OŚRODEK PRODUKCJI I BADANIA RADIOFARMACEUTYKÓW W ŚRODOWISKOWYM LABORATORIUM CIĘŻKICH JONÓW – STAN AKTUALNY I PERSPEKTYWY

Jarosław Choiński
Środowiskowe Laboratorium Ciężkich Jonów
Uniwersytet Warszawski

SEMINARIUM FIZYKI JĄDRA ATOMOWEGO, WYDZIAŁ FIZYKI, UNIWERSYTET WARSZAWSKI
7.11.2019 R.

Plan

- historia powstania OPBR
- zainstalowana aparatura
- projekty badawcze nad radioizotopami i radiofarmaceutykami
- perspektywy rozwoju ośrodka w najbliższych latach

historia powstania OPBR

- **grudzień 2000 r.**

decyzja o budowie ośrodka produkcji radiofarmaceutyków dla PET w zaadoptowanych pomieszczeniach ŚLCJ

zespół:

Jerzy Jastrzębski – pomysłodawca i kierujący projektem do 2010 r.

Paweł Napiorkowski – „starszy nad budżetem”

Jarosław Choiński – współodpowiedzialny za projekt (2008 – 2010) a następnie samodzielnie kierujący projektem od 1 marca 2010 do III kw. 2014 r.

14.07.2005

MAEA ogłasza przetarg na adaptację części budynku ŚLCJ i dostawę wyposażenia dla Warszawskiego Ośrodka Produkcji Radiofarmaceutyków PET

11.11.2005

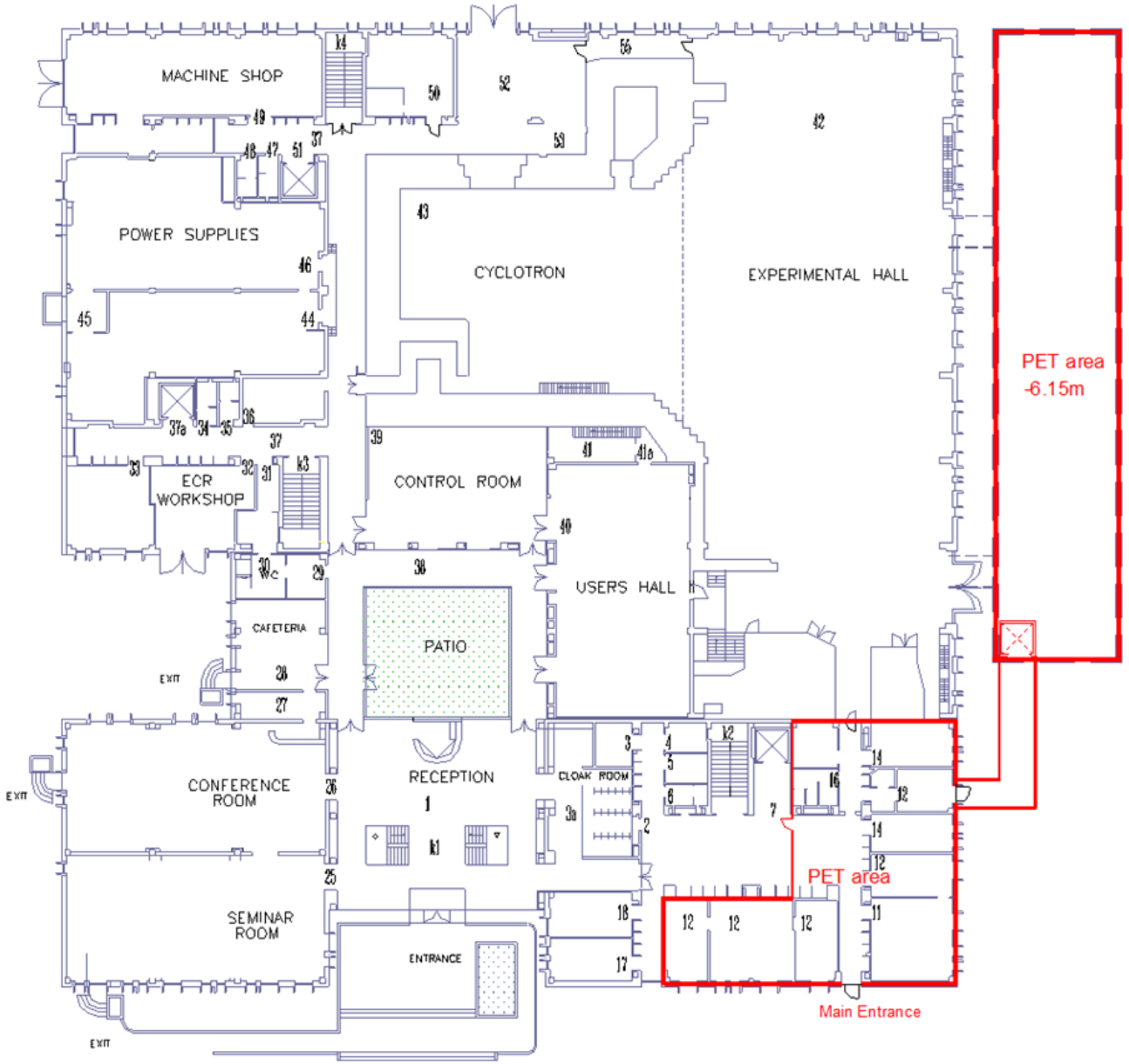
rozstrzygnięcie przetargu

17.02.2006

MAEA oficjalne ogłasza zwycięzcę przetargu spółkę

GE Medical Systems Société en commandite Simple

23.10.2007 uroczyste podpisanie kontraktu „pod klucz”

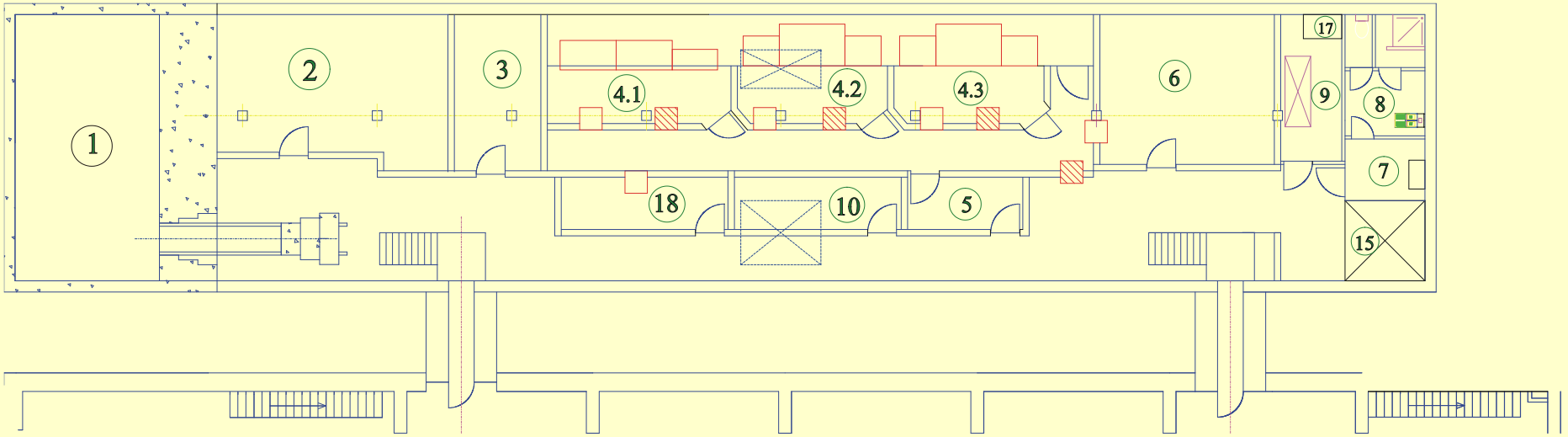


GROUND-FLOOR 0.00 m

Ruszają prace budowlane w 2008 r.

19.10.2010	**w Wiedniu odbyło się posiedzenie przedstawicieli UW – MAEA – GEMS**
	Dyskutowano harmonogram prac i termin zakończenia projektu
27.10.2010	Podpisanie Aneksu nr I do Umowy budowlanej pomiędzy UW a GEMS; Podpisującymi byli: ze strony UW Prorektor **M. Pałys** a ze strony GEMS **Dimitri TSINIKAS**, General Manager i VP GE Healthcare EE oraz **Bartłomiej GRZELAK**, Commercial Finance Manager GE Healthcare NEE Przyjęto nowy harmonogram prac zaś termin zakończenia Umowy został określony na „**do dnia 22 września 2011 roku**”

Oddział produkcji radiofarmaceutyków w budynku ŚLCJ (projekt wstępny)



