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# OPTIMISATION OF CYCLOTRON PRODUCTION YIELD FOR RADIOMETAL OF ZIRCONIUM 89

PETIC
WALES POSITRON EMISSION TOMOGRAPHY IMAGING CENTRE
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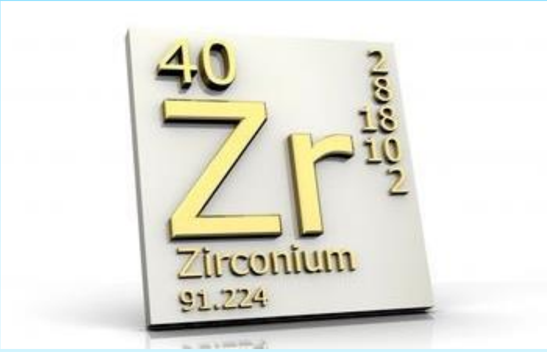
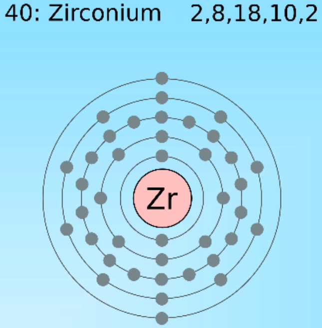
*II Symposium on Positron Emission Tomography*
*September 21th – 24th 2014, Jagiellonian University, Krakow, Poland*

# Outline:

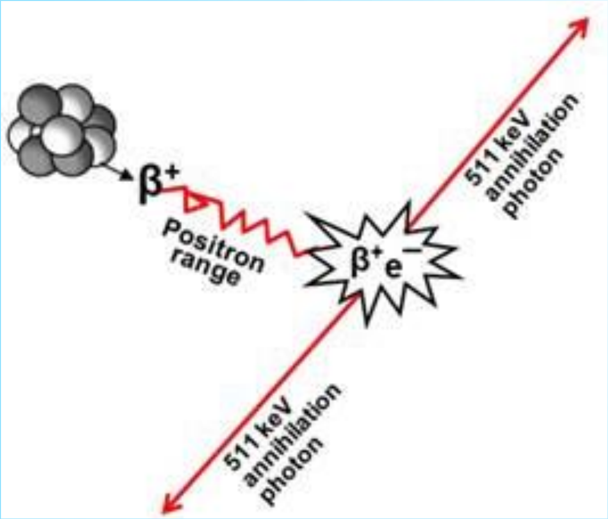
- Zirconium 89 properties and applications
- Zirconium 89 modes of production
- Materials and methods (targetry)
- Results and discussion (yield and optimisation)



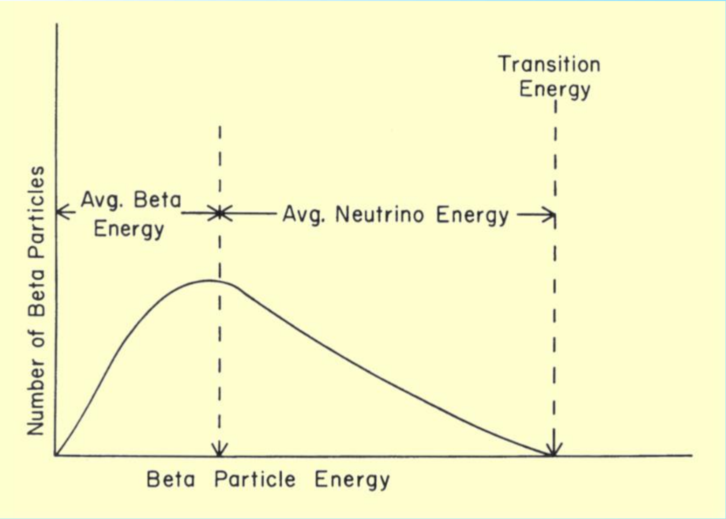




**Isotopes:** $^{90}Zr$, $^{91}Zr$, $^{92}Zr$, and $^{94}Zr$ are stable. $^{96}Zr$ is the longest lived radioisotope of Zirconium. $^{90}Zr$ is the most common. It also has 28 artificial isotopes.

## Zr-89 very important for immuno-PET:



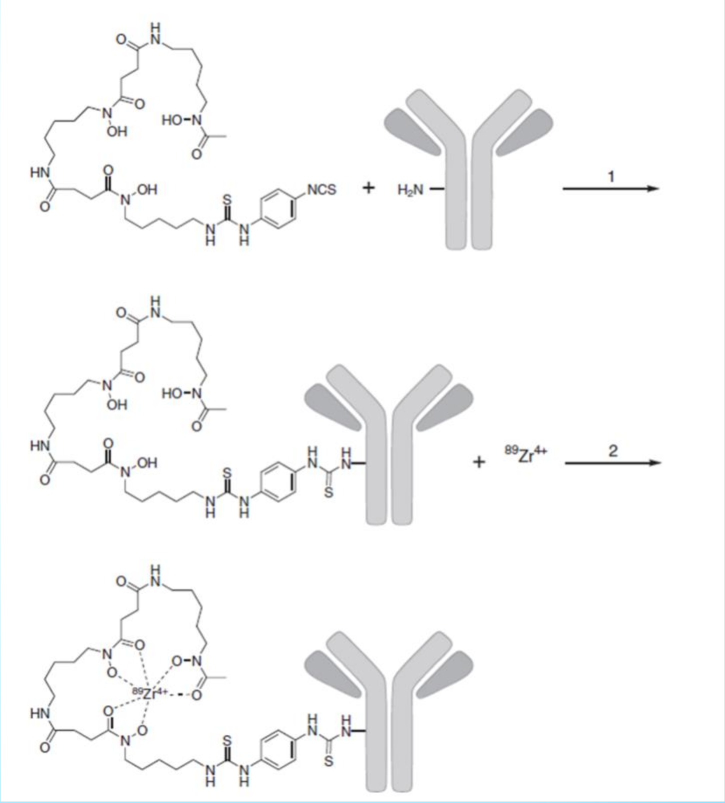

**$t_{1/2}$ 78.14 h**
**ec = 76.6%**
**$\beta^+$ = 22.3%**
**$E_{max}(\beta^+)$ = 897 keV**
**$E_{avg.}(\beta^+)$ = 396.9 keV**
**$R_{avg.}$ = 1.18 mm**
**$E_\gamma$ = 909 keV**
**$I_\gamma$ = 99%**



# Possible applications in PETIC:

- Antibody labelling

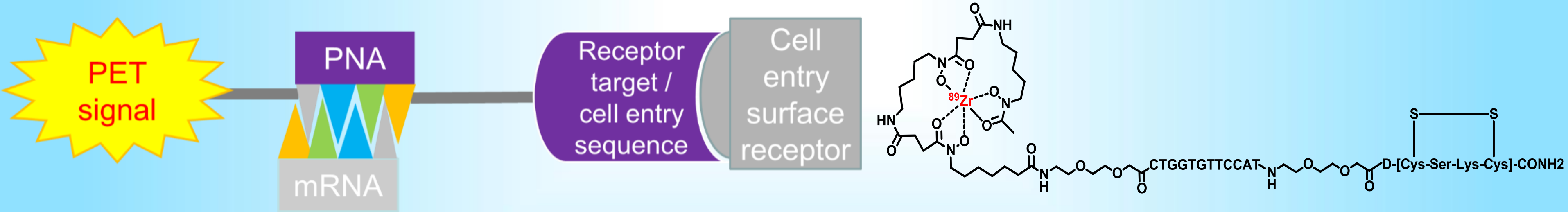
Conjugation of the $^{89}Zr$ to the antibody can be achieved by binding of the apo chelating group desferrioxamne to a lysine side chain of the antibody using a benzyl-NCS linker (37$^{o}$C, pH 9, 30 min). The $^{89}Zr$ is then mixed with the antibody-chelate conjugate at pH 7, 37$^{o}$C, 60 min. This preparation can be applied to almost any antibody allowing for rapid testing of new biological targets for PET imaging using locally developed or commercially available antibodies.



# Possible applications in PETIC:

- Targeting mRNA expression

We are also developing synthetic PNA chimeras to target mRNA expression in vivo using $^{89}$Zr as the radio tag. PNA (peptide nucleic acid) is a sequence of RNA bases connected together by a peptide backbone. An anti-sense PNA sequence will bind strongly to mRNA and is stable to degradation by RNases and proteases.

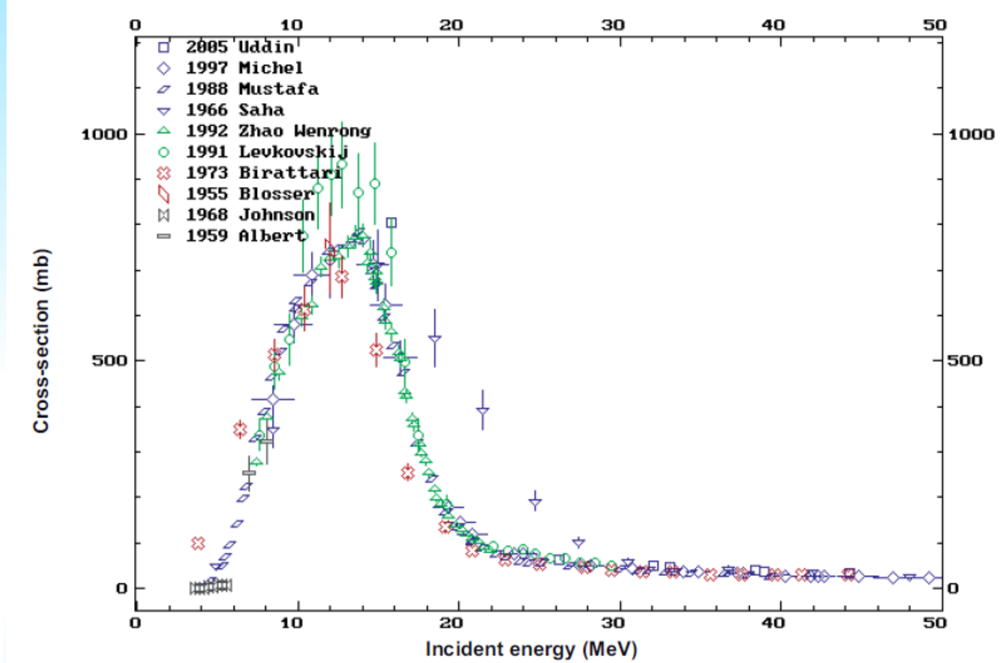



Our initial chimera design targets cyclinD1 mRNA expression and is linked to a TAT cell entry peptide sequence for use in Apc$^{f/+}$/Pten$^{-/-}$/Kras$^{mt/-}$ colon cancer mice. This flexible design adapted from Wickstrom et al coupled with our in house peptide synthesiser allows us to rapidly develop tracers to target alternative mRNA sequences.

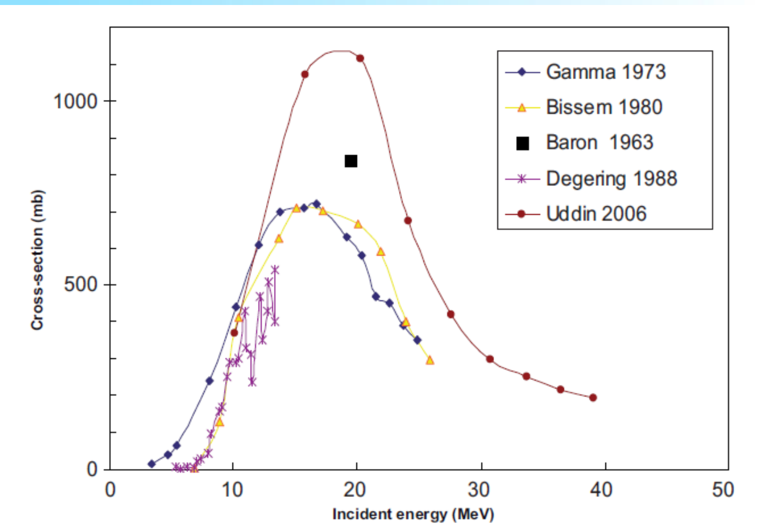
***For further information contact Dr Stephen Paisey, email: paiseysj@cf.ac.uk***
***www.medicine.cf.uk/petic***

# Nuclear reactions for Zr-89 production:

| |
|---|
| $^{89}Y(p,n)^{89}Zr$ |
| $^{89}Y(d,2n)^{89}Zr$ |
| $^{nat}Sr(\alpha,xn)^{89}Zr$ |




Excitation function for the $^{89}Y(p,n)^{89}Zr$ reaction.



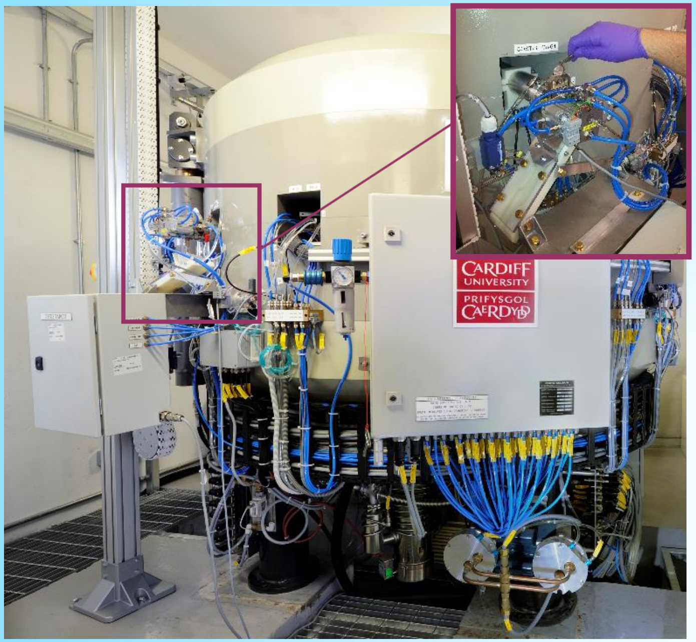

Excitation function for the $^{89}Y(d,2n)^{89}Zr$ reaction.

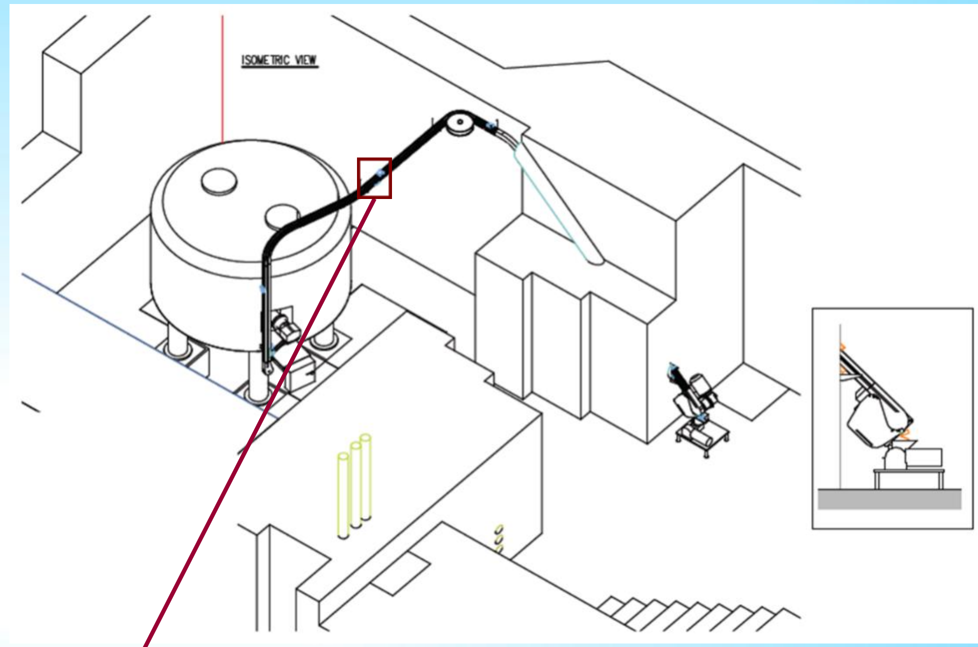
## Competing nuclear reactions:

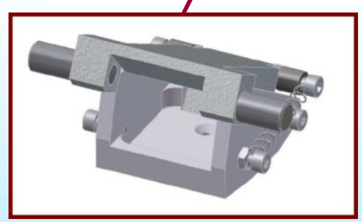
$^{89}Y(p,2n)^{88}Zr$ (>13.076 MeV, 83.4 d)

$^{89}Y(p,pn)^{88}Y$ (>11.609 MeV, 106.6 d)

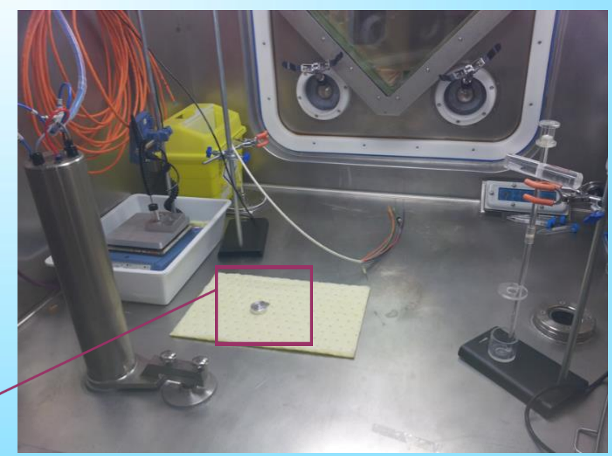
# IBA CYCLONE 18/9



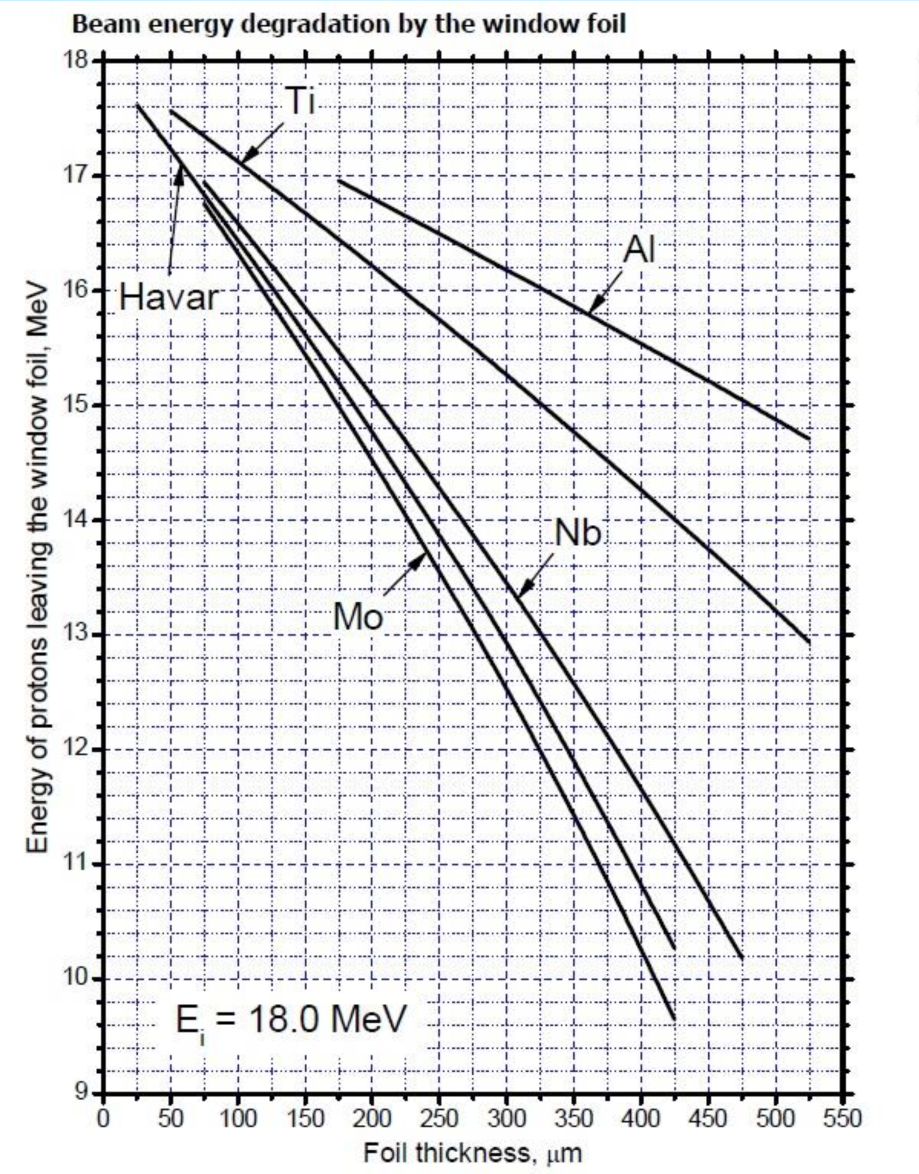


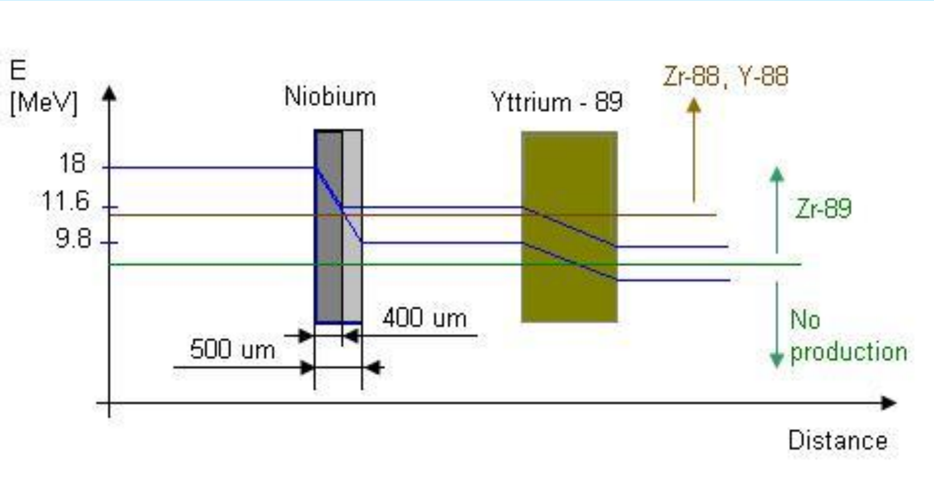



SHUTTLE RUNNING ON THE CONVEYOR BELT

# Energy degradation vs. Yield optimisation

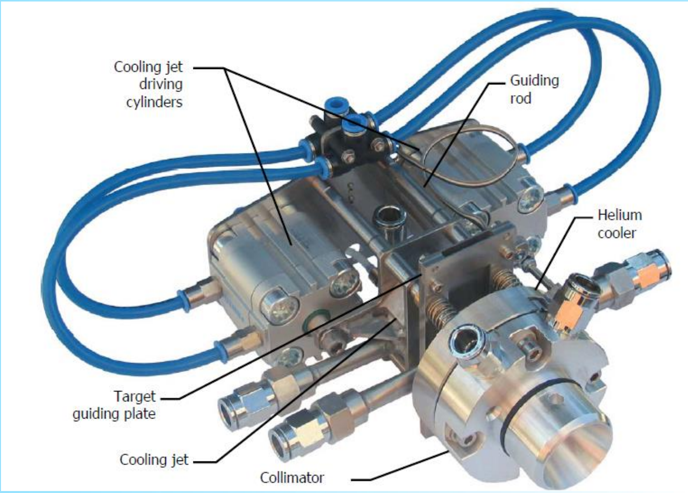


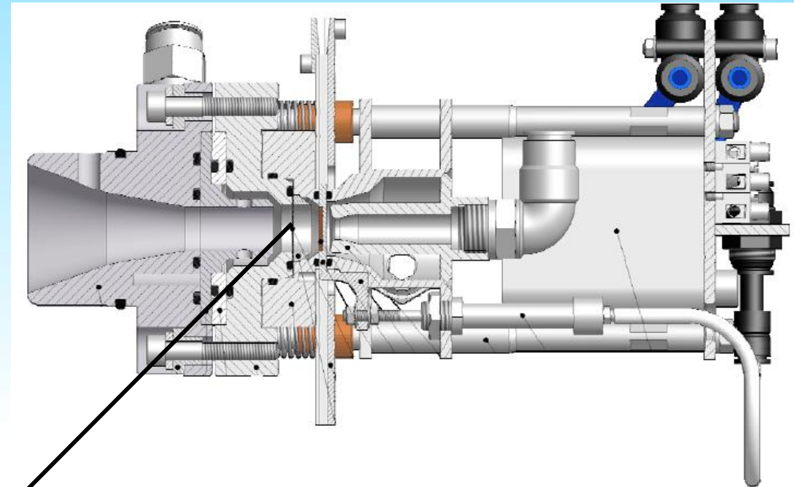



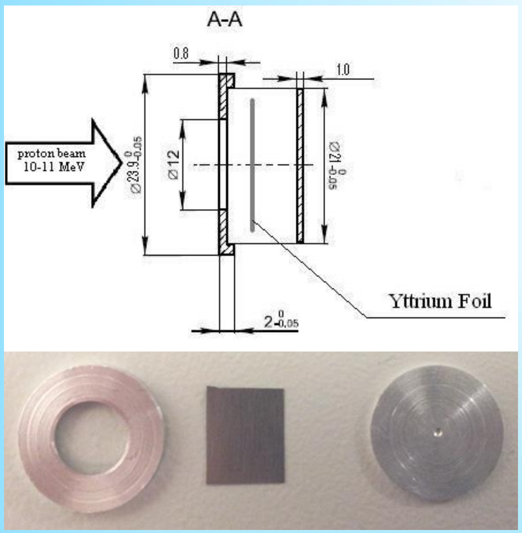

$^{89}Y(p,2n)^{88}Zr$ (>13.076 MeV)

$^{89}Y(p,pn)^{88}Y$ (>11.609 MeV)

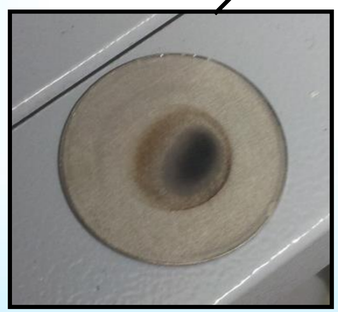
# COSTIS Solid Target System



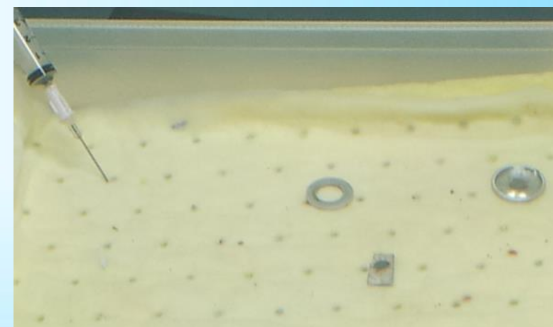






**Aluminium solid target holder (coin) with Y-89 target foil (150 μm).**

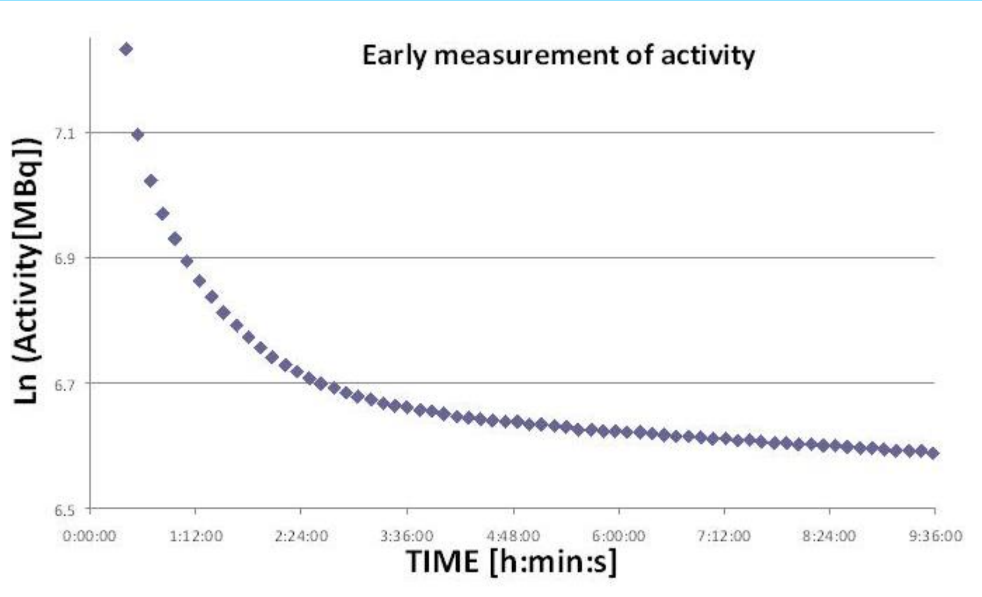


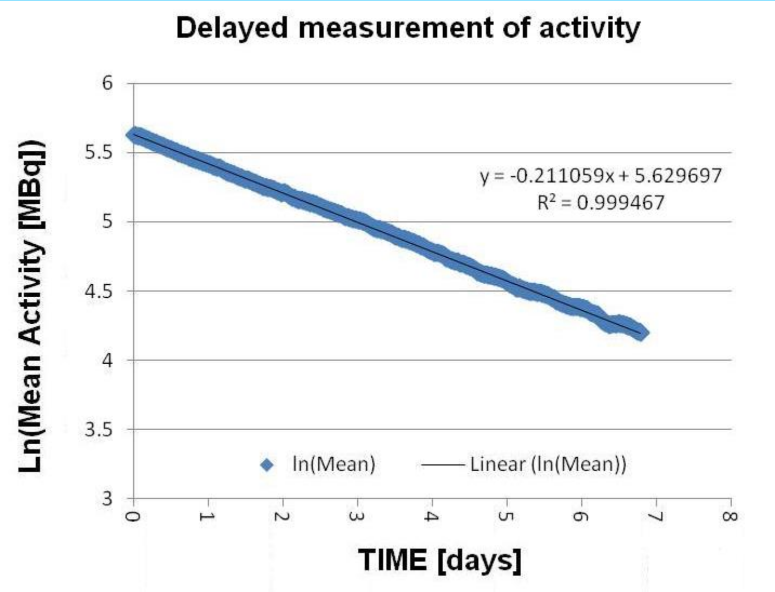
**Niobium vacuum window for the beam energy degradation (500 μm).**



**Tool for solid target opening.**

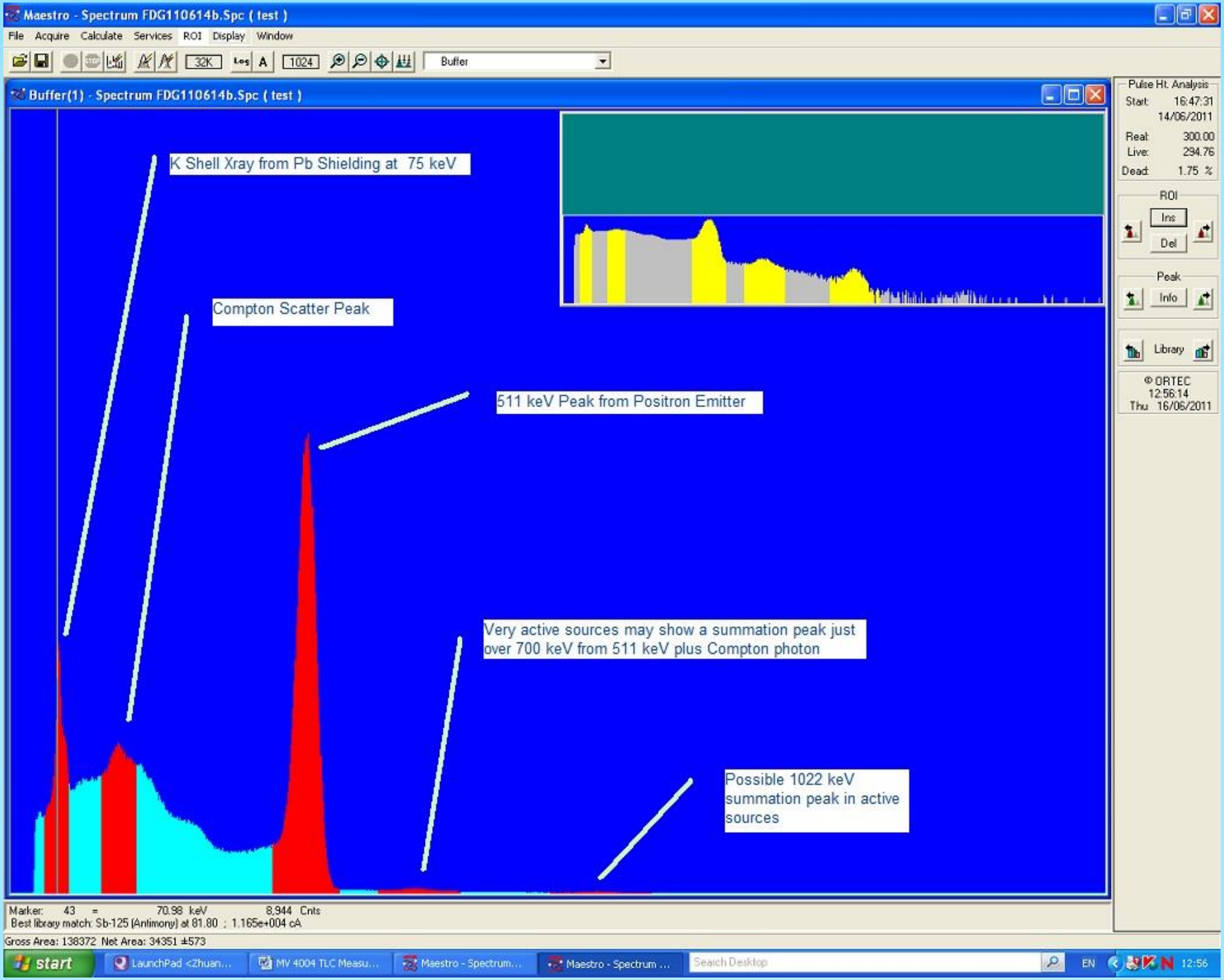
*The solid target holder used in PETIC was based on the design described by Walther et al*



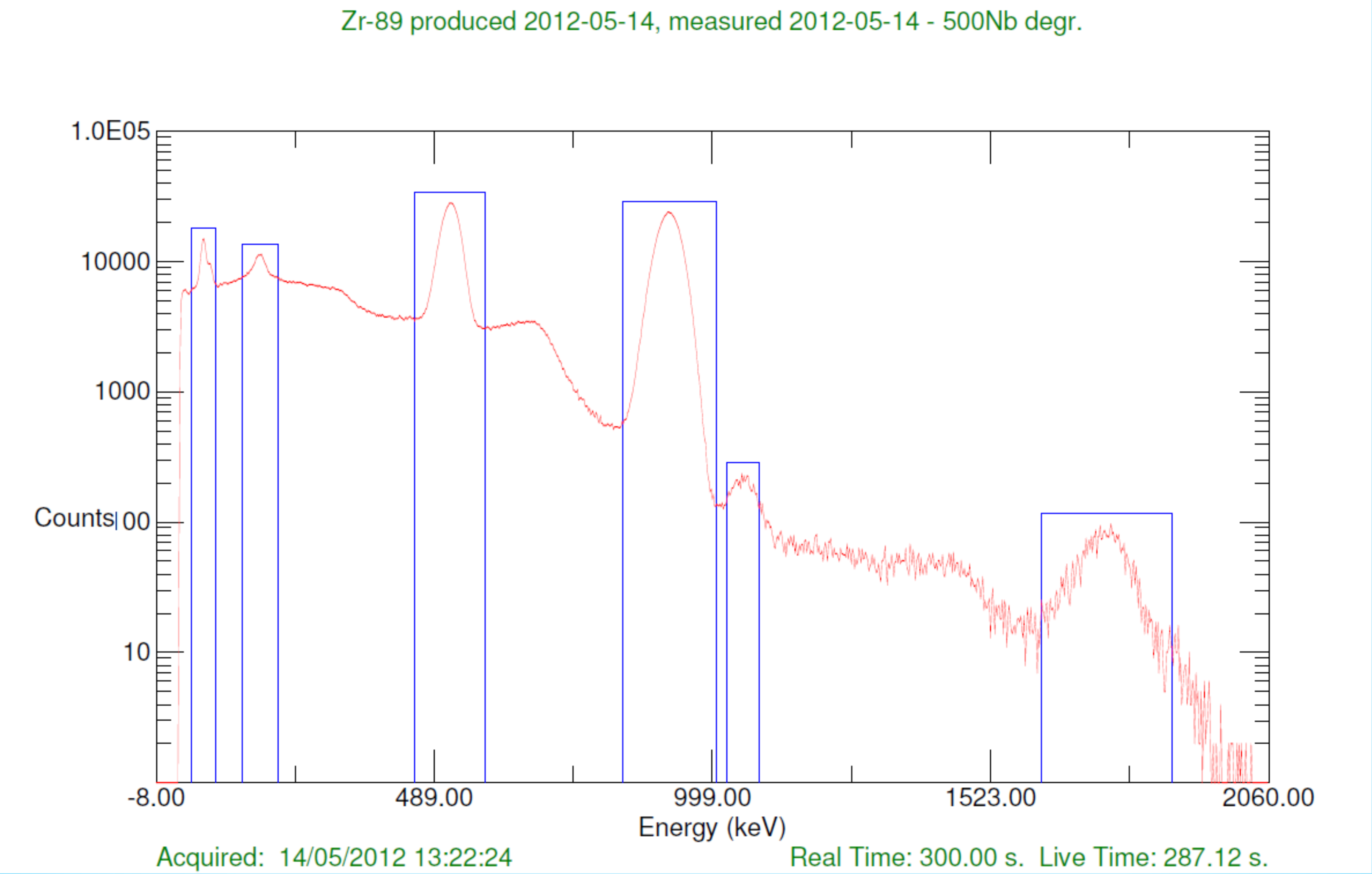




**Early measurement of Activity shows clearly that there is a bi-exponential decay of radioactivity with a short-lived radionuclide and a long-lived one.**
**This is consistent with $^{89m}Zr$ (4.16 min) and $^{89g}Zr$ (78.4 h).**
**Good base for $^{89}Zr$ activity extrapolation constitutes delayed measurement after 4h from EOB.**

*The activity of the $^{89}Zr$ produced was measured using a CRC 25R CAPINTEC Dose Calibrator set to a dial factor of 465 (490) at least four hours after the end of beam, to allow for the decay of short lived $^{89m}Zr$ which is also produced alongside $^{89}Zr$, and decay corrected to End of Beam (EOB).*




Long lived impurities were assessed using an Ortec (NaI) Multi Channel Analyser.




**Energy spectrum from $^{89}$Zr produced with 0.5 mm thick Niobium beam degrader shows the characteristic 511 and 909 keV gamma emissions from $^{89}$Zr.**

# *Expected Characteristics for:*

***$^{89}Zr$***

Half Life = 78.41 hours

Energy Spectrum

| | |
|---|---|
| 511 keV | 23% |
| 909 keV | 99% |
| 1713 keV | 0.8% |
| 1745 keV | 0.1% |
| 1657 keV | 0.1% |

***$^{88}Zr$***

Half Life = 83.4 days

Energy Spectrum

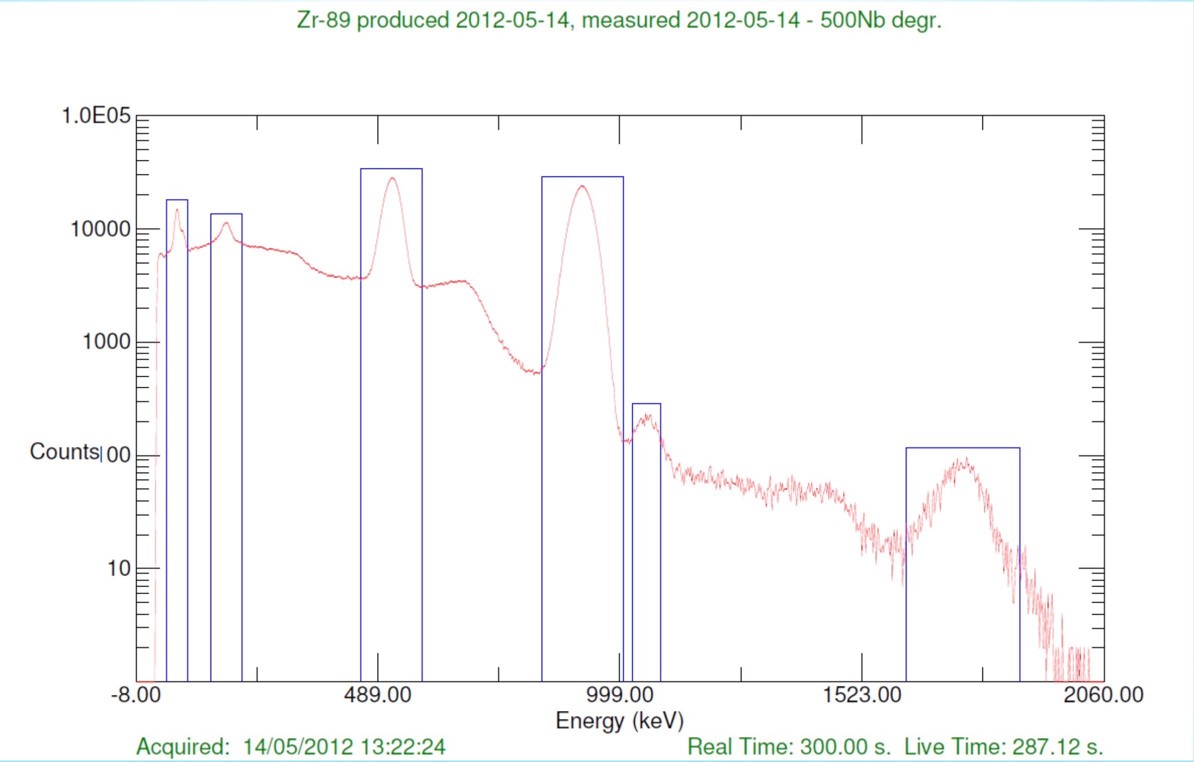
| | |
|---|---|
| 393 keV | 97% |

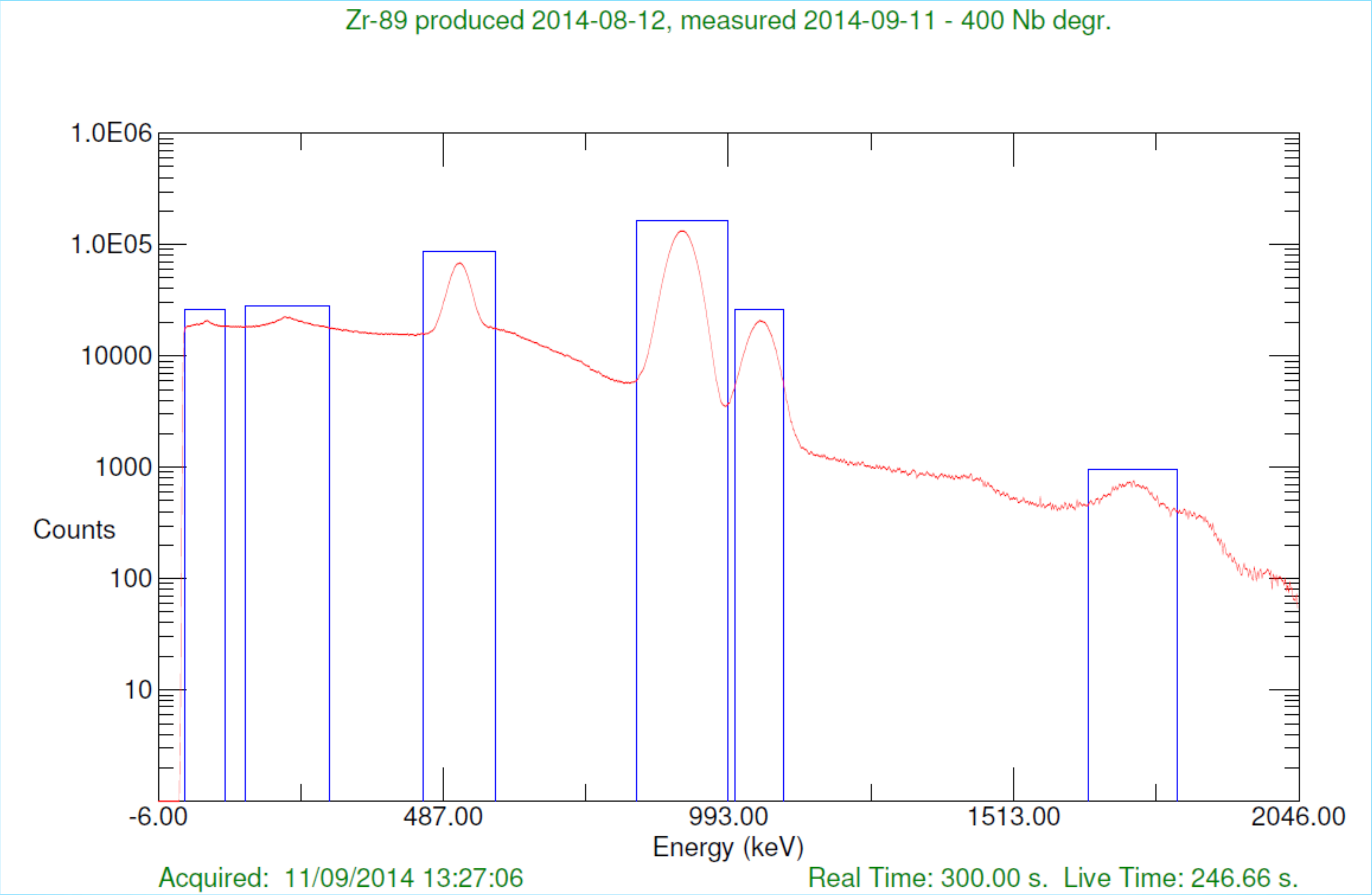
***$^{88}Y$***

Half Life = 106.6 days

Energy Spectrum

| | |
|---|---|
| 511 keV | 20% |
| 1836 keV | 99% |
| 898 keV | 94% |
| 2734 keV | 0.7% |
| 851 keV | 0.1% |






**Energy spectrum from $^{89}Zr$ produced with 0.4 mm thick Niobium beam degrader also shows mainly the characteristic 511 and 909 keV gamma emissions from $^{89}Zr$.**

# *Expected Characteristics for:*

## $^{89}Zr$

Half Life = 78.41 hours

Energy Spectrum

| | |
|---|---|
| 511 keV | 23% |
| 909 keV | 99% |
| 1713 keV | 0.8% |
| 1745 keV | 0.1% |
| 1657 keV | 0.1% |

## $^{88}Zr$

Half Life = 83.4 days

Energy Spectrum

| | |
|---|---|
| 393 keV | 97% |

## $^{88}Y$

Half Life = 106.6 days

Energy Spectrum

| | |
|---|---|
| 511 keV | 20% |
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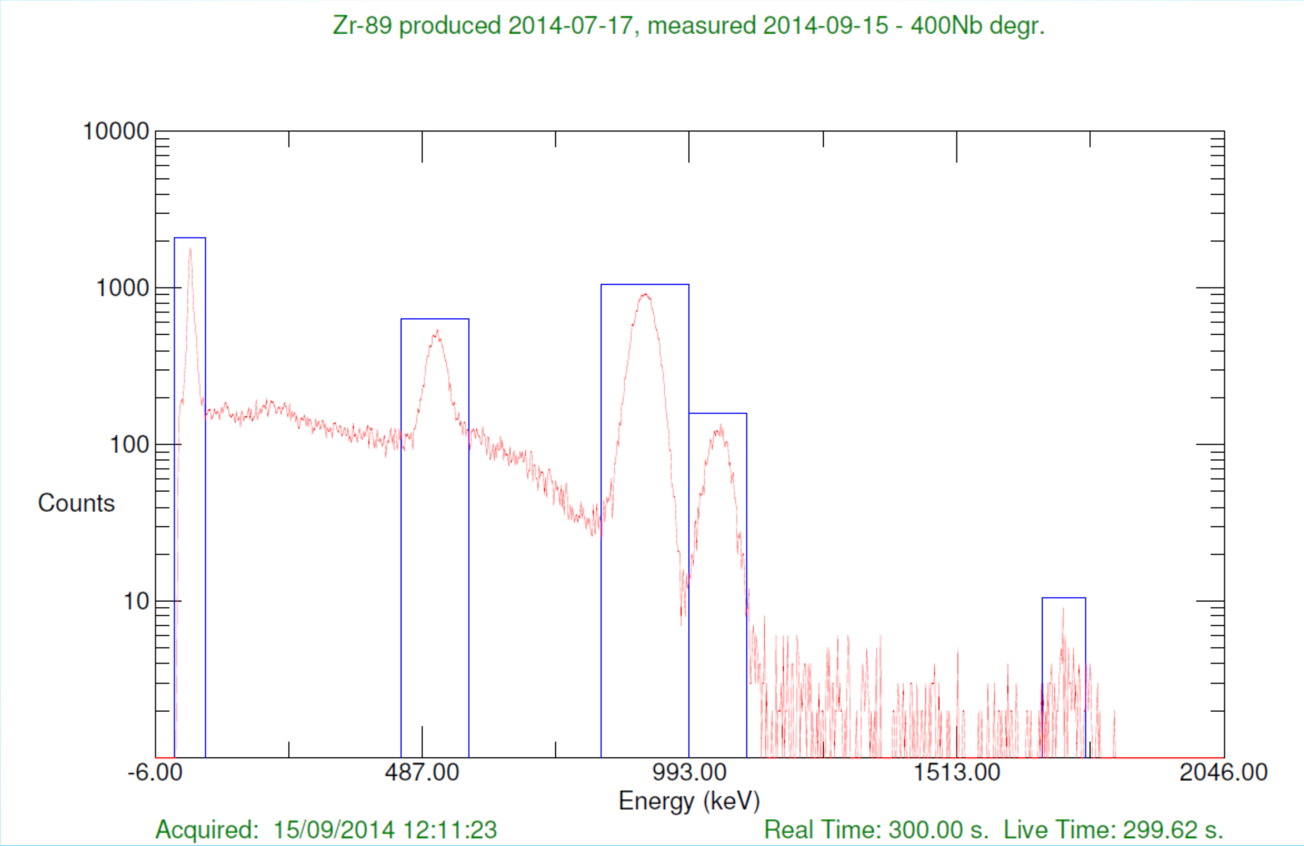

# Zr-89 productions parameters and yields

| Beam Time [h] | Beam Current [uA] | Niobium Thickness [μm] | Beam Energy [MeV] | $^{89g}Zr$ Activity EOB [MBq] | