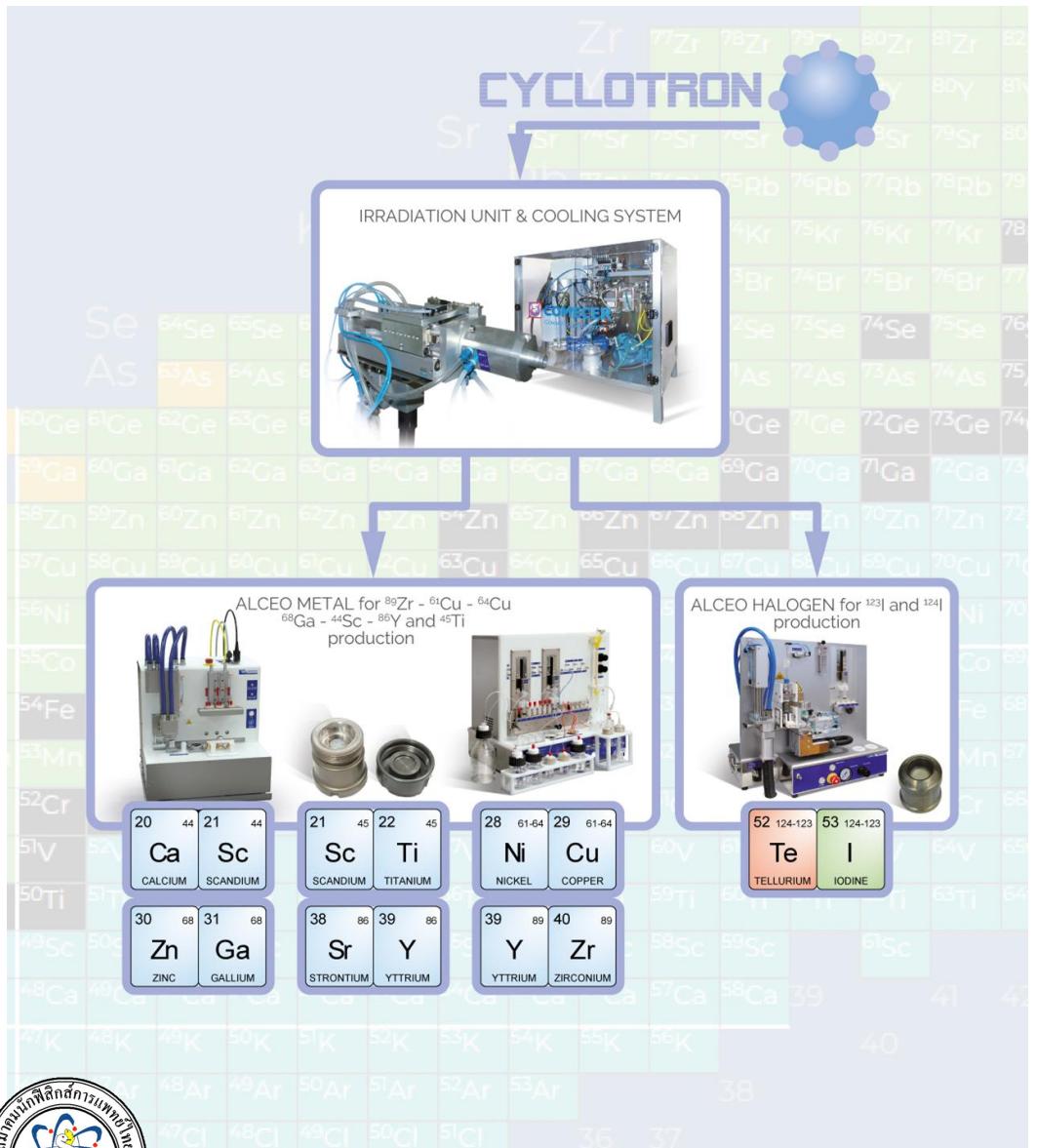


Liquid



Gas

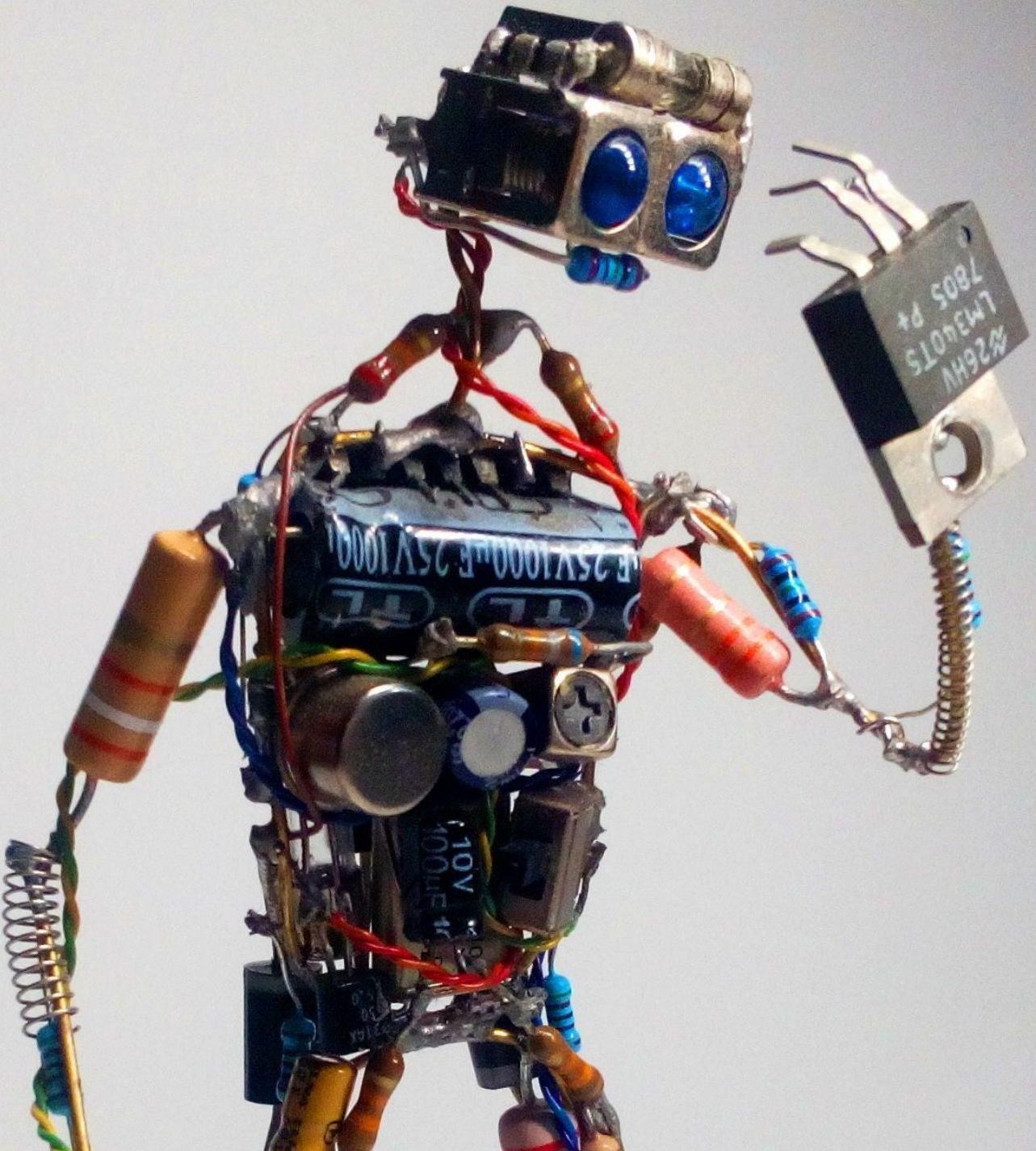
Alceo 4.0: solid target processing system configurations

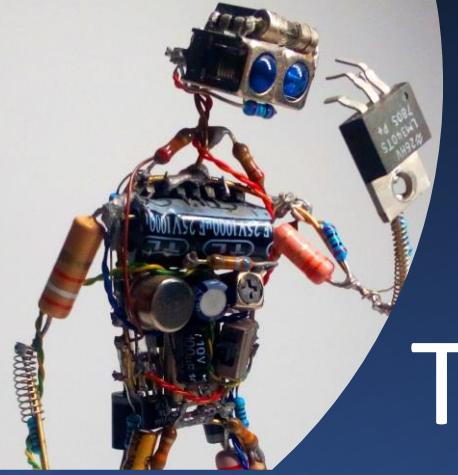


 **COMECER**
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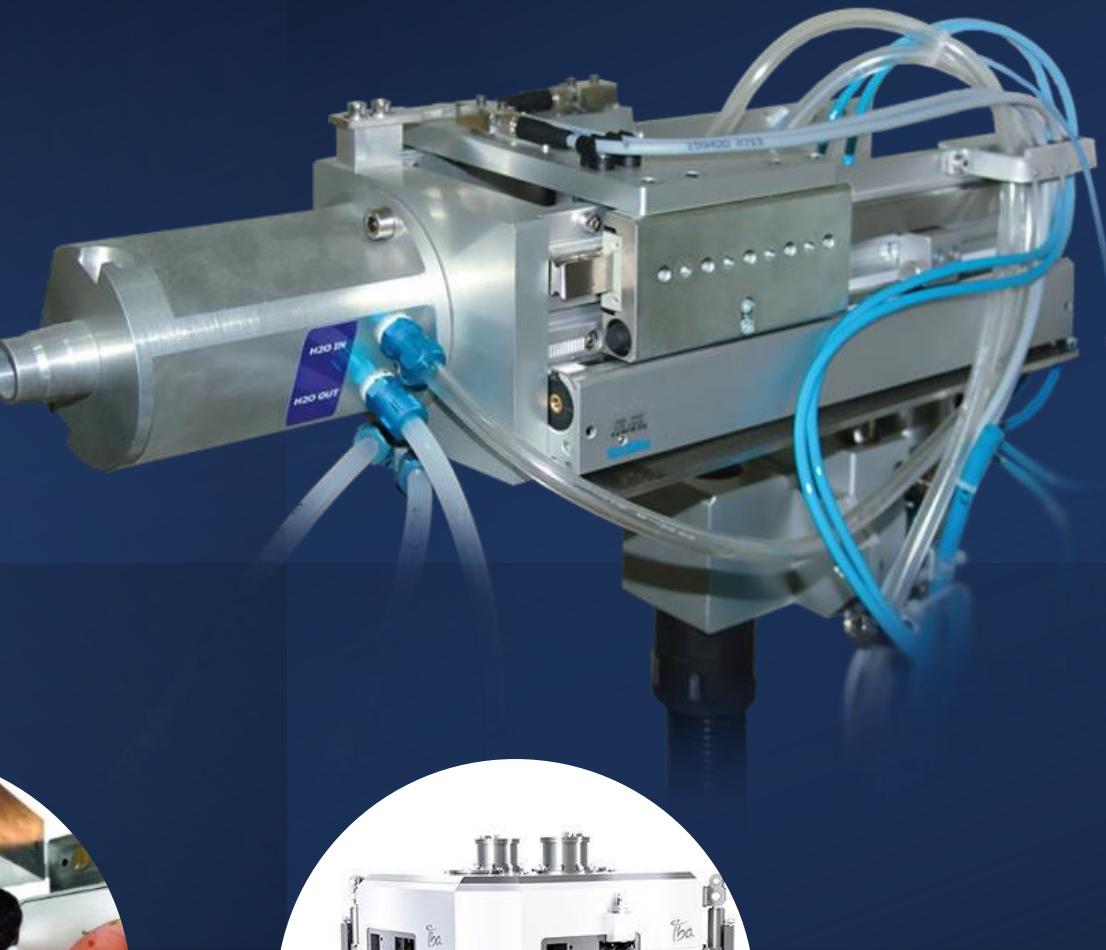


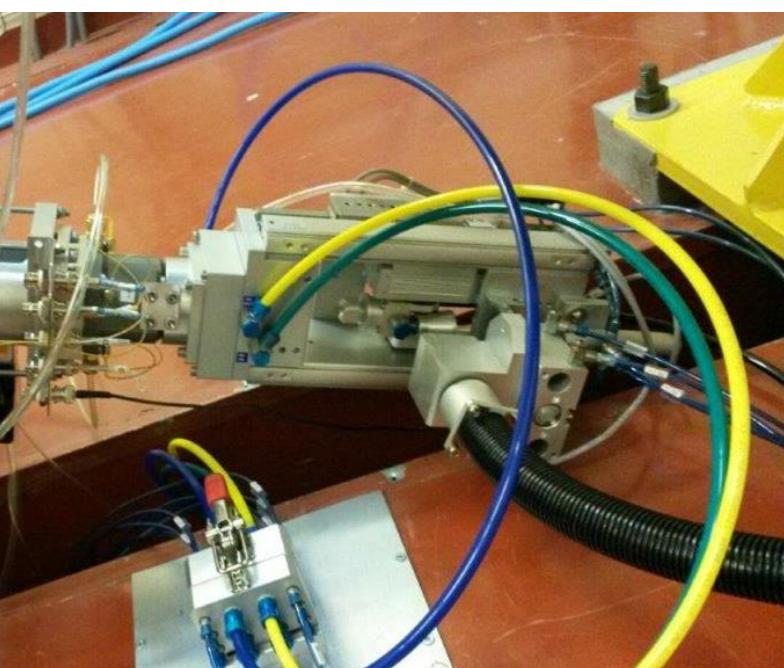
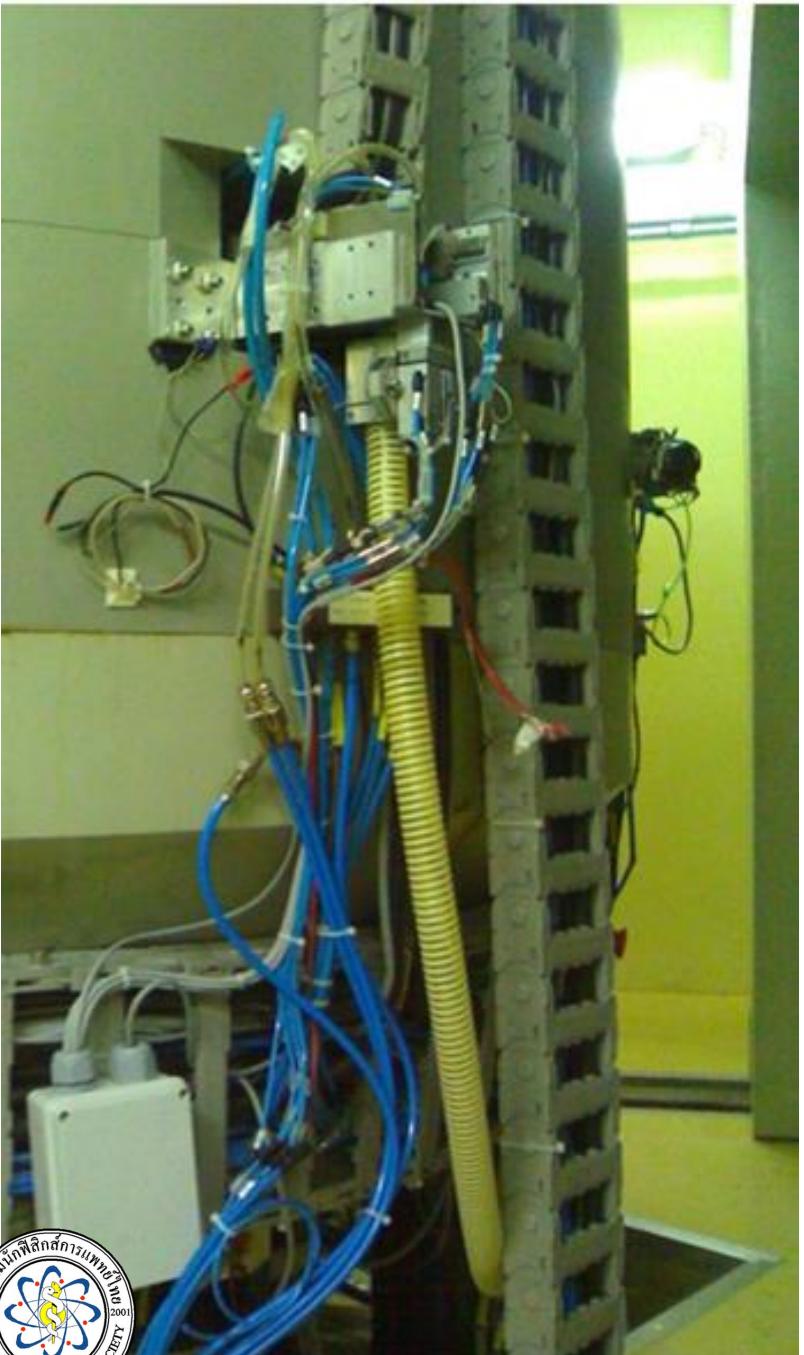
COMPONENTS



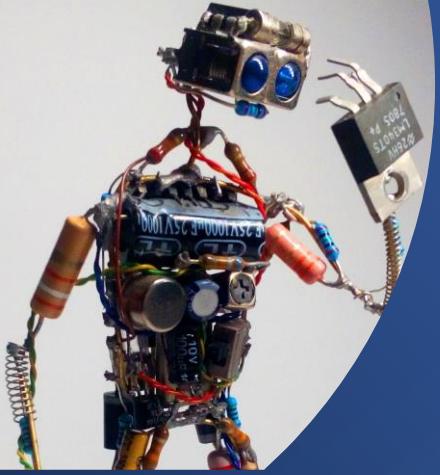


Target System - PTS

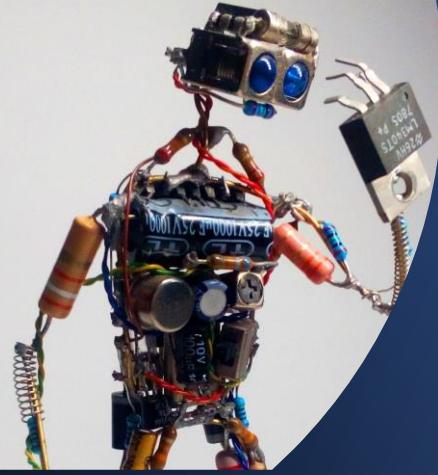




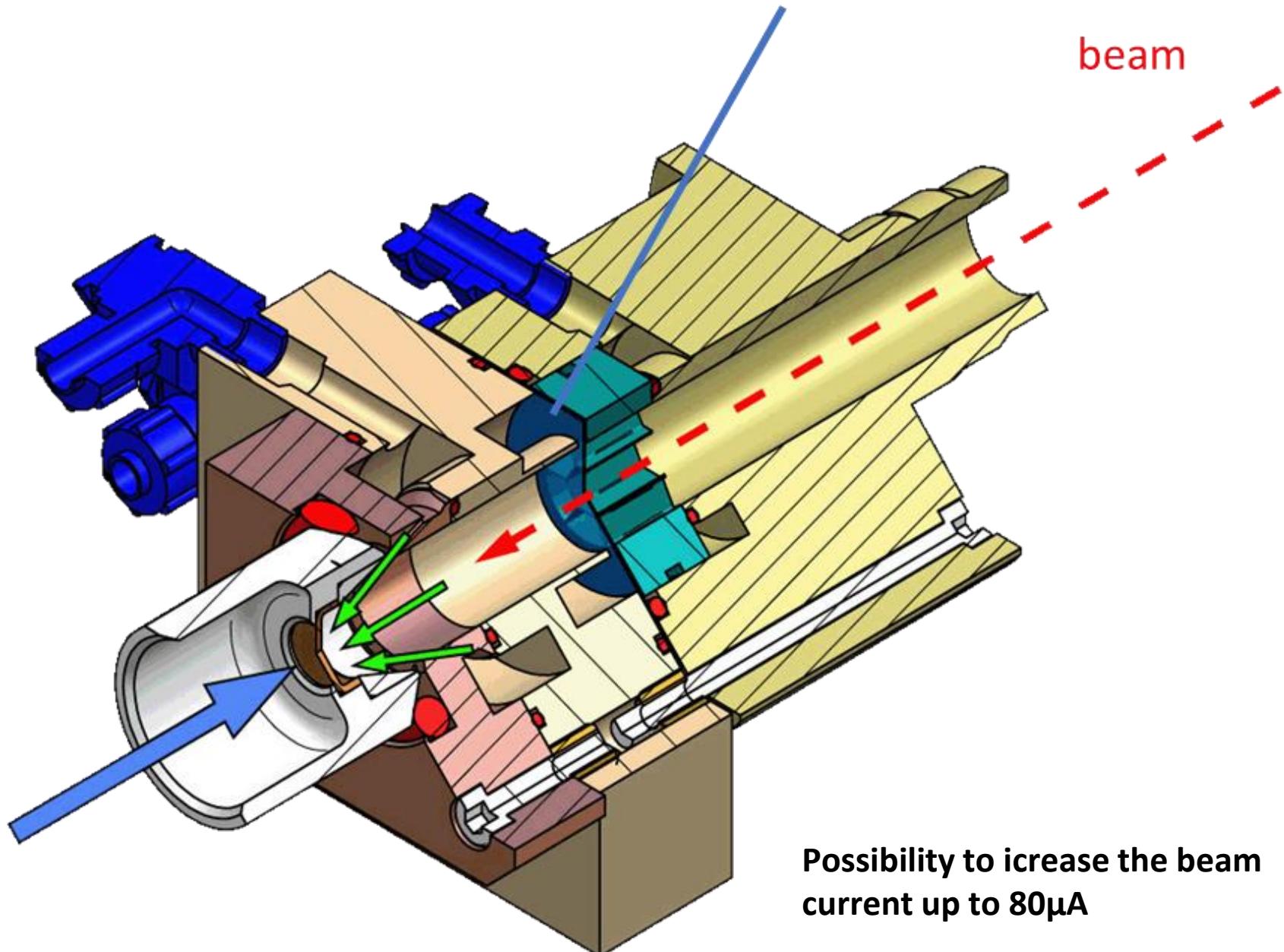
Cooling system



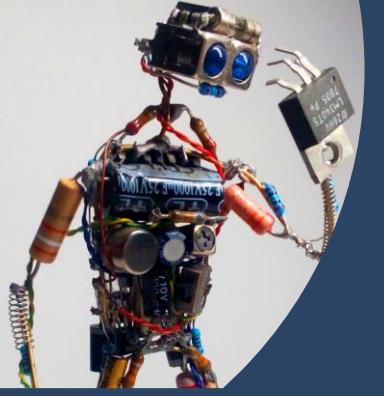
Cooling system



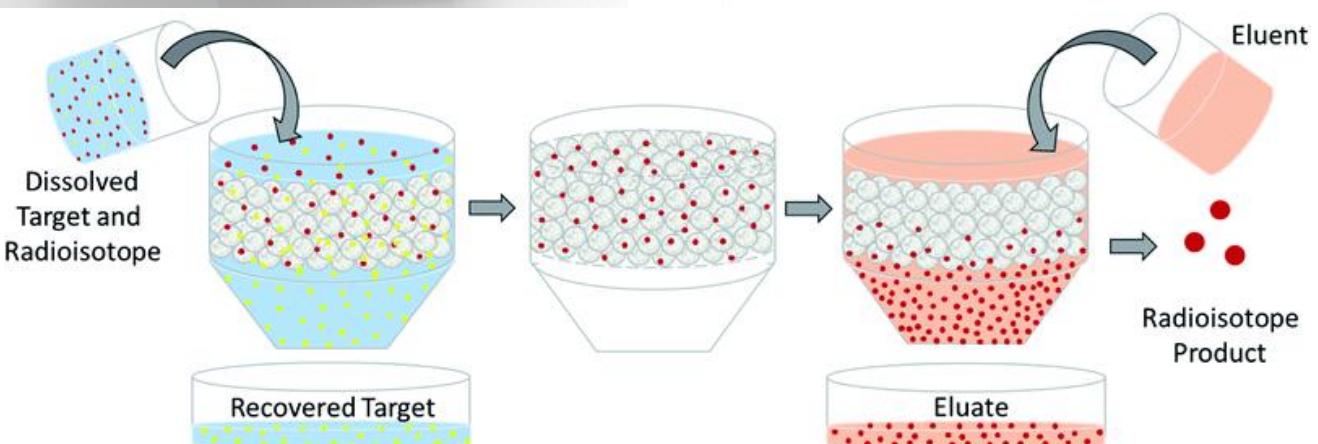
Degrader Al foil



Possibility to increase the beam current up to $80\mu\text{A}$

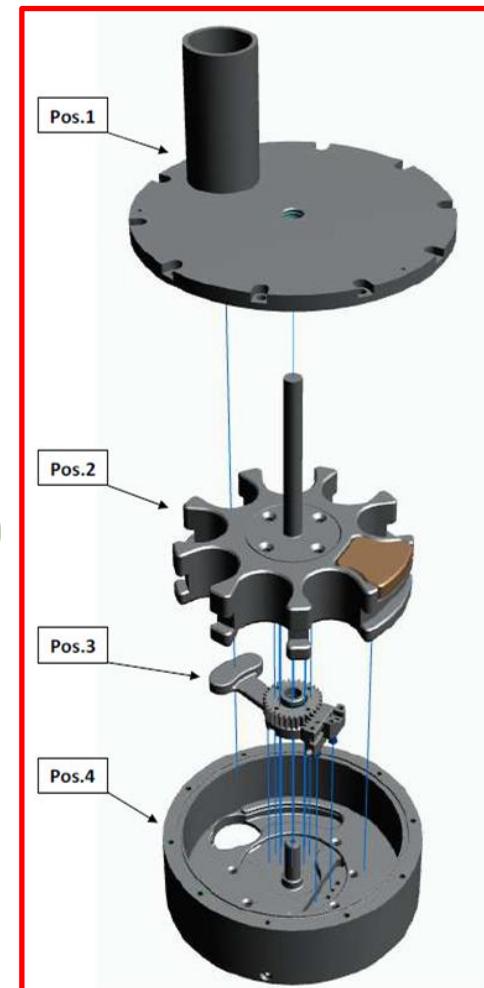
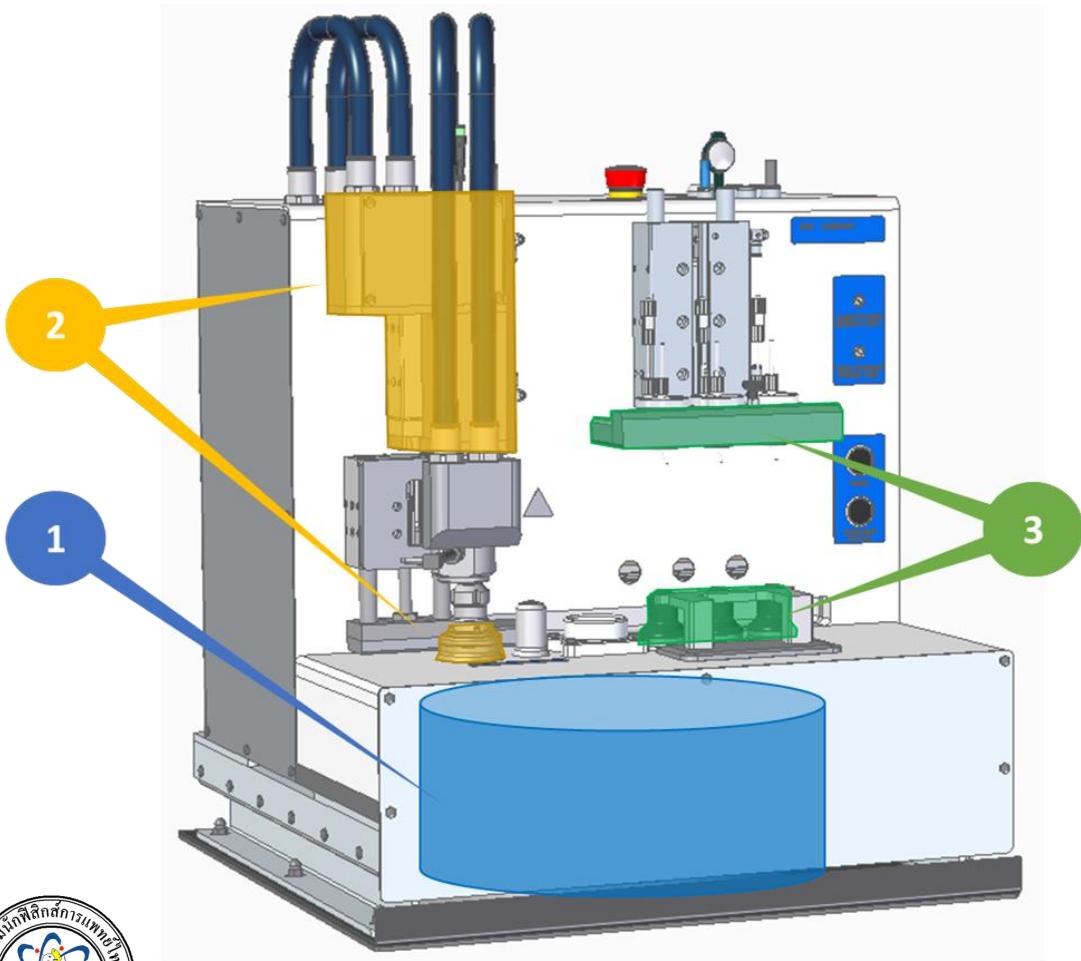


MODULES: TADEO-PRF & EDS



George, K J H et al. "Expanding the PET radioisotope universe utilizing solid targets on small medical cyclotrons." *RSC advances* vol. 11,49 31098-31123. 21 Sep. 2021,
doi:10.1039/d1ra04480j

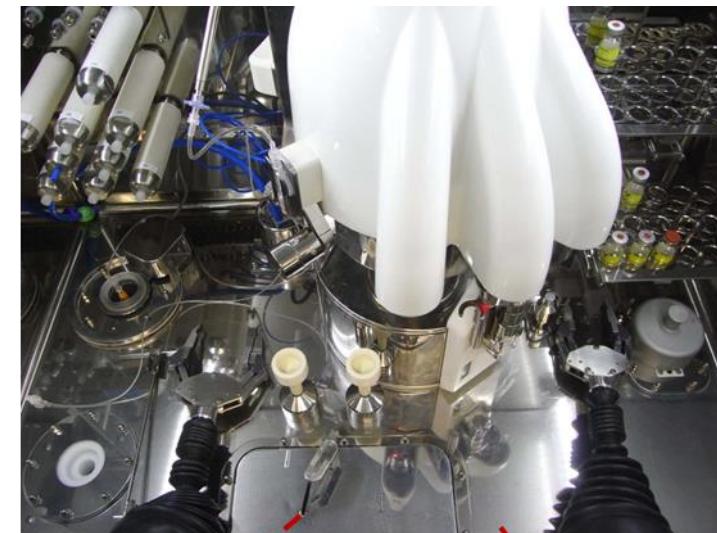
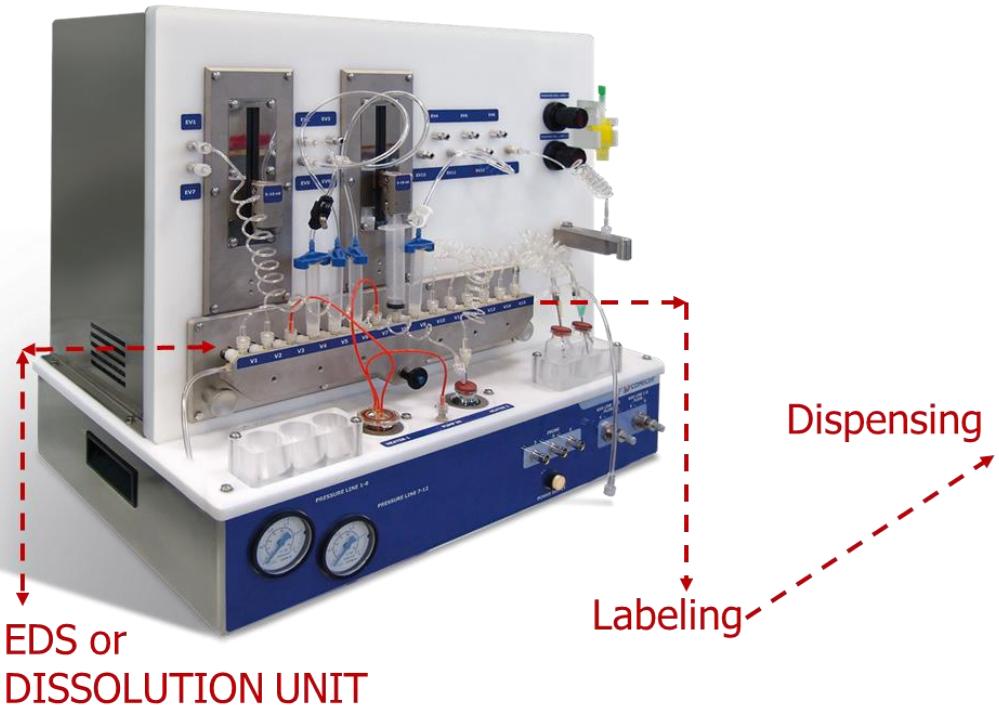
Alceo 4.0



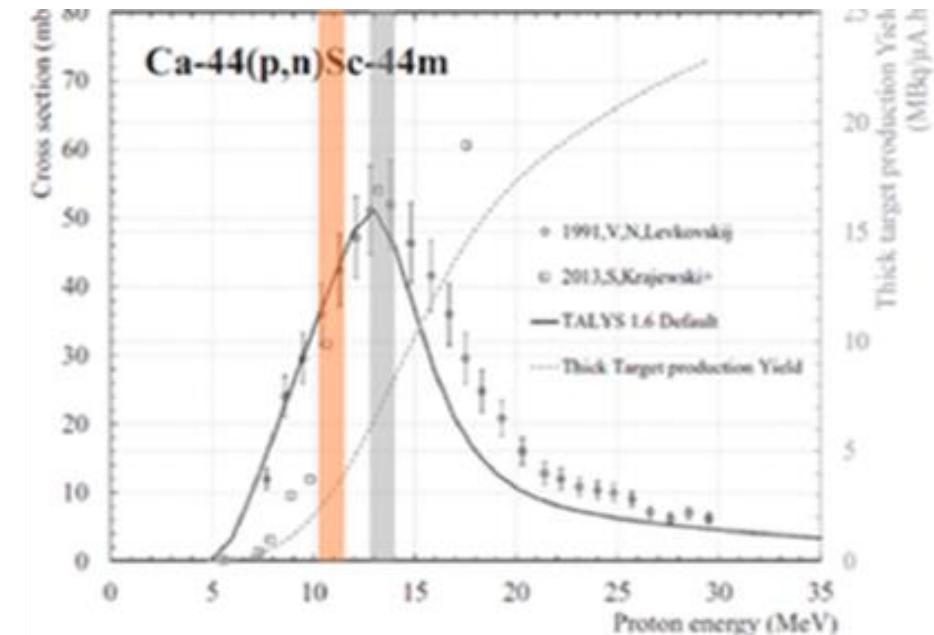
- ① INTEGRATED ROTATING STORAGE FOR THE SHUTTLES
- ② SCREW\UNSCREW HEAD FOR THE NEW SHUTTLE
- ③ 7 DISSOLUTION STATIONS



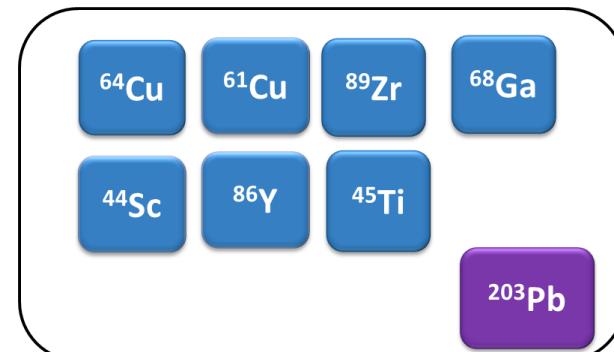
TADDEO-PRF



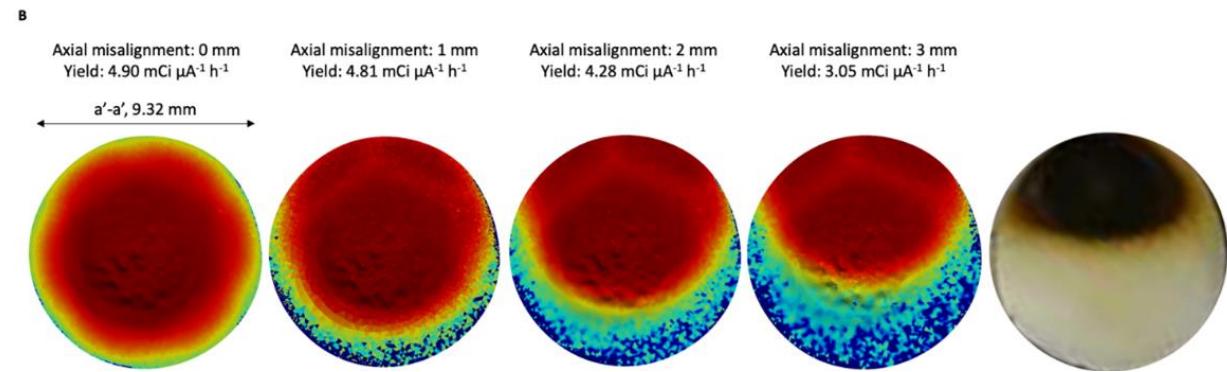
SHUTTLE



- UNIVERSAL SHUTTLE FOR ELECTROPLATING, POWDER CHEMISTRY OR COMMERCIAL FOIL!
- INTEGRATED DEGRADER FOIL
- LARGER PLATING

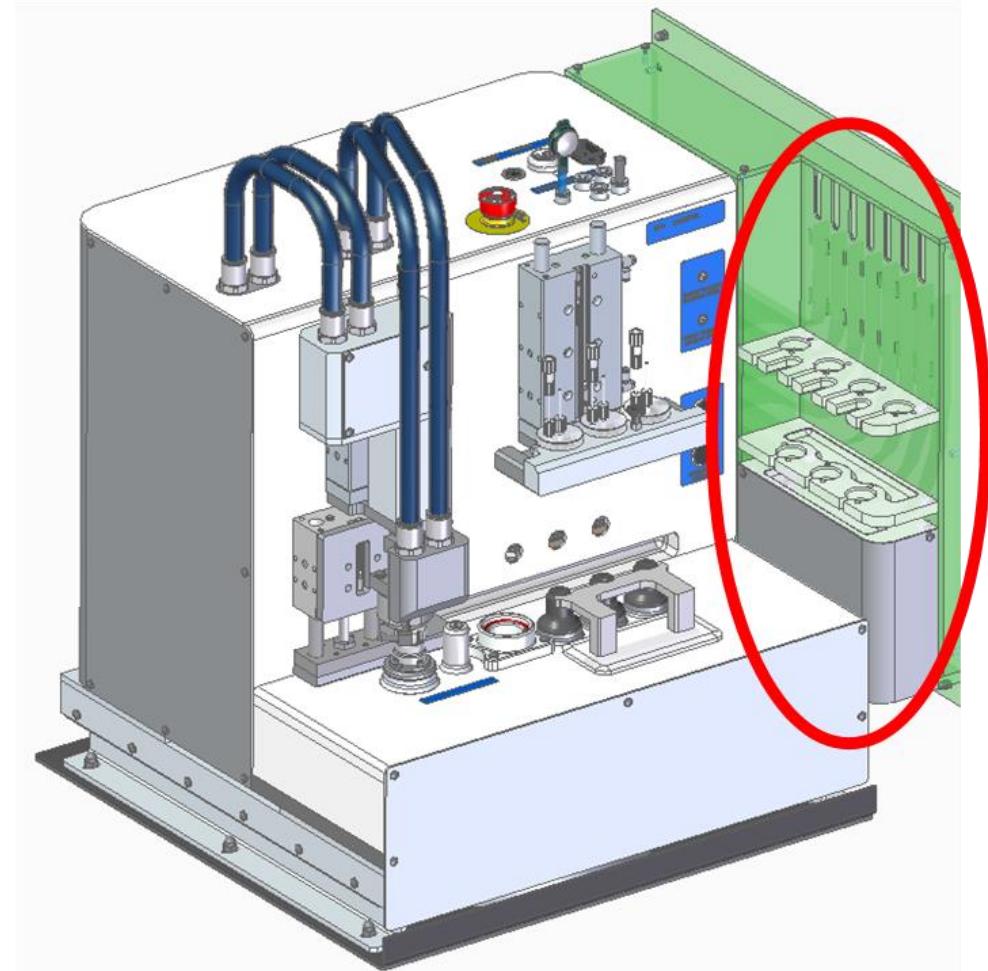
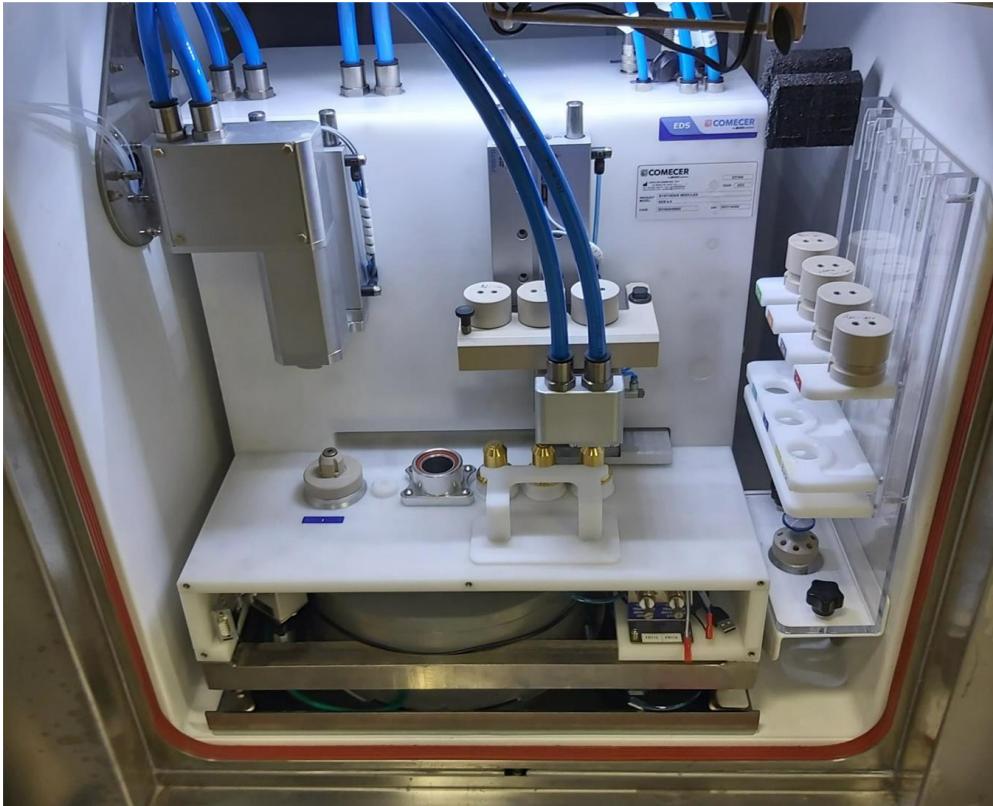
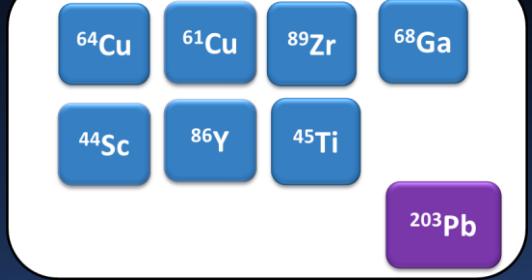


Electroplating



Isolan L, Malinconico M, Tieu W, et al. A digital twin for ^{64}Cu production with cyclotron and solid target system. *Sci Rep.* 2022;12(1):19379. Published 2022 Nov 12. doi:10.1038/s41598-022-23048-5

7 DISSOLUTION STATIONS

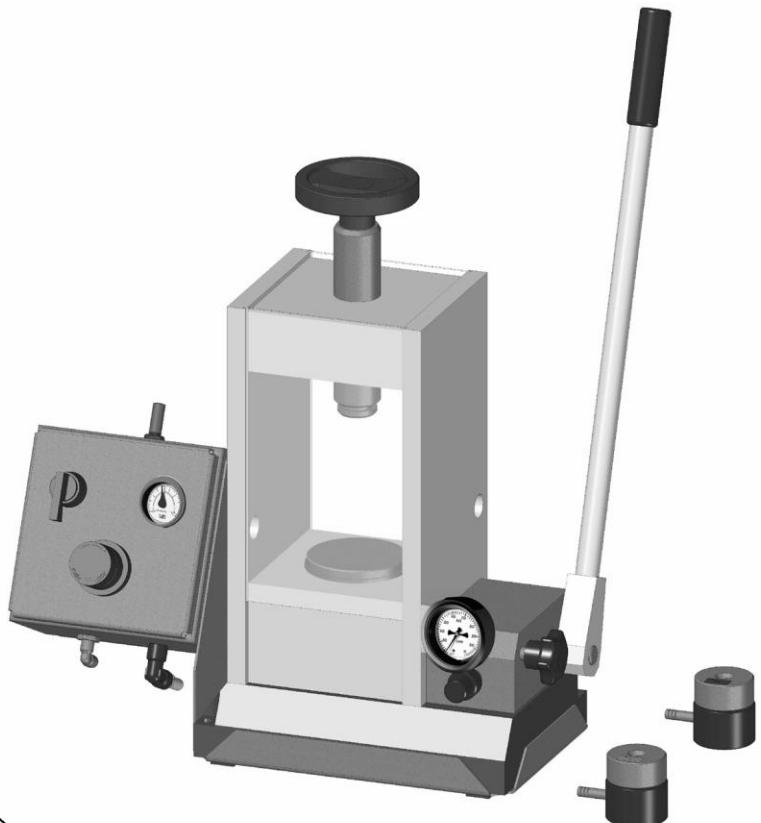


**BEAM
ON**

How to
prepare the
target(s)...



Powder compressing station



^{44}Sc

^{86}Y

^{203}Pb



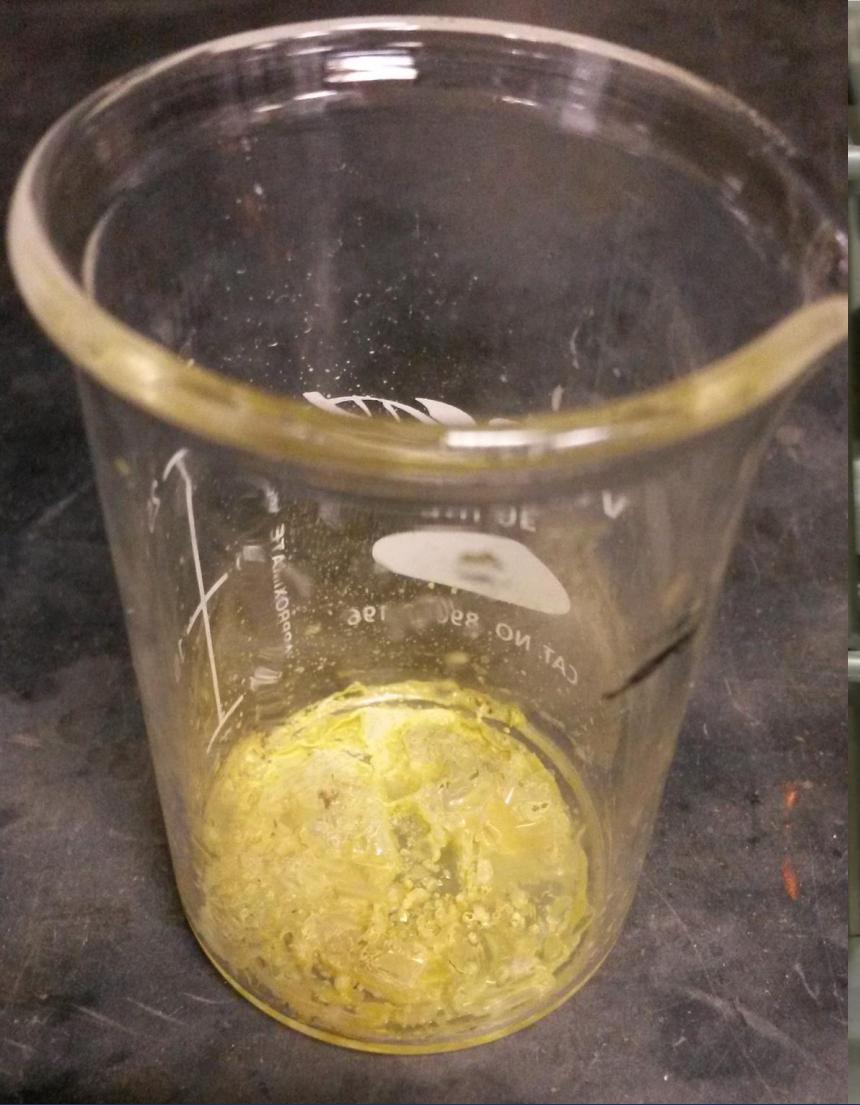
External plating module



^{64}Cu

^{61}Cu

^{68}Ga

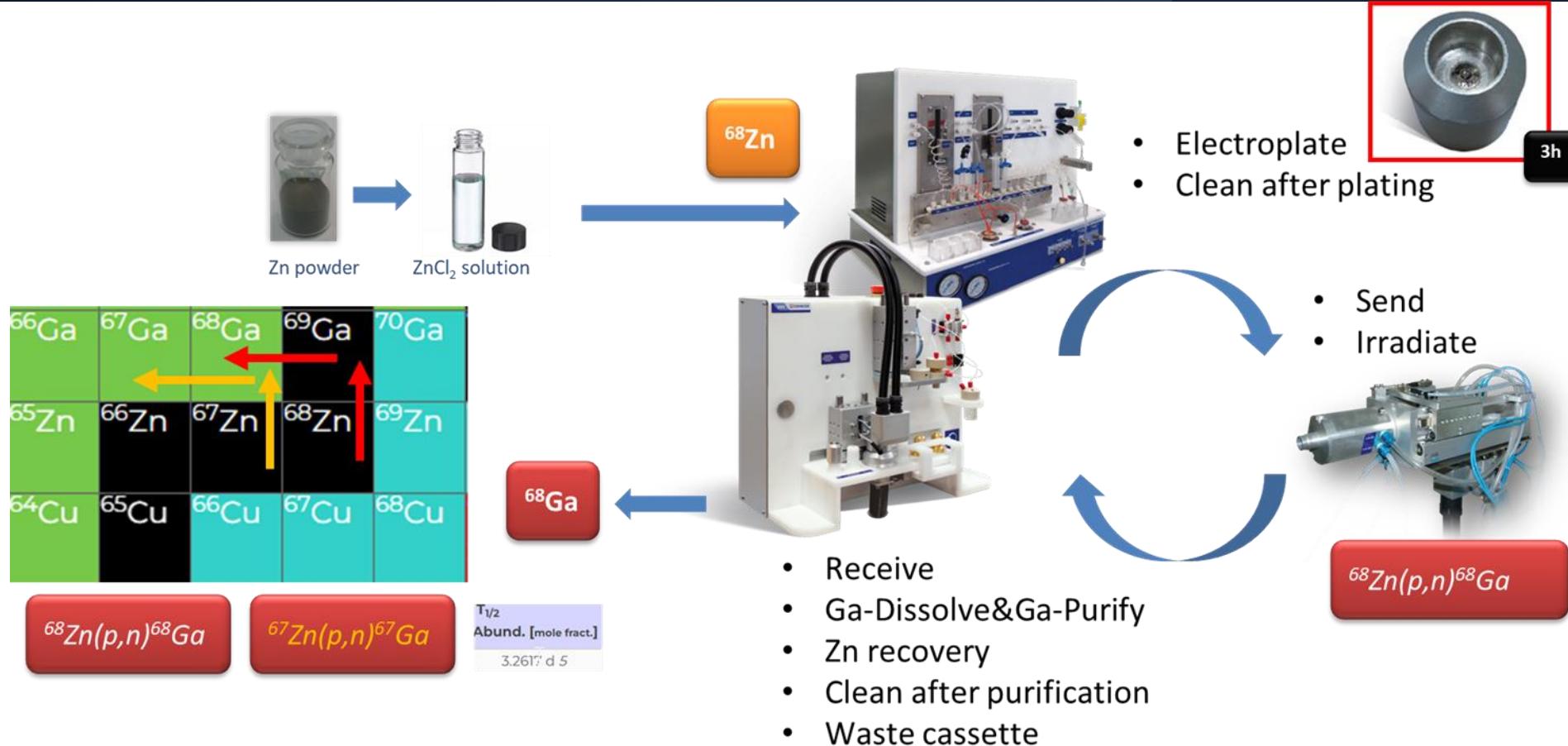


Possibility to recover the enriched material!

Product Video



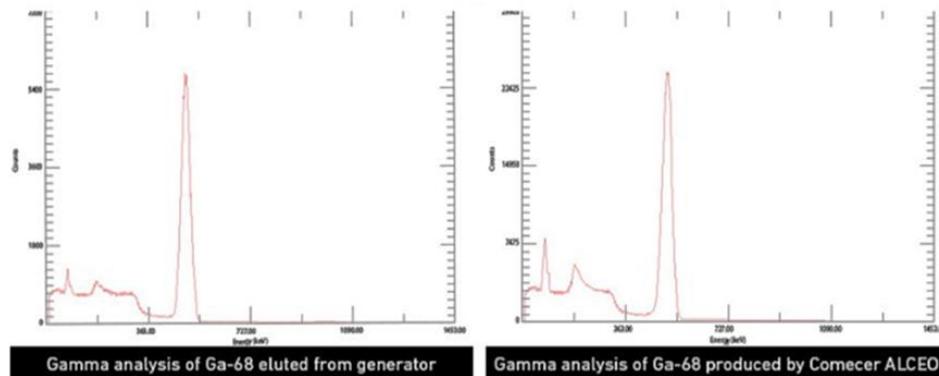
^{68}Ga Production



❖ 5mL Gallium Chloride in HCl 1M

❖ Expected saturation yield 45mCi/uA (max current 35uA)

Performances



Batch No. Ga test 100 uL

Enter 1st data point→
Enter 2nd data point→
Enter 3rd data point→
Enter 4th data point→
Enter 5th data point→

Time (hh:mm:ss)	Activity (MBq)	Time (min)	In(At/A0)
14:16:45	23.200	0.0	0.0000
14:18:45	22.700	2.0	-0.0218
14:20:46	22.300	4.0	-0.0396
14:22:47	21.800	6.0	-0.0622
14:24:47	21.400	8.0	-0.0808

Test	Result	
Radionuclidic purity	% ^{67}Ga at EOP = 0,019%	
pH	<2	
Fe (ppb)	Prod1: 332	Prod2: 1350
Zn (ppb)	Prod1: 371	Prod2: 5130

GALLIUM (68Ga) CHLORIDE SOLUTION FOR RADIOLABELLING

Gamma analysis comparison ALCEO-GENERATOR production

European Pharmacopoeia

- Half life: 62-74min



Regression Analysis:

Slope

R-squared

Results:

Theoretical Half life

BP Specification

Calculated Half life

Difference

-0.01010

0.99882

67.629 min

62-74 min

68.64 min

1.5 %



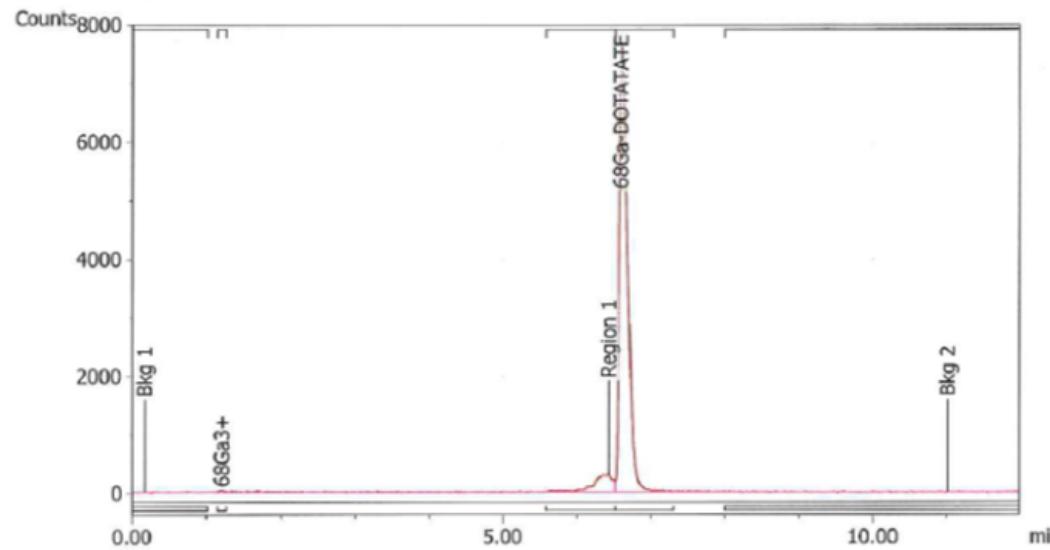
GALLIUM (68Ga) CHLORIDE SOLUTION FOR RADIOLABELLING

European Pharmacopoeia

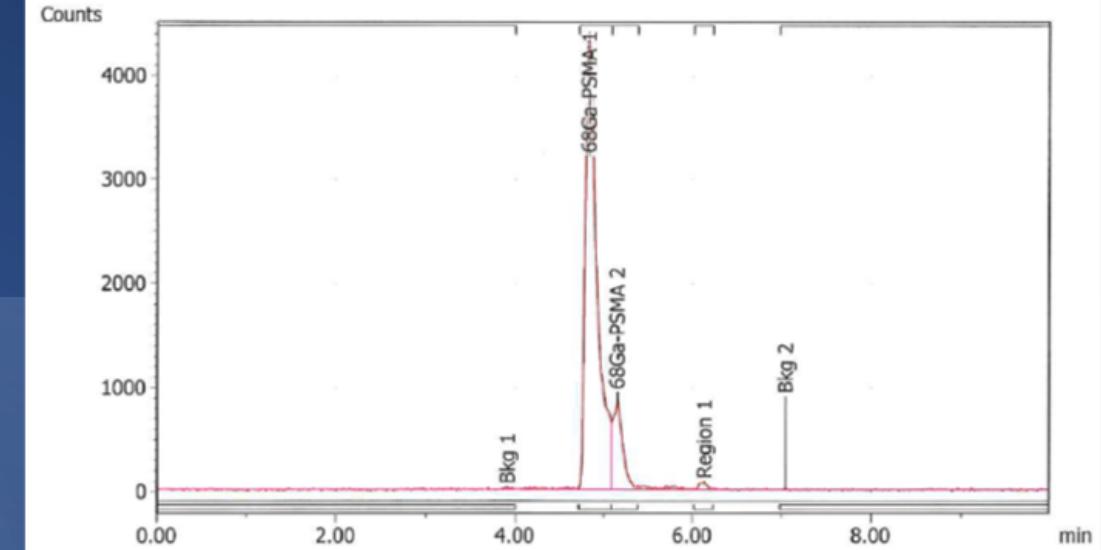
Gallium-68: min 99.9 % of the total radioactivity

- pH = max 2.
- Iron = maximum 10 $\mu\text{g}/\text{GBq}$.
- Zinc = maximum 10 $\mu\text{g}/\text{GBq}$.



Radiodetector (FlowRAM) Results:Chromatogram: ^{68}Ga **Region Table:**

Name	Start (min)	End (min)	Retention (min)	Area (Counts)	%ROI (%)	Signal to Noise Ratio
Bkg 1	0.00	1.02	0.17			
68Ga ³⁺	1.15	1.27	1.22	162	0.25	2.47
Region 1	5.58	6.52	6.43	5572	8.49	25.61
68Ga-DOTATATE	6.52	7.30	6.60	59861	91.26	713.57
Bkg 2	8.00	11.98	11.02			
3 Peaks				65595	100.00	

Radiodetector (FlowRAM) Results:Chromatogram: ^{68}Ga **Region Table:**

Name	Start (min)	End (min)	Retention (min)	Area (Counts)	%ROI (%)	Signal to Noise Ratio
Bkg 1	0.00	4.00	3.92			
68Ga-PSMA 1	4.72	5.08	4.83	40095	84.40	304.52
68Ga-PSMA 2	5.08	5.38	5.15	6929	14.58	56.97
Region 1	6.02	6.23	6.13	483	1.02	4.76
Bkg 2	6.98	9.98	7.05			
3 Peaks				47507	100.00	

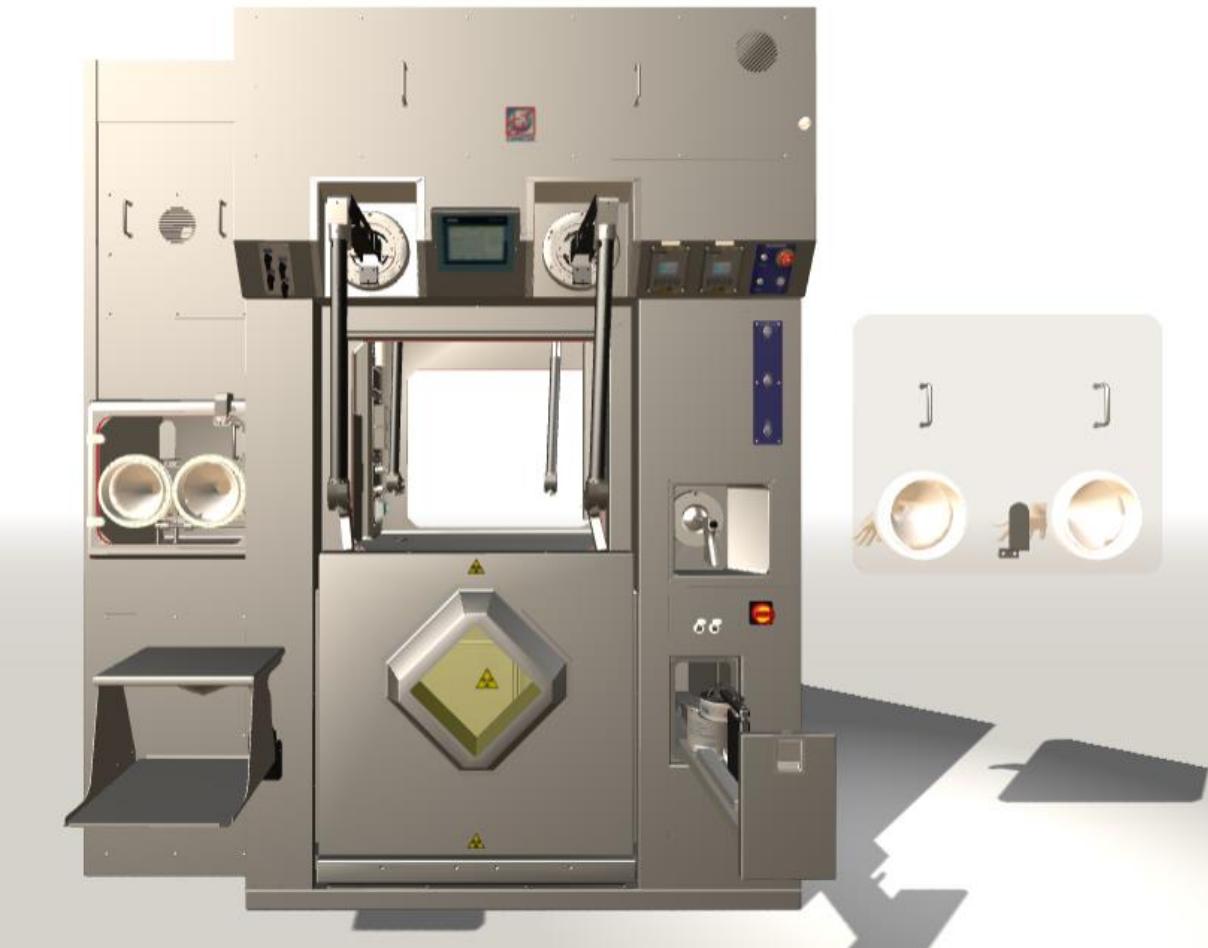
Products	EOS activity (MBq)	SYNTHESIS		HPLC	
		Synthesis yield	Decay corrected yield	Radiochemical purity	Free $^{68}\text{Ga}^{3+}$
DOTATATE	888	76,0%	88,6%	91,3%	0,25% Not detected
PSMA	570	79,2%	89,6%	99,0%	



RADIOLABELING - MIP HOT CELL



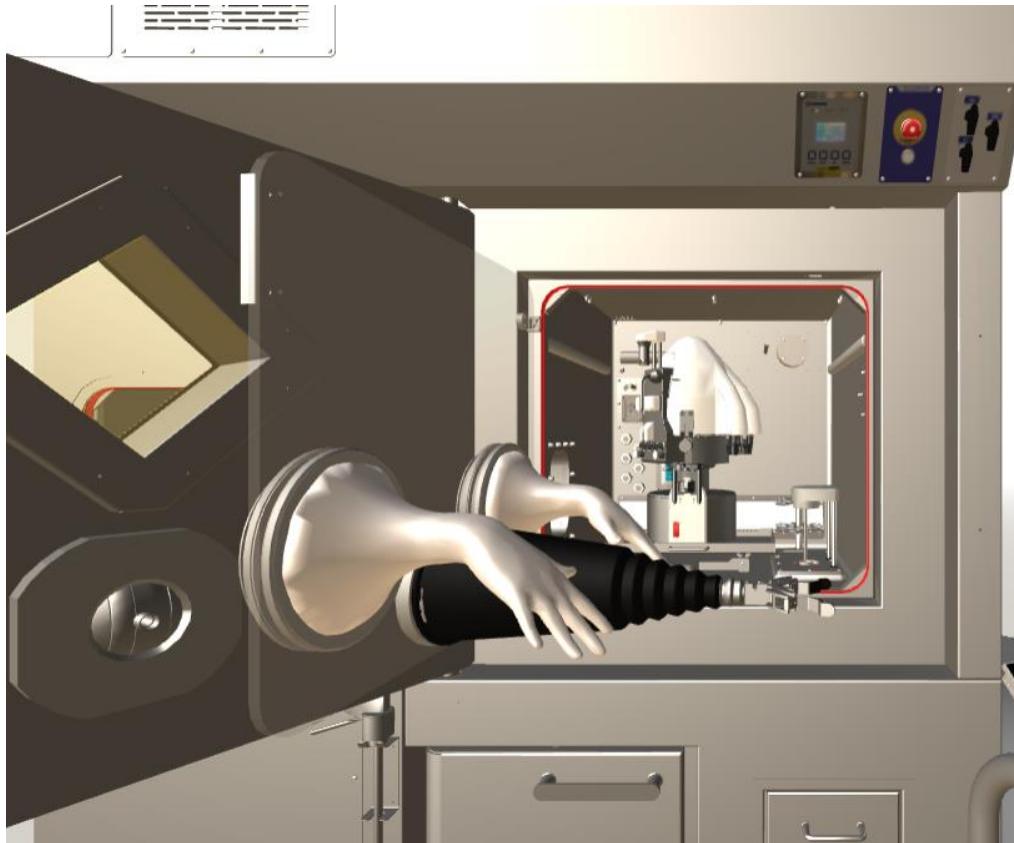
RADIOLABELING - MIP HOT CELL



DISPENSING HOT CELL - PHAEDRA



DISPENSING HOT CELL - PHAEDRA



Radiopharmaceutical injection



Why an automatic radiopharmaceutical injector?



Significant staff exposure is generally expected during PET- and PET/CT applications. Whole-body doses as well as extremity doses are usually higher per procedure compared with SPECT applications. Dispensing individual patient doses and manual injection involves high extremity doses even when heavy weighted syringe shields are used. In some cases the external radiation causes an exposure to the fingertips of more than 500 mSv y^{-1} , which is the yearly limit. Whole-body doses per procedure are relatively lower compared with extremity doses and are generally spread over the entire procedure (Guillet, B.,

TABLE 4

Mean \pm SD ($n = 10$) Dose Rates Measured by TLD Positioned Either on Syringe Shield Inside Injector or on External Face of Injector

TLD location	Dose rate (mSv/h)	Dose rate (mSv/h) per MBq
Syringe	58.7 ± 13	0.19 ± 0.02
Injector	0.047 ± 0.062	0.00017 ± 0.000014

REFERENCES:

Covens P, Berus D, Vanhavere F, Caveliers V. The introduction of automated dispensing and injection during PET procedures: a step in the optimisation of extremity doses and whole-body doses of nuclear medicine staff. Radiat Prot Dosimetry. 2010 Aug;140(3):250-8. doi: 10.1093/rpd/ncq110. Epub 2010 Mar 23. PMID: 20335185.

Guillet B, Quentin P, Waultier S, Bourrelly M, Pisano P, Mundler O. Technologist radiation exposure in routine clinical practice with ^{18}F -FDG PET. J Nucl Med Technol. 2005 Sep;33(3):175-9. PMID: 16145226.

IRIS

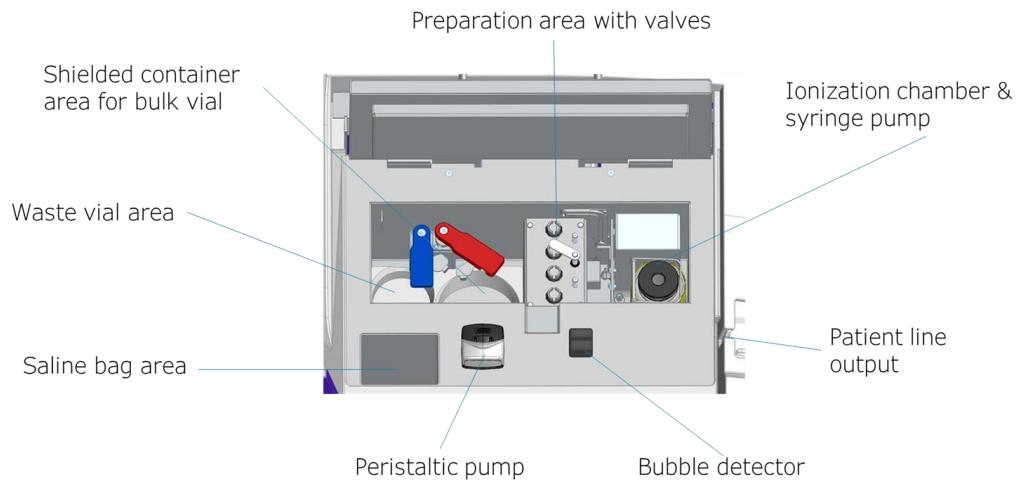


IRIS – automatic radiopharmaceutical injector



Weight	kg	330 (+/-5)
External dimensions (handle open)	cm	63,5 x 114 x 96,5 (w x d x h)
External dimensions (handle closed)	cm	63,5 x 90 x 81 (w x d x h)

Main components



DC Quality Control

QMM-101

Quality controls	Status	Execute
Every day	Failed	9/24/2015
Zero adjustment	Overdue	9/24/2015
Bias correction	Failed	9/24/2015
Background effect	Overdue	9/24/2015
Accuracy and constancy test	OK	9/25/2015
Every week	OK	10/1/2015
High voltage check	OK	10/1/2015
Other	Paused	9/24/2015
Linearity test	Paused	9/24/2015
Calibration check	OK	9/23/2016

Close **X**
Start **Overview**

- QMM is an integrated module in the IRIS software suitable for executing and keeping quality controls updated.
- The QMM will give a pop-up on the HMI when a quality check is required

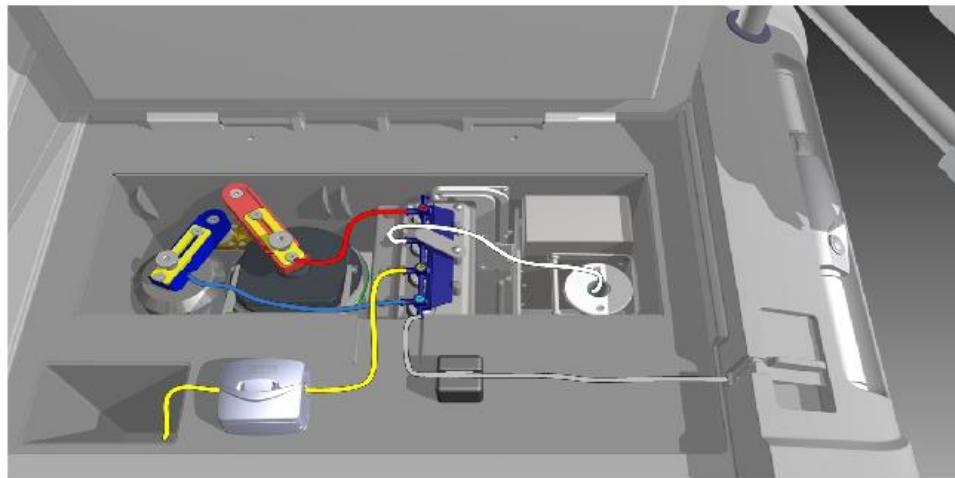
System preparation



Admin

Prepare system

Place the needle in the holder and connect the needle to the mother vial as shown in the picture



Close both hatches and start Prime & Measure when enabled. The bulk will be mixed 3 time(s) before the measurement starts.

Mixing the bulk... (2 of 3)

Cancel

Abort

Mix bulk



32340.65 MBq in 20.3 ml

995 ml



FOG

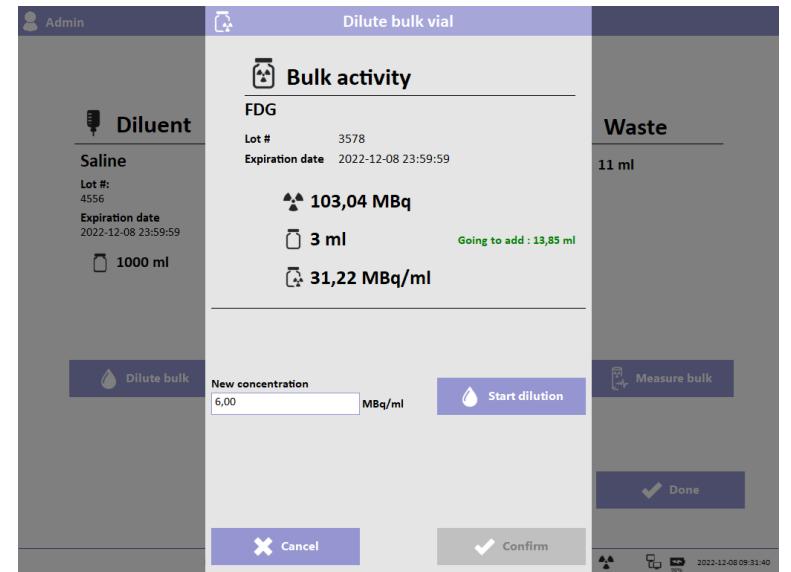


99%

07-12-2021, 15:48

Multi-dose vial management

- Measurement of multi-dose vial activity/concentration
- Dilution of multi-dose vial in bulk vial



Patient selection



Admin Worklist

12/7/2022 Today + Edit X E

Planned dose Dose to inject

Patient insert manually

Patients downloaded from the hospital net.

Patient name
Patient number
Date of birth
Weight
Height
Gender

Print label Prepare injection

IPS 2.0.3

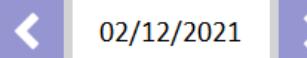
1117.84 MBq in 10.3 ml 995 ml 07-12-2022, 16:47

THAI MEDICAL PHYSICIST SOCIETY 2001

The screenshot shows a medical software interface titled "Worklist". At the top, there are navigation buttons for date (12/7/2022, Today), and actions (+, Edit, X, E). Below the date is a section labeled "Planned dose" with a radiation symbol icon. To the right is a section labeled "Dose to inject". A red arrow points from the text "Patient insert manually" to the "Planned dose" section. Another red arrow points from the text "Patients downloaded from the hospital net." to the "Dose to inject" section. The "Patient" section contains fields for name, number, date of birth, weight, height, and gender. At the bottom are buttons for "Print label" and "Prepare injection". The software version IPS 2.0.3 is shown at the bottom right, along with a timestamp (07-12-2022, 16:47) and some status icons.

Patient selection

Admin Worklist 

02/12/2021 Today     

Planned dose	Dose to inject
 100 MBq FDG	48.88 MBq
10.00 ml	
02-12-2021, 17:45	
FDG Examination (F-18)	

Patient

Patient name	Patient 1
Patient number	001
Date of birth	10/10/1980
Weight	92 kg
Height	183 cm
Gender	Male

 Print label  Prepare injection

IPS 2.0.0

1117.84 MBq in 10.3 ml  995 ml  100% 07-12-2022, 16:47

17:45 FDG Examination (F-18)
Patient 1
001 10/10/1980 92 kg 183 cm
 100 MBq FDG

18:00 FDG Examination (F-18)
Patient 2
002 15/02/1965 68 kg 172 cm
 100 MBq FDG

19:00 FDG Examination (F-18)
Patient 3
003 02/05/1975 98 kg 186 cm
 100 MBq FDG

19:20 FDG Examination (F-18)
Patient 4
004 15/08/1996 83 kg 184 cm
 100 MBq FDG

20:10 FDG Examination (F-18)
Patient 5
005 23/11/2001 71 kg 168 cm
 85 MBq FDG

20:40 FDG Examination (F-18)

8 patients    

Safety system

Date of birth	05/07/1979	Diluent	2.86 ml (27.40 ml/min)
Weight	92 kg	For injection	2.00 ml (27.40 ml/min)
Height	191 cm	For pre-injection (per cycle)	10.00 ml (27.40 ml/min)
Gender	Male	For rinsing (per cycle)	

Inject cycles:

Cycle 1: Planned: 138.38 MBq in 1.65 ml - Stopped

Injecting in progress... (cycle 1 - 1)

42%

Due to safety reasons, resume is no longer possible. Please
abort the injection

✓ Abort injection

✓ Done



System halted, inject patient stopped.

2118.18 MBq in 25.3 ml

973 ml



100% 09-12-2021, 18:12

- Increase in pressure detection
- During test injection
- During radiopharmaceutical injection



Clean line procedure



Admin

Clean lines (End run)

Press "Clean lines" to clean the system

After cleaning the lines the current run is ended. The system needs to be prepared again to start a new run.



Diluent

Saline

Lot #:

100456

Expiration date

07/12/2021 23:59:00



995 ml



Activity

FDG

Lot #:

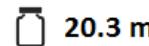
100456

Expiration date

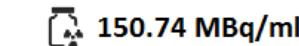
07/12/2021 23:59:00



3059.96 MBq @ 16:56:51



20.3 ml



150.74 MBq/ml



Waste



3 ml

Cancel

Clean lines

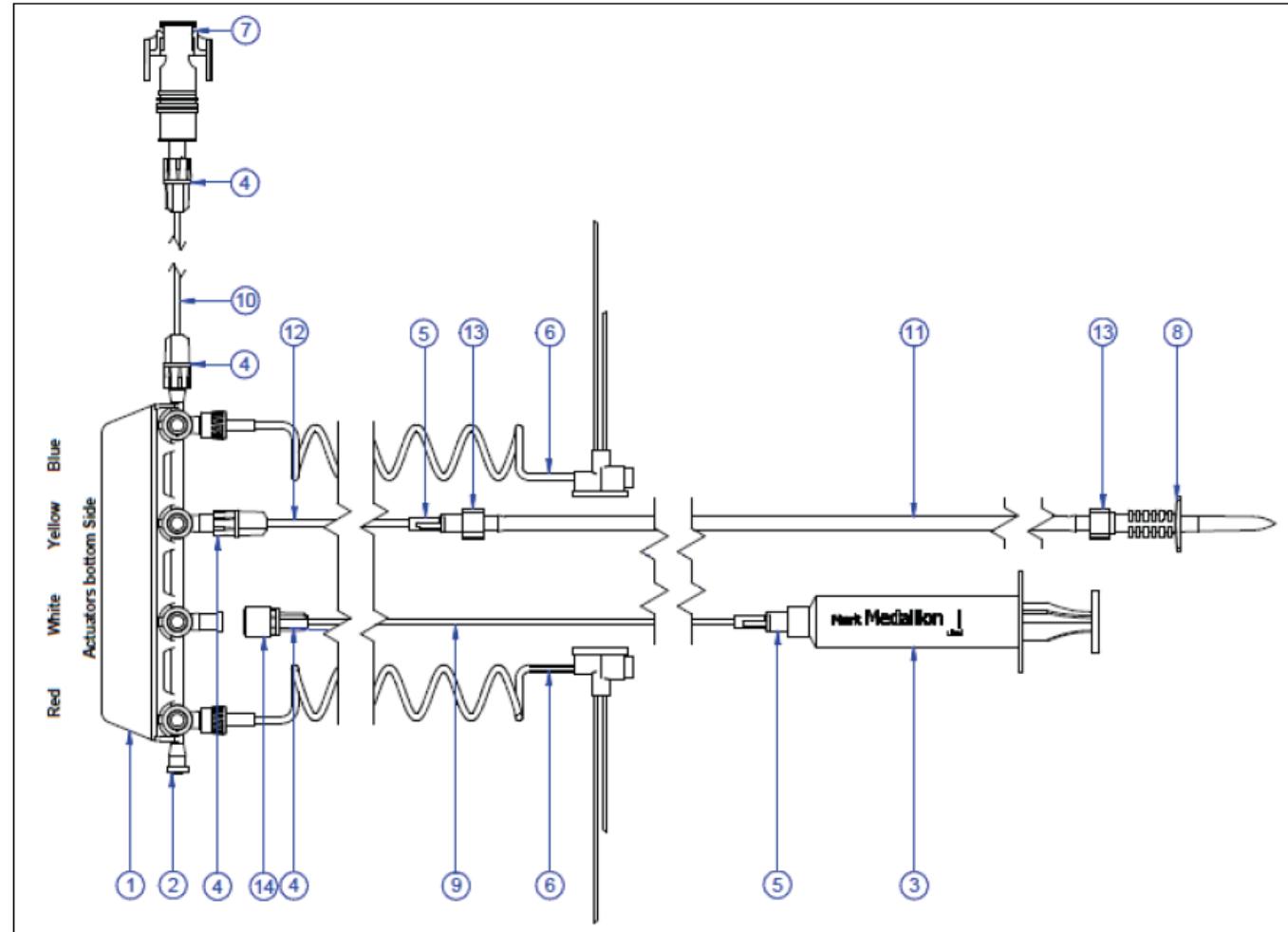
3056.12 MBq in 20.3 ml

995 ml



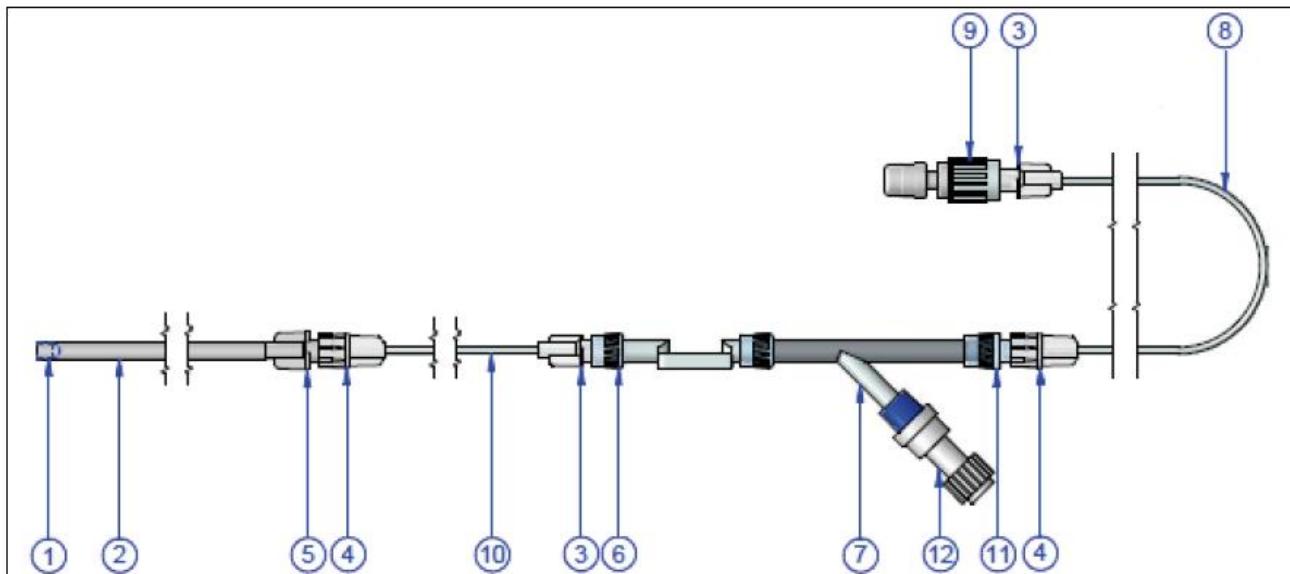
07-12-2021, 16:57
99%

Disposable main kit



Batch kit

Disposable patient kit



Label management

- The system is equipped with a label printer, connected to the operator panel, which prints self-adhesive labels of various lengths according to the layout and information required. The layout is adjustable.

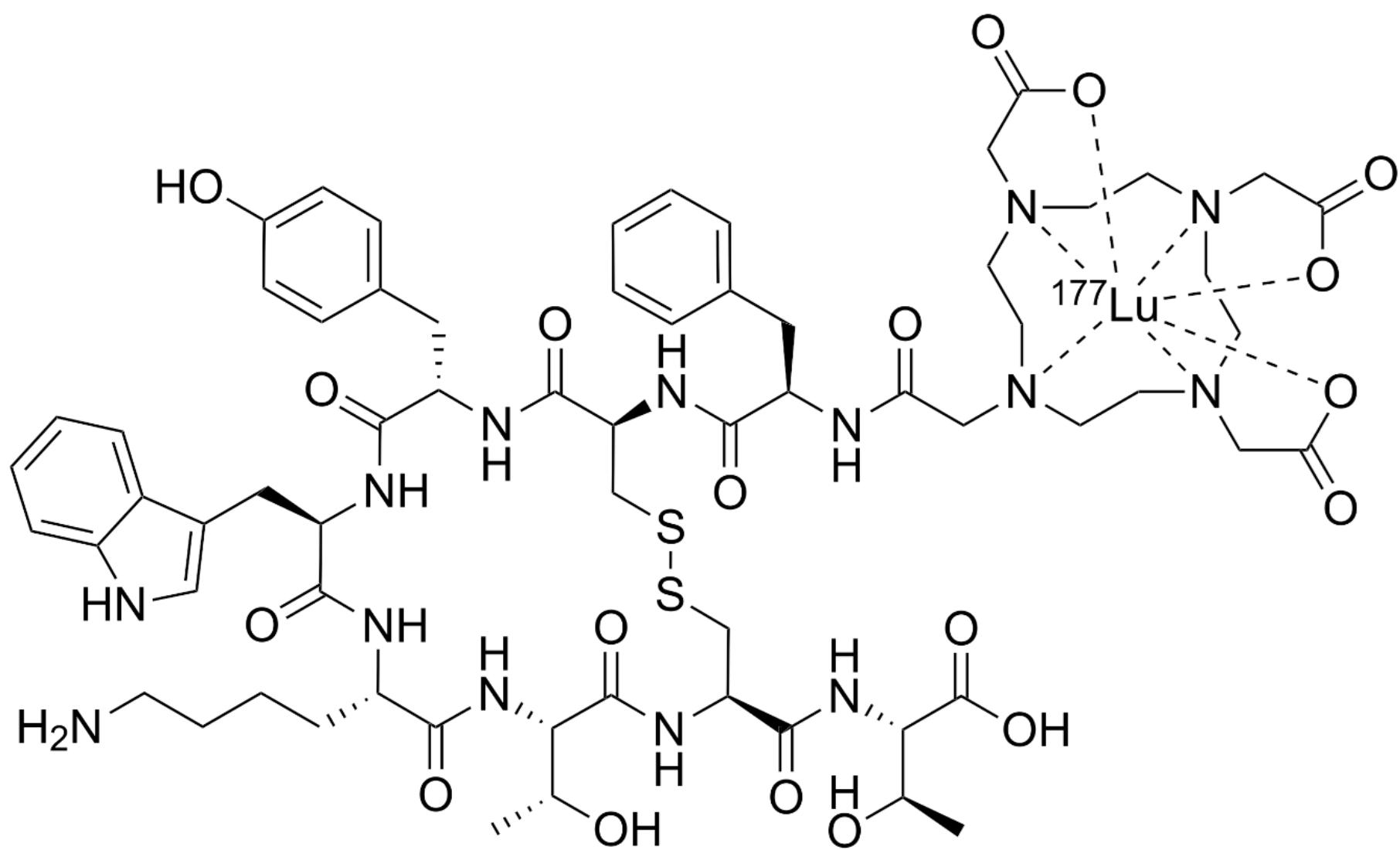


Radio Pharmaceutical name

Patient: Patient name
Patient number 01-10-1974 112,5 kg 195 cm

Exam: Examination name
07-10-2015 10000 MBq @ 11:39 20 ml

IRIS Injector www.comecer.com



LUTATHERA® injection experience

National Cancer
Institute Pascale
Foundation



Radioactivity injection flow: 15mL\min
Saline injection flow: 10mL\min



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How to avoid extravasation of ^{177}Lu -DOTATATE

• REFERENCES:

- Tylski P, Pina-Jomir G, Bournaud-Salinas C, Jalade P. Tissue dose estimation after extravasation of ^{177}Lu -DOTATATE. EJNMMI Phys. 2021 Mar 31;8(1):33. doi: 10.1186/s40658-021-00378-3. PMID: 33788043; PMCID: PMC8012450.
- Reynolds PM, MacLaren R, Mueller SW, Fish DN, Kiser TH. Management of extravasation injuries: a focused evaluation of noncytotoxic medications. Pharmacotherapy. 2014 Jun;34(6):617-32. doi: 10.1002/phar.1396. Epub 2014 Jan 13. PMID: 24420910.

Radioactivity injection flow: **15mL\min**
Saline injection flow: **10mL\min**

Total time: 20 minutes

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