1. bunkier cyklotronu
2. zasilaczownia cyklotronu
3. sterownia cyklotronu

4.1 pom. z kom. gorącymi do produkcji FDG

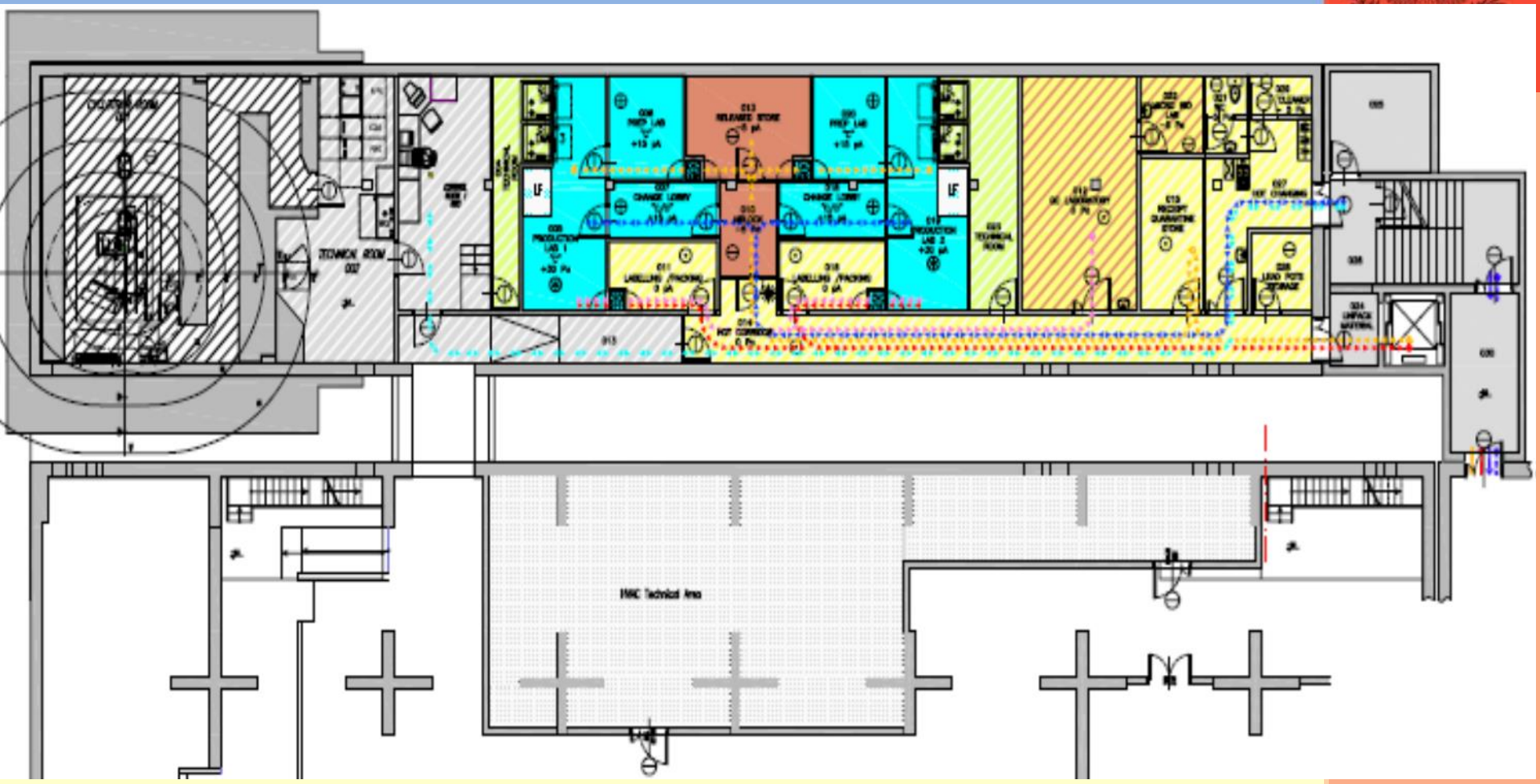
4.2 pom. z kom. gorącymi do produkcji radiofarmaceutyków zawierających ^{11}C and $^{18}F_2$

4.3 pom. z kom. gorącymi do realizacji prac R&D

5. szatnia czysta
6. pokój kontorli jakości
7. szatnia “brudna”
8. pokój dekontaminacji z prysznicem
9. pom. do przemywania i dezynfekowania pojemników transportowych
10. pomocniczy magazyn chemiczny
15. winda
17. wyciąg chemiczny
18. Główny magazyn chemiczny

PET area	ŚLCJ
-6.15 m	J. Choiński I. Skrzeczanowska

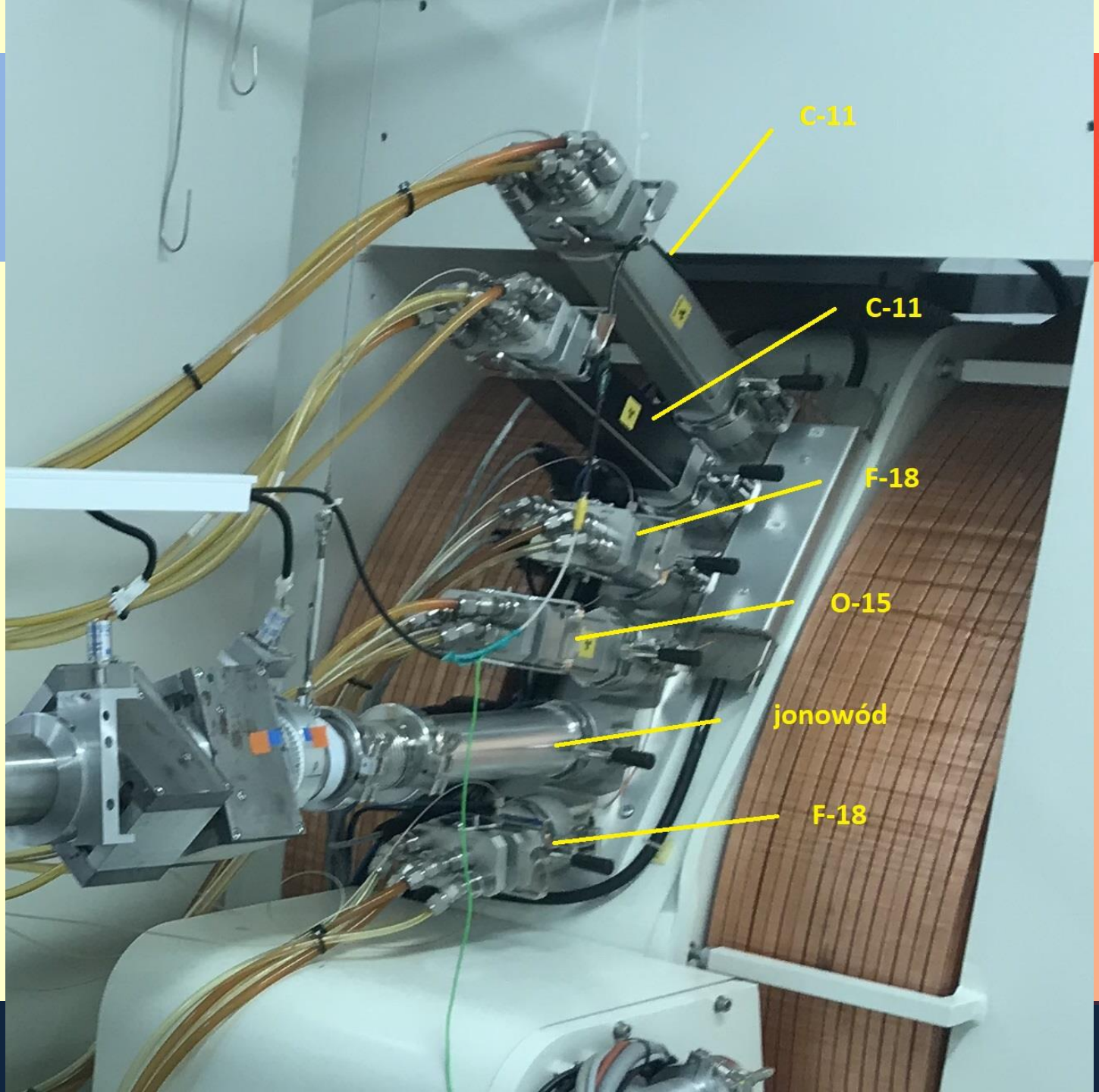
Schemat OPBR – część podziemna



zainstalowana aparatura

cyklotron General Electric PETtrace 840 - parametry

- Proton beam on target ≥ 80 µA
- Deuteron beam on target ≥ 60 µA
- length 1.25 m
- width 1.2 m
- height 1.91 m
- electricity consumption in running mode < 70 kW
- all-up weight 20 ton


C-11
C-11
F-18
O-15
jonowód
F-18

Laboratorium produkcji FDG


Laboratorium R&D

Laboratory no 2

equipment: - 1 water O-15 unit, 1 C-11 „process unit”

3 units of C-11 synthesizers: - Synthra MeI, - Synthra MeIplus, - Synthra GPextent

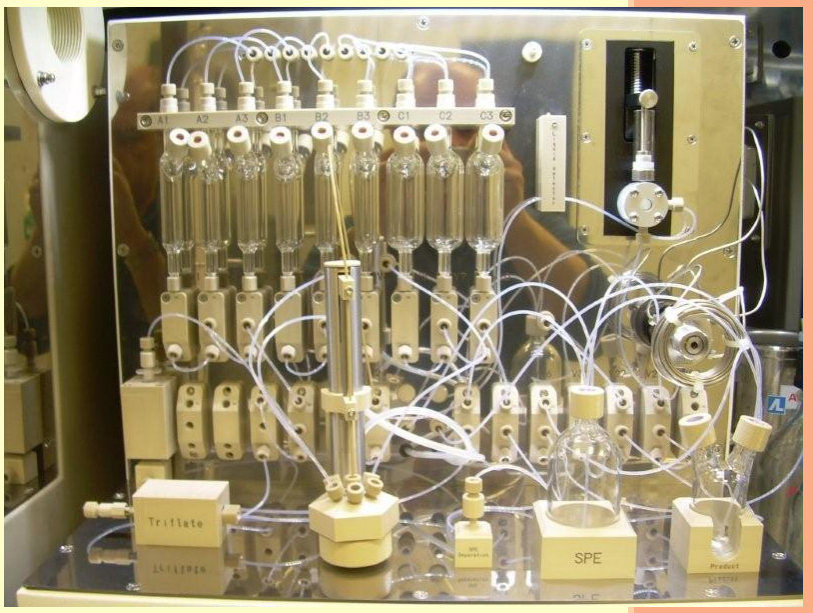
PET Radiopharmaceuticals

TRACERlab FX F-N

nucleophilic substitution with [18F] F^-

Synthra - synthesizers

methylation reactions using methyl iodide or methyl triflate



^{18}F Fluoromisonidazole

^{18}F Methylbenperidol

^{18}F Fluorostradiol

^{18}F Altanserine

^{11}C Raclopride

^{11}C Methionine

^{11}C Acetate

^{11}C Palmitate


Quality Control Lab

Instrumentation of the Quality Control Lab

HPLC Agilent with additional detector GabiStar	1 pcs.
TLC Bioscan	1 pcs.
Dose calibrator Atomlab	1 pcs.
LAL System	1 pcs.
HPLC Agilent with additional detector GabiStar	1 pcs.
GC+Headspace+Hydrogen generator+"zero-air generator"	1 pcs.
Gamma Spectrometer	1 pcs.
Analytical balance Mettler Toledo	1 pcs.
Precise (technical) Balance Radwag	1 pcs.
pHmeter Mettler Toledo	1 pcs.
Osmometer Knauer	1 pcs.
Water Purification system MilliQ	1 pcs.
UV-VIS Spectrometer Perkin Elmer Lambda 25	1 pcs.
FTIR Spectrometer Perkin Elmer BXII	1 pcs.
HPLC with mass spectrometer	1 pcs.
Microwave synthesizing automat	1 pcs.

Budowlanego dla m.st. Warszawy, ul. Bagatela 14, 00-585 Warszawa w terminie 14 dni od dnia doręczenia.

Z up. Powiatowego Inspektora
Nadzoru Budowlanego dla m. st. Warszawy
Kierownik I Oddziału Terenowego
Barbara Matalińska

Otrzymuje:

1. Uniwersytet Warszawski
   Ul. Krakowskie Przedmieście 26/28
   00-927 Warszawa

Do wiadomości:

1. Wydział Architektury i Budownictwa
   dla Dzielnicy Ochota
   Urząd Dzielnicy Ochota m. st. Warszawy
   Ul. Grójecka 17A
   02-021 Warszawa
2. Urząd Dzielnicy Ochota m. st. Warszawy
   Wydział Budżetowo-Księgowy
   Ul. Grójecka 17A
   02-021 Warszawa
3. a/a

Zgodnie z art. 130 § 4 - Kodeksu Postępowania Administracyjnego
Decyzja podlega wykonaniu przed upływem terminu do wniesienia
Odwołania, gdy jest zgodna z żądaniem stron.

Z up. Powiatowego Inspektora
Nadzoru Budowlanego dla m. st. Warszawy
Kierownik I Oddziału Terenowego
Barbara Matalińska
22.03.2012r

Prawomocne pozwolenie na użytkowanie

Zespół ośrodka PET w maju 2012 r.

dr Jarosław Choiński - kierownik projektu UW PET
prof. dr hab. Jerzy Jastrzębski – pomysłodawca projektu
dr Paweł Napiorkowski
dr Krzysztof Kilian
mgr inż. Ireneusz Mazur
mgr Dorota Szczepaniak
mgr Anna Pękal
mgr Izabela Cydzik

projekty badawcze nad radioizotopami i radiofarmaceutykami

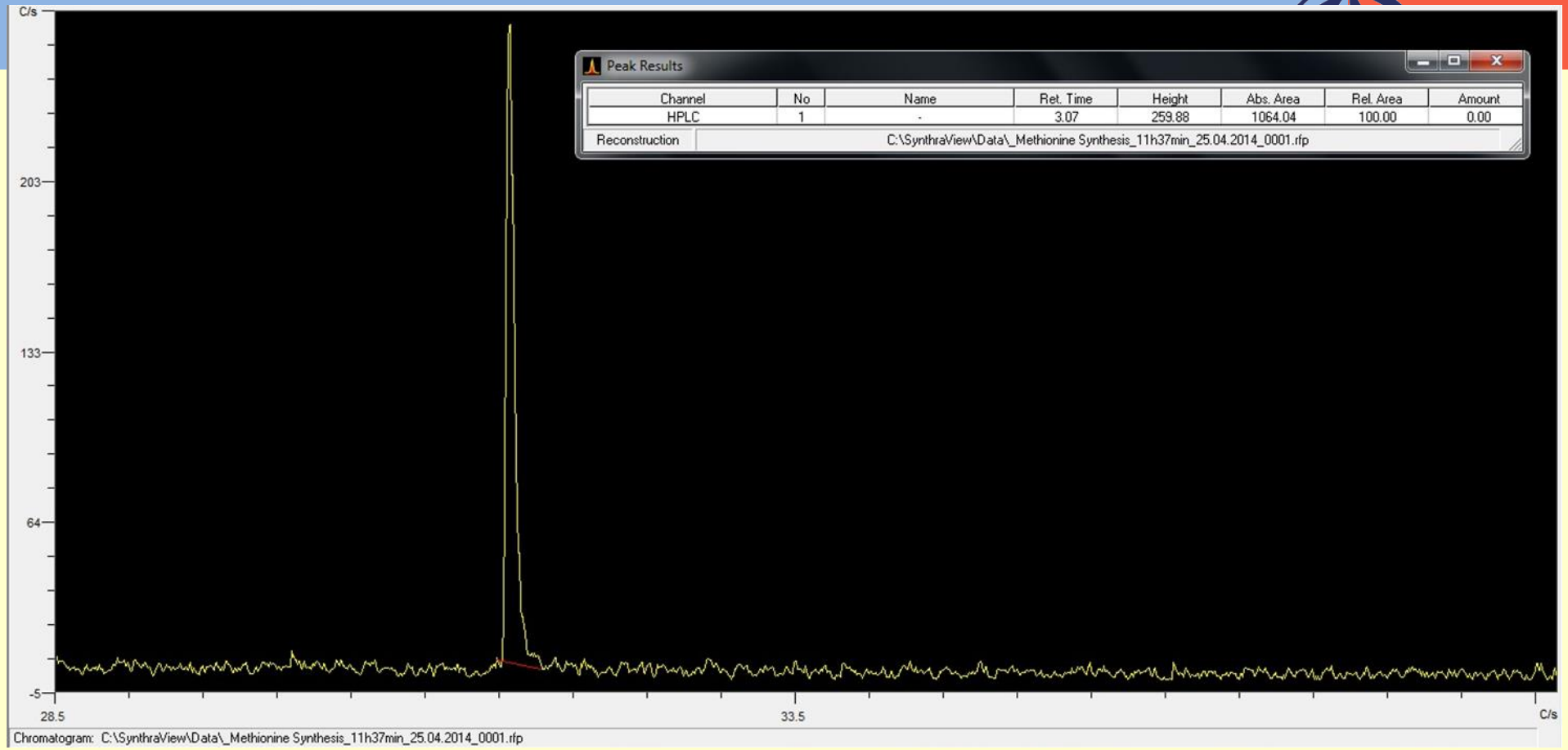
The first important aim was to establish synthesis of:

- **^{11}C-methionine**

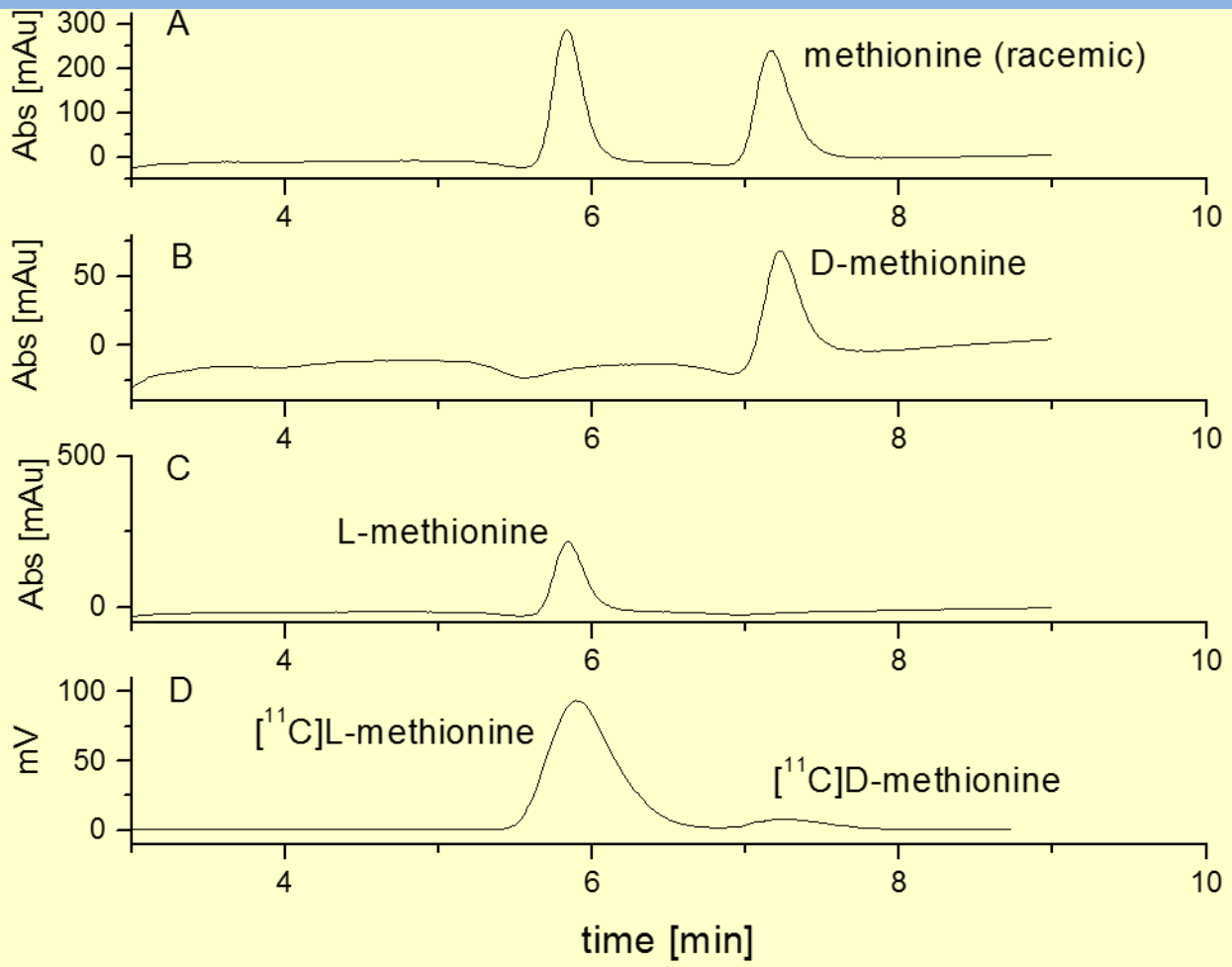
and

- **^{11}C-Carbon acetate**

Radiochemical purity



Enantiomeric purity



Alternative Methods for the ^{99m}Tc Production

Agreement No PBS1/A9/2/2012 funded by the National Centre for Research and Development

The consortium of:
the Polatom – National Centre for Nuclear Research
the Institute of Nuclear Chemistry and Technology
the University of Warsaw

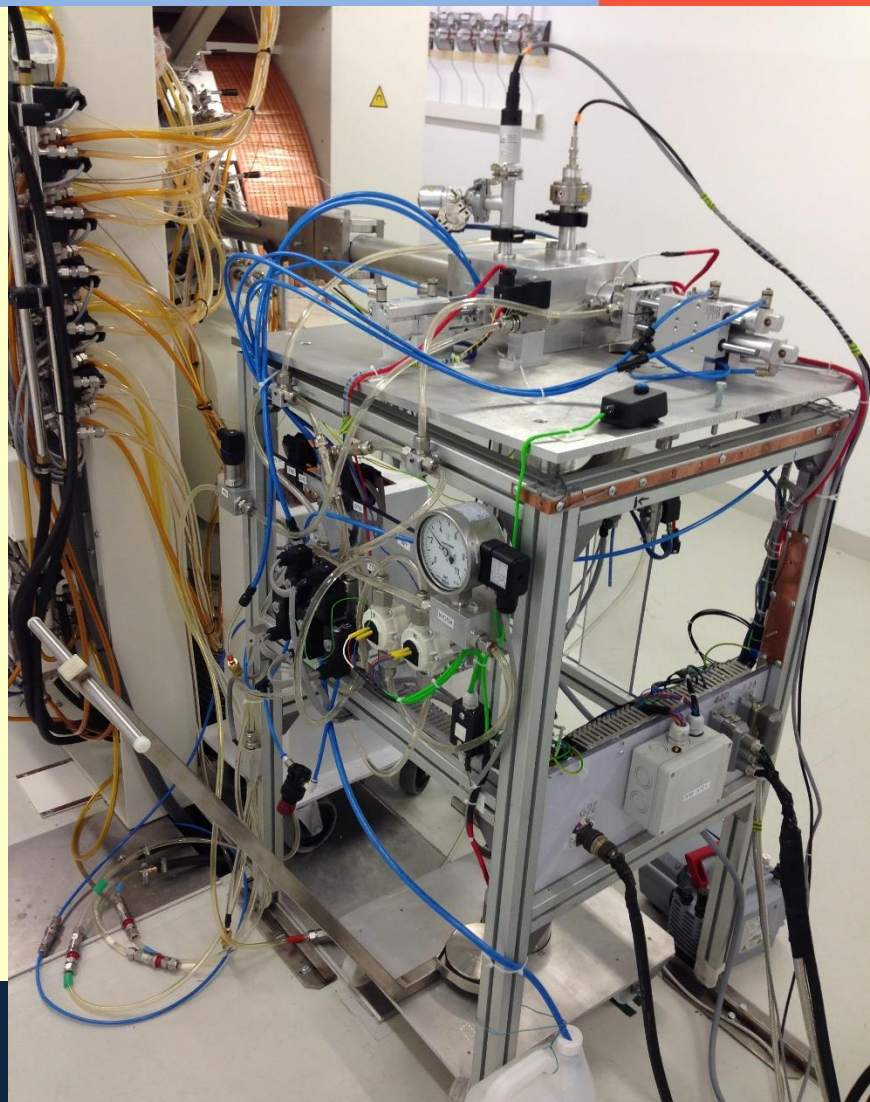
01.11.2012 – 31.10.2015

^{100}Mo(p,2n)^{99m}Tc

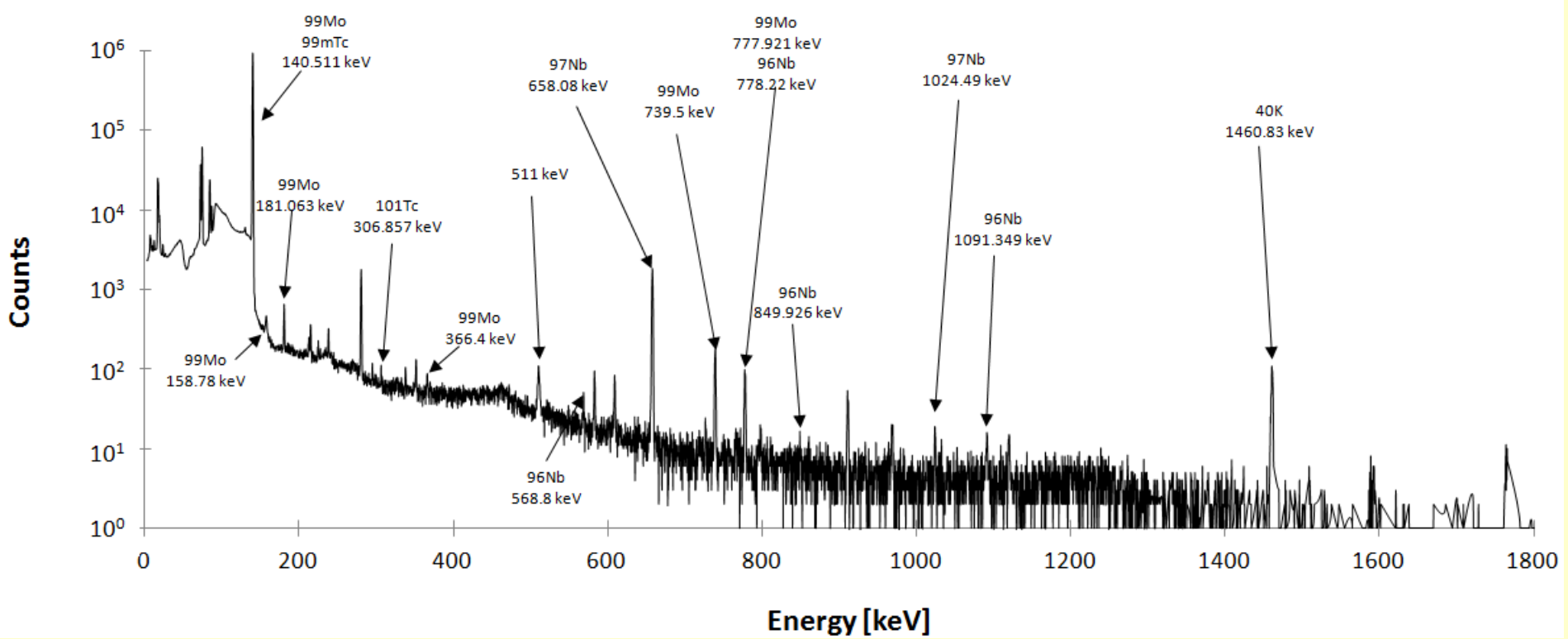
As the outcome of the ALTECH project.

The HIL team implementing this task in the project:

J. Choiński, T. Bracha, B. Radomyski, Ł. Świątek, M. Antczak, A. Jakubowski, P. Jasiński, J. Jastrzębski, R. Kopik, M. Kopka, K. Łabęda, A. Pietrzak

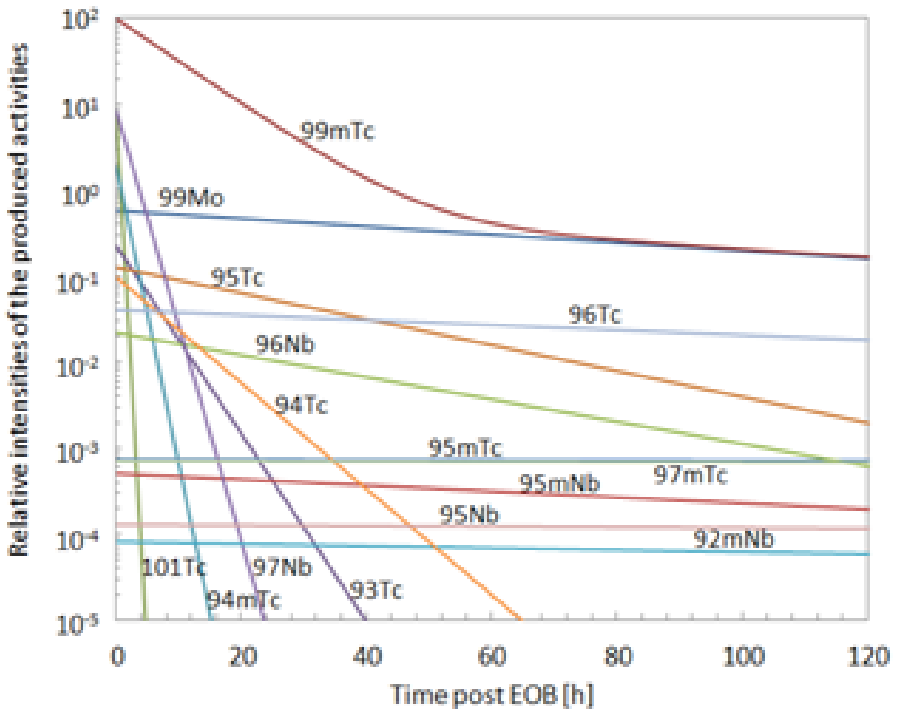


Gamma-ray spectrum of 99.815% ^{100}Mo irradiated with 16 MeV protons during 6h



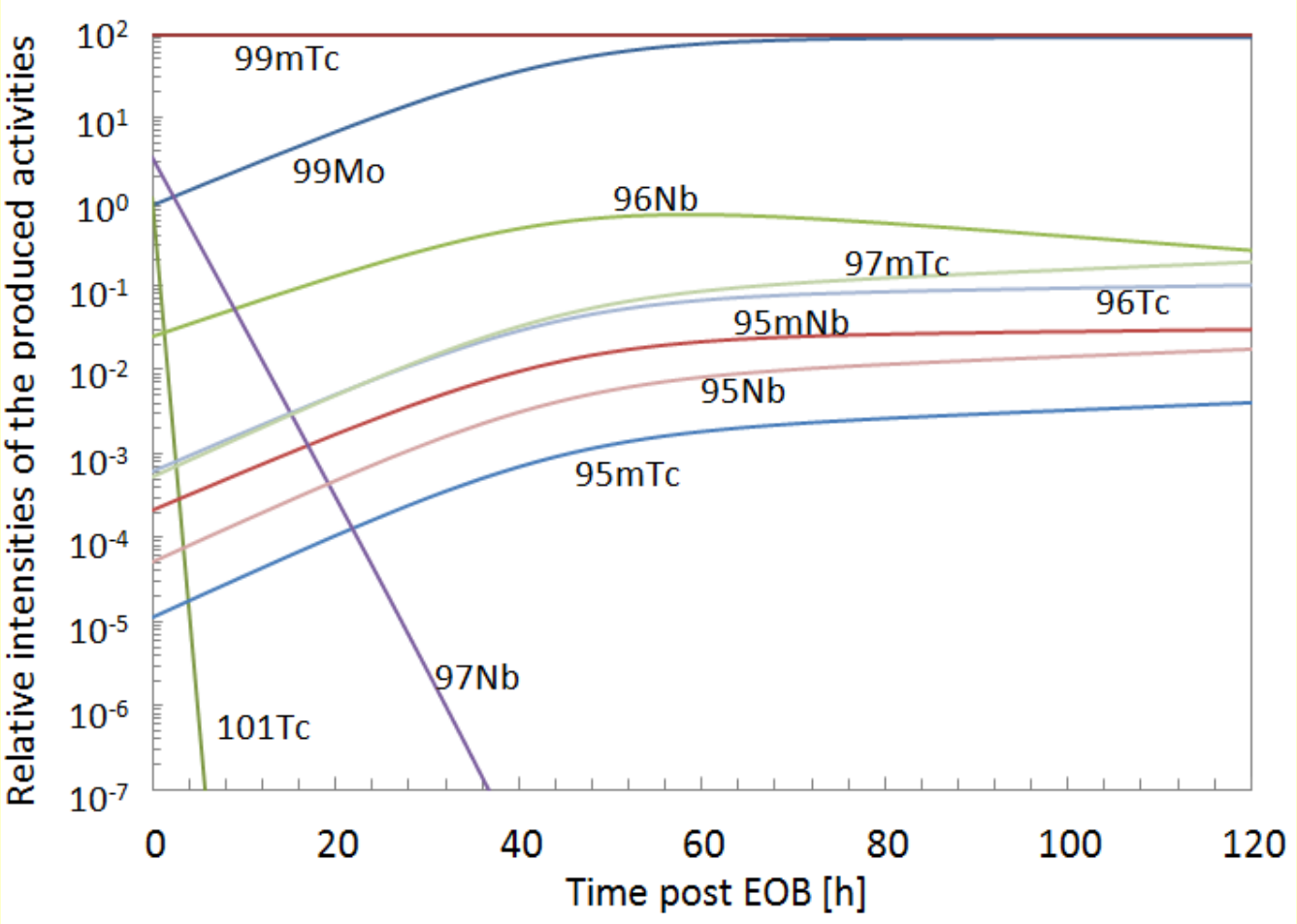
Gamma ray spectrum obtained with a HPGe detector placed at 93.5 cm distance from the ^{100}Mo (99.815%) target with thickness of 373.98 mg/cm^2 irradiated during 6 h by proton particles of 16 MeV energy and the intensity of 22 nanoamp. Beginning of the measurement 1.95 h after EOB. Measurement time 0.26 h.

Activity balance (1)



Activity balance of technedium radioisotopes as a function of time after a 0.05 h irradiation of a thick target at 16-8 MeV

Activity balance (2)



Activity balance of technetium radioisotopes as a function of time after a 6 h irradiation of a thick target at 16-8 MeV

Since 2015 till Oct 2018 we executed the grant ***"The development of methods for production of new radiopharmaceuticals based on Sc radionuclides used in positron tomography (PET)" [PET-SKAND]*** agreement no PBS3/A9/28/2015 awarded to a consortium, and financed by the National Centre for Research and Development.

Production of:

$^{43}Ca(p,n)^{43}Sc$

$^{42}Ca(d,n)^{43}Sc$

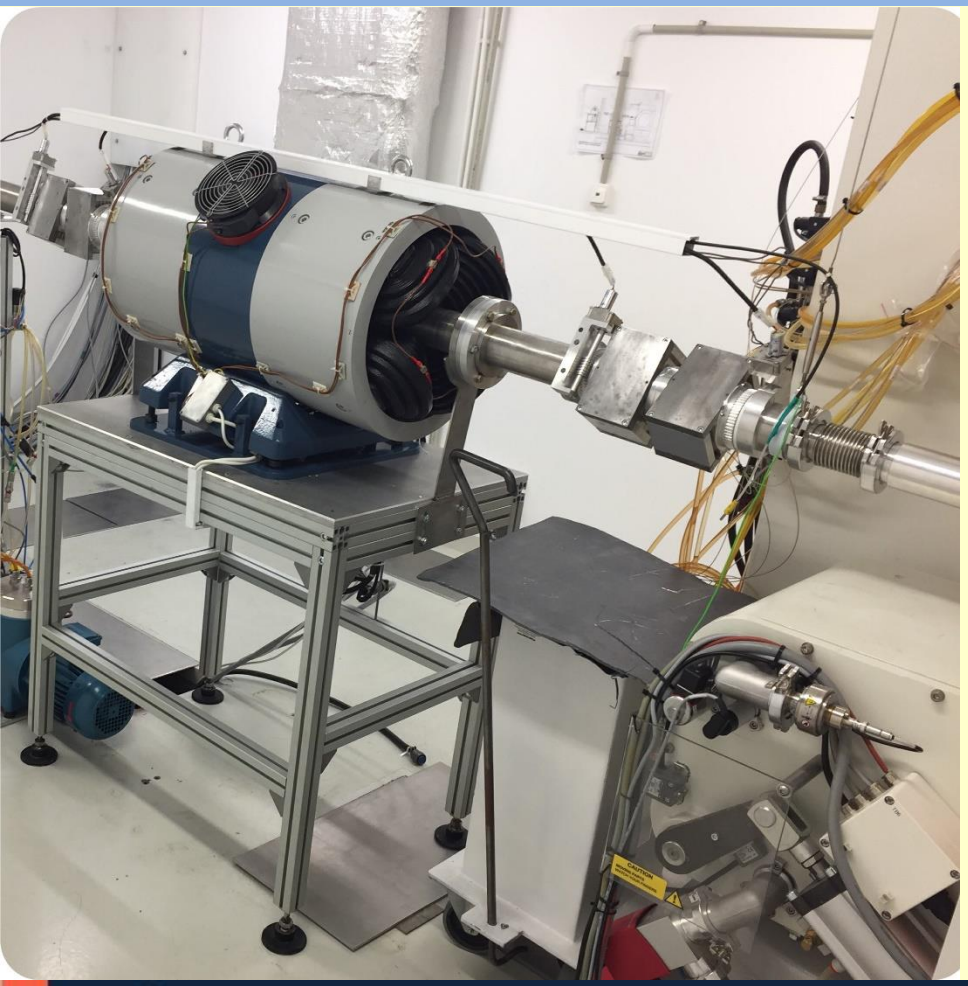
$^{44}Ca(p,n)^{44}Sc$

consortium of:
the Institute of Nuclear Chemistry and Technology
the Polatom – National Centre for Nuclear Research
the University of Warsaw

A standalone external target system at Radiopharmaceuticals Production and Research Center at HIL UW

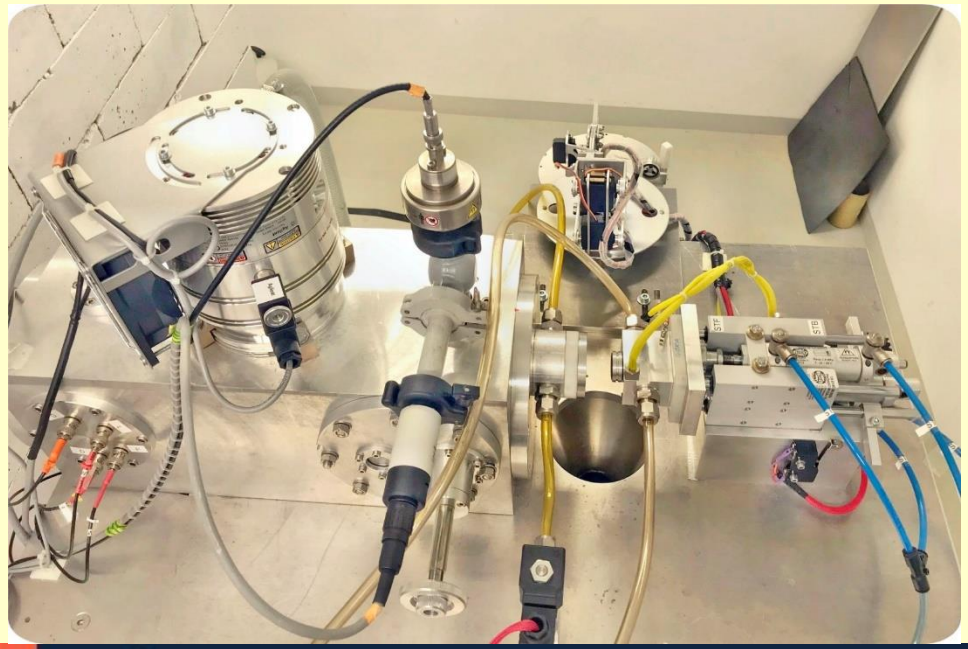
It is protected by RP patent No. 227402

A standalone external target system has been upgraded.

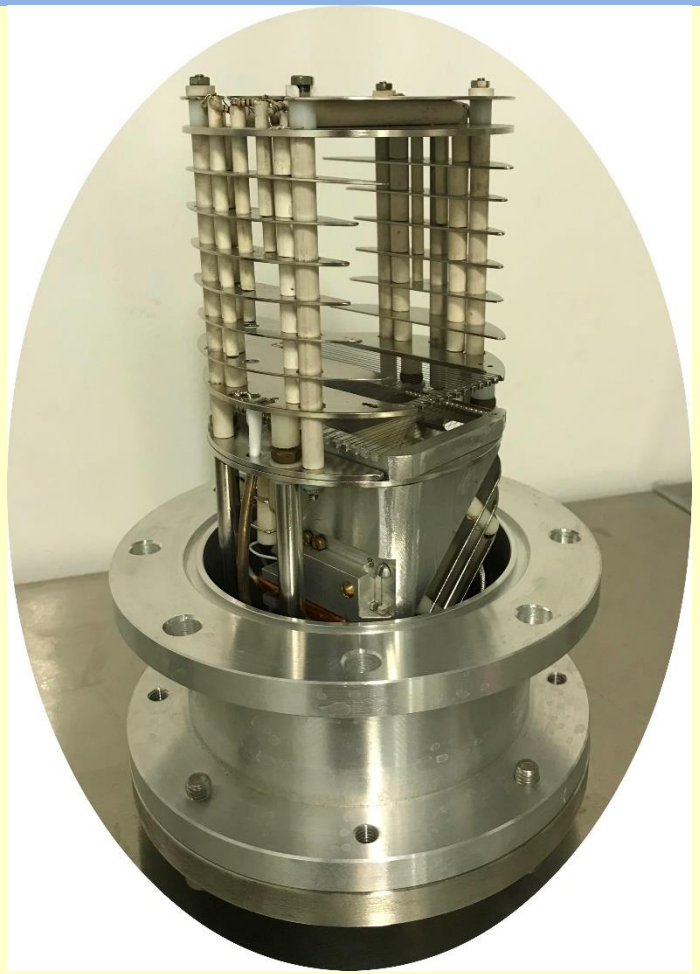


The beam line:

- length 340 cm,
- one electro-magnetic quadruple dublet and
- four correction magnets made of permanent magnets;

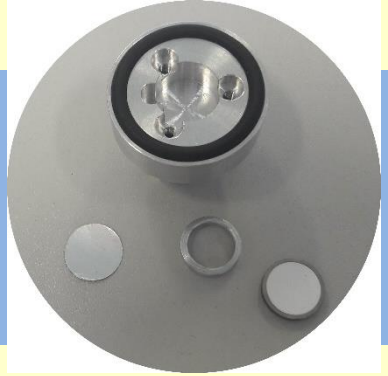


- a vacuum chamber equipped with a diagnostic system consisting of a tantalum collimator and a Faraday cup and with its complete, autonomous vacuum system; the tantalum collimator consists of four independent electrodes;
- a target chamber;
- a helium cooling system of the vacuum window;
- a water cooling system of the Faraday cup;
- a water cooling system of the target chamber;
- a compressed air system;
- a robot that loads targets to the target chamber;
- an autonomous control system;



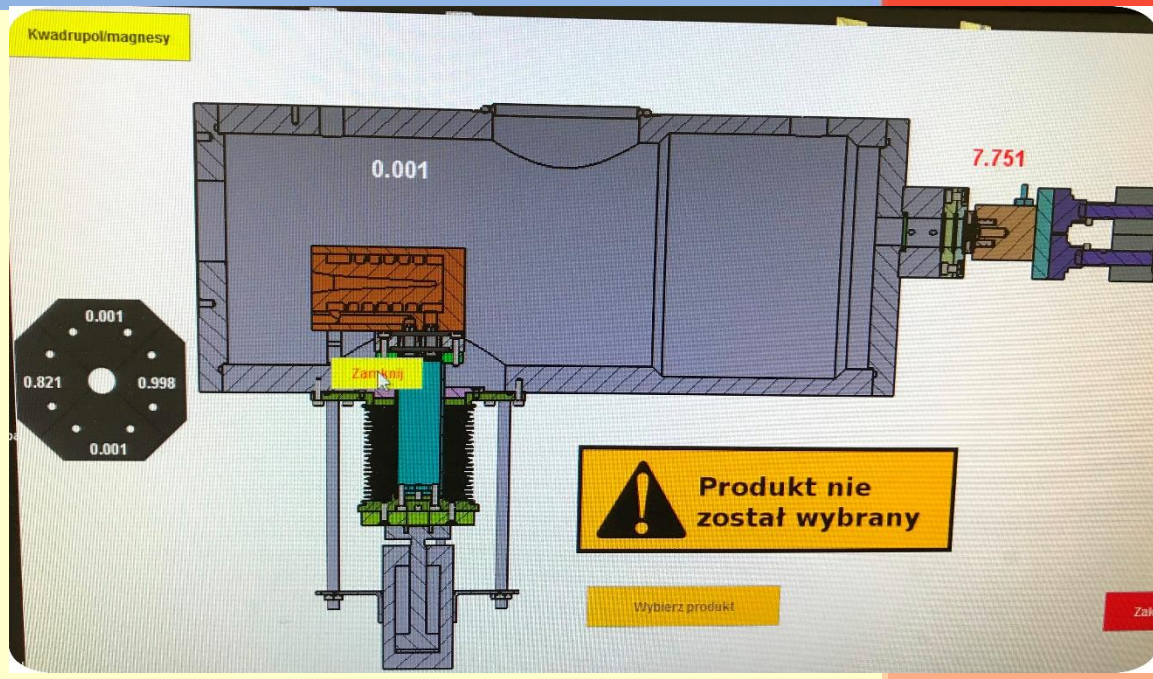
Ionization Beam Profile Monitor

collaboration with Dubna group of prof. A.S. Fomichev, FLNR, JINR, the head of the sector 6



$CaCO_3$ target
courtesy of Anna Stolarz

Target after irradiation



GUI

The objective of this system is the production of different isotopes from metallic or powder targets.

References:

The Radiopharmaceuticals Production and Research Centre established by the Heavy Ion Laboratory of the University of Warsaw
Choiński J. et al.
Conference: International Nuclear Physics Conference (INPC) Location: Firenze, ITALY Date: JUN 02-07, 2013
INPC 2013 - INTERNATIONAL NUCLEAR PHYSICS CONFERENCE, VOL. 2 Book Series: EPJ Web of Conferences Volume: 66 Article Number: 10003 Published: 2014

Synthesis, quality control and determination of metallic impurities in ^{18}F-fludeoxyglucose production process
Krzysztof Kilian et al.
Reports of Practical Oncology and Radiotherapy 1 9 (2 0 1 4) S22–S31

A fast method for the determination of residual solvents in ^{18}FDG and ^{11}C-methionine samples
Krzysztof Kilian et al.
Microchemical Journal 115 (2014) 95–99

Radiopharmaceutical Production for PET Imaging in Poland
Choiński J.
Conference: 2nd Symposium on Positron Emission Tomography Location: Krakow, POLAND Date: SEP 21-24, 2014 ACTA PHYSICA POLONICA A Volume: 127 Issue: 5 Pages: 1520-1522 Published: MAY 2015

Medical Radioisotopes Produced Using the Alpha Particle Beam from the Warsaw Heavy Ion Cyclotron
Szkliniarz K. et al.
Conference: 2nd Symposium on Positron Emission Tomography Location: Krakow, POLAND Date: SEP 21-24, 2014 ACTA PHYSICA POLONICA A Volume: 127 Issue: 5 Pages: 1471-1474 Published: MAY 2015

Cyclotron production of 43Sc-new radionuclide for PET technique
Bilewicz A. et al.
Conference: 28th Annual Congress of the European-Association-of-Nuclear-Medicine (EANM) Location: Hamburg, GERMANY Date: OCT 10-14, 2015
EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING Volume: 42 Supplement: 1 Pages: S196-S197 Meeting Abstract: OP478 Published: OCT 2015

Gold Nanoparticle-Substance P(5-11) Conjugate as a Carrier for ^{211}At in Alpha Particle Therapy
Bilewicz A. et al.
Conference: 28th Annual Congress of the European-Association-of-Nuclear-Medicine (EANM) Location: Hamburg, GERMANY Date: OCT 10-14, 2015
EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING Volume: 42 Supplement: 1 Pages: S245-S245 Meeting Abstract: OP584 Published: OCT 2015

Cyclotron production of Sc-43 for PET imaging
Walczak R. et al.
EJNMMI PHYSICS Volume: 2 Issue: 1 Article Number: 33 Published: DEC 2015

Synthesis of Endogenous Compounds Labeled with ^{11}C for Positron Emission Tomography
Krzysztof Kilian et al.
ACTA PHYSICA POLONICA A, Vol. 127 (2015), No. 5

Production yield and isotopic purity of medical Sc radioisotopes formed by proton, deuteron and alpha particle beams
Sitarz M. et al.
Conference: Annual Congress of the European-Association-of-Nuclear-Medicine (EANM) Location: Barcelona, SPAIN Date: OCT 15-19, 2016
EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING Volume: 43 Supplement: 1 Pages: S200-S200 Meeting Abstract: OP675 Published: OCT 2016

Cyclotron production of theranostic pair Sc-43-Sc-47 on calcium targets
Bilewicz A.; et al.
Conference: Annual Congress of the European-Association-of-Nuclear-Medicine (EANM) Location: Barcelona, SPAIN Date: OCT 15-19, 2016
EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING Volume: 43 Supplement: 1 Pages: S135-S136 Meeting Abstract: OP445 Published: OCT 2016

Production of medical Sc radioisotopes with an alpha particle beam
Szkliniarz K. et al.
APPLIED RADIATION AND ISOTOPES Volume: 118 Pages: 182-189 Published: DEC 2016

The fast method of Cu-porphyrin complex synthesis for potential use in positron emission tomography imaging
Krzysztof Kilian et al.
Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 159 (2016) 123–127

Imaging of hypoxia in small animals with ^{18}F fluoromisonidasole
Krzysztof Kilian et al.
NUKLEONIKA 2016;61(2):219-223

Distribution and separation of metallic and radionuclidic impurities in the production of ^{18}F-fluorodeoxyglucose
Krzysztof Kilian et al.
J Radioanal Nucl Chem (2016) 307:1037-1043

Synthesis of 11C-methionine through gas phase iodination using Synthra MeIPlus synthesis module
Krzysztof Kilian et al.
NUKLEONIKA 2016;61(1):29-33

Manufacturing and characterization of molybdenum pellets used as targets for Tc-99m production in cyclotron
Cieszykowska I. et al.
APPLIED RADIATION AND ISOTOPES Volume: 124 Pages: 124-131 Published: JUN 2017

Production efficiency and radioisotopic purity of Tc-99m formed using the (p, 2n) reaction on a highly enriched Mo-100 target
Szkliniarz K. et al.
Conference: 12th Workshop of the European-Cyclotron-Network (CYCLEUR) held together with the 2nd Bern Cyclotron Symposium Location: Bern, SWITZERLAND Date: JUN 23-24, 2016
the 2nd Bern Cyclotron Symposium Location: Bern, SWITZERLAND Date: JUN 23-24, 2016

Targets for Production of the Medical Radioisotopes with alpha and proton or deuteron Beams
Stolarz A. et al.
PROCEEDINGS OF THE 28TH WORLD CONFERENCE OF THE INTERNATIONAL NUCLEAR TARGET DEVELOPMENT SOCIETY (INTDS2016) Book Series: AIP Conference Proceedings Volume: 1962

Ga(III) complex with morin for kidney cancer cell labelling
Sentkowska A. et al.
Appl Organometal Chem. 2017;e3882. https://doi.org/10.1002/aoc.3882

Separation of Sc-44 from Natural Calcium Carbonate Targets for Synthesis of Sc-44-DOTATATE
Kilian K. et al.
MOLECULES Volume: 23 Issue: 7 Article Number: 1787 Published: JUL 2018

Production of Sc medical radioisotopes with proton and deuteron beams
Sitarz M. et al.
APPLIED RADIATION AND ISOTOPES Volume: 142 Pages: 104-112 Published: DEC 2018

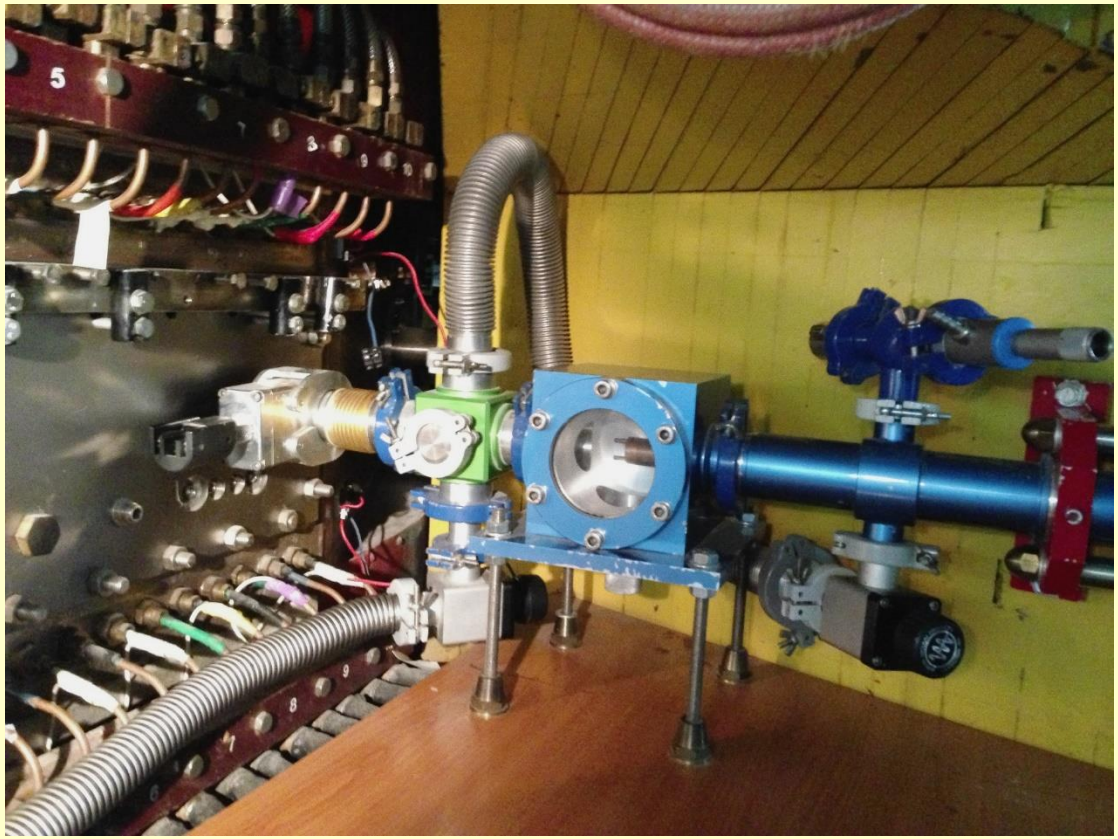
Influence of metal ions on the ^{44}Sc-labeling of DOTATATE
Walczak R. et al.
Journal of Radioanalytical and Nuclear Chemistry (2019) 322:249–254, https://doi.org/10.1007/s10967-019-06700-9

Cyclotron production of scandium-44 from enriched calcium-44 targets
Wojdowska W. et al.
JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS, Volume 62, Page S572-S573, Published 2019

Improved procedures of $Sc(OH)_3$ precipitation and UTEVA extraction for ^{44}Sc separation
Wojdowska W. et al.
Nuclear Medicine Review 2019, 22, 2: 1–4

A standalone target system for internal beam irradiation U-200P

Currently the cyclotron is equipped with a simple station which was designed for other purposes then production of medical radioisotope. The range of available beam energies may be varied from a very initial up to maximal (32 MeV, 1 pμA) obtainable form the cyclotron.



Unfortunately, this station also has several shortcomings like for example a very weak water cooling system of the target and not automated operations.

Investigated medical radioisotopes

- Since several years ago, the Heavy Ion Laboratory has been involved in medical radioisotope production, mainly Astatine-211 element utilizing alfa beam from the U-200P cyclotron ...

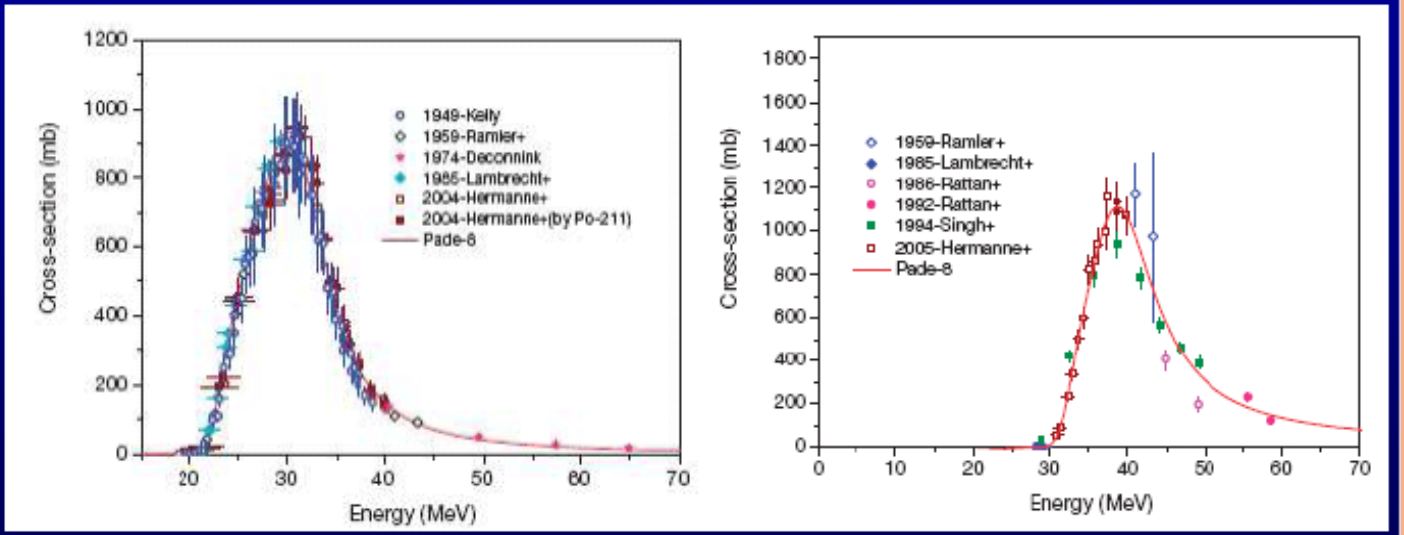
  … but also isotopes:

– ^{211}At via the reaction ^{209}Bi(α,2n); – therapeutic α
– ^{43}Sc ^{40}Ca(α,n); – diagnostic β^+
– ^{44gd}Sc ^{42}Ca(α,2n); –diagnostic β^+
  ^{44m}Sc ^{42}Ca(d,n);
– ^{72}Se/^{72}As ^{70}Ge(α,2n); – β^+generator
– ^{44}Ti/^{44}Sc ^{42}Ca(α,2n); – β^+generator

Alfa emitter – Astatine 211

Production of Astatine-211 by Irradiation of Natural Bismuth Targets

(α, 2n)^{211}At **(α, 3n)^{210}At**

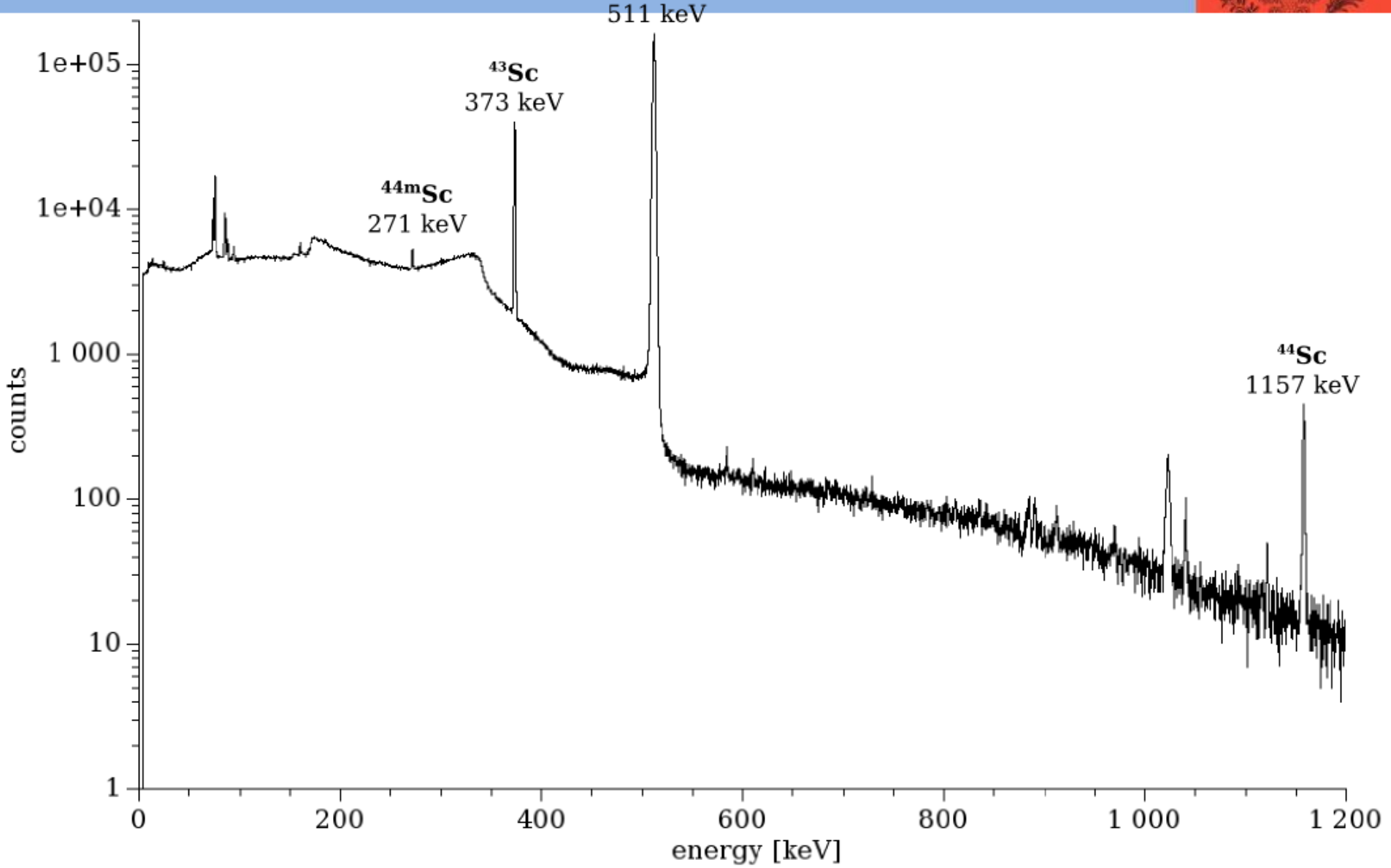


IAEA Tech Report 468, 2009

Gamma ray spectrum measured 14 h after EOB

^{nat}CaO (109.5 mg/cm^2) + Al foil (40 µm), α 32.5 MeV, 0.9 µA, 4 h 20 min

spectrum measured 14 h after EOB, time of measurement: 2 h



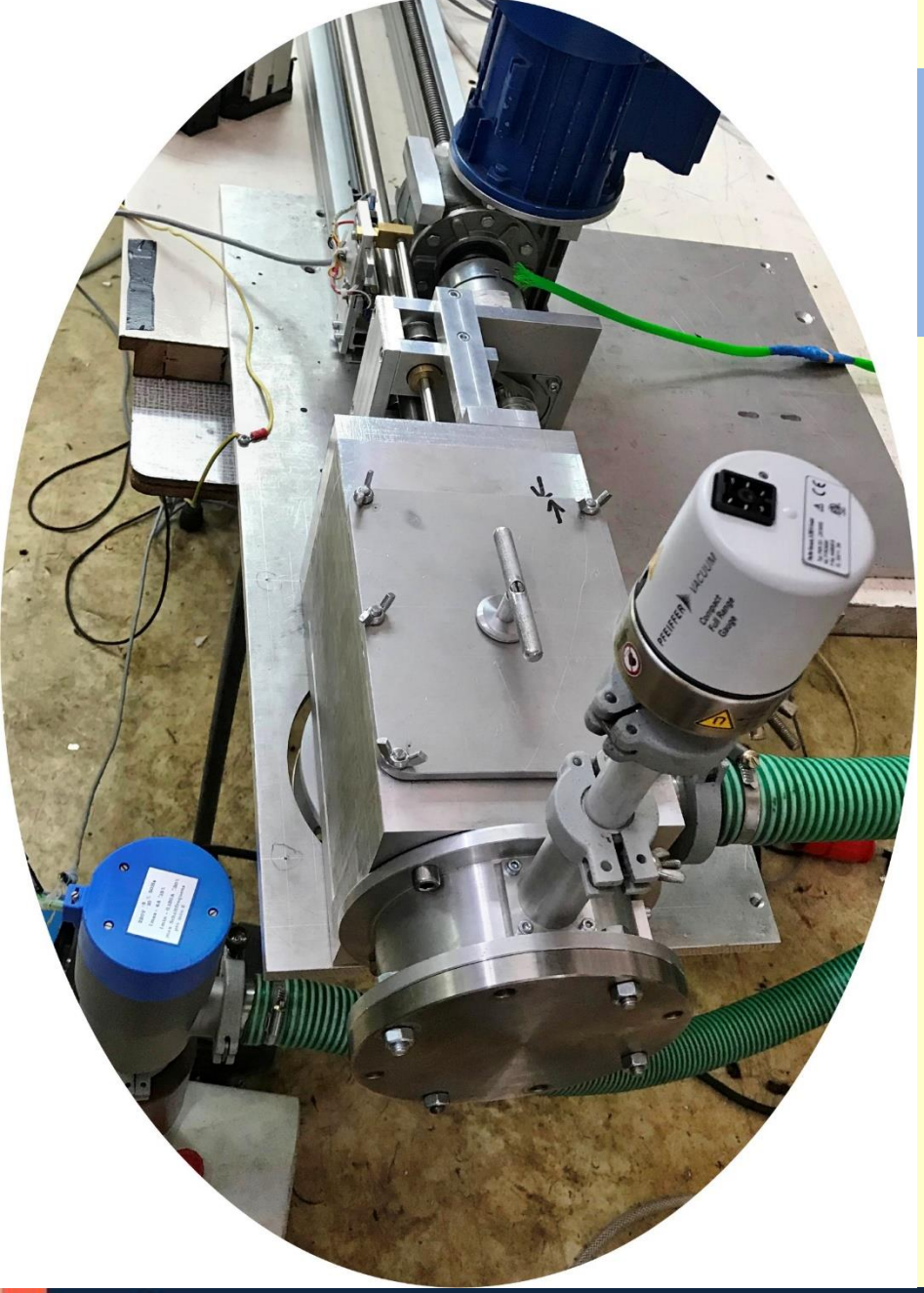
A paper target with an alfa beam shadow fixed to a target holder

Because we have noticed a need for higher beam intensities,
it was decided in 2016 to design and construct a new, well cooled target station for internal beam irradiation.

The team implementing this project:

J. Choiński, T. Bracha, B. Radomyski, Ł. Świątek, M. Antczak, A. Jakubowski, P. Jasiński, J. Jastrzębski, R. Kopik, K. Łabęda, A. Pietrzak

A tilted target with an alfa beam shadow fixed to a target holder



This station has a new vacuum chamber, a target holder with tilted target, a drive system of the target holder, a drive system of the target station. All operations can be performed remotely using a standalone PLC-based system.

Działalność dydaktyczna

- prace licencjackie
- prace magisterskie
- prace doktorskie
- habilitacje

perspektywy rozwoju ośrodka w najbliższych latach

Połączenie obu cyklotronów w celu akceleracji wiązek radioaktywnych o energiach do 10 MeV/amu

J-PET

dzięki uprzejmości prof. P. Moskala

Produkcja ^{135}La i synteza związków zawierających ten izotop

Współpraca IChTJ z ŚLCJ

Podsumowanie

Zespół zaangażowany w wytwarzanie izotopów i radiofarmaceutyków w ŚLCJ

w kolejności alfabetycznej

Tomasz Bracha
Jarosław Choiński
Andrzej Jakubowski
Jerzy Jastrzębski †
Krzysztof Kilian
Joanna Kowalska
Mateusz Pęgier
Bogdan Radomyski
Mateusz Sitarz
Anna Stolarz
Łukasz Świątek
Roman Tańczyk
Agnieszka Trzcińska

Serdecznie dziękuję za uwagę !

www.slcj.uw.edu.pl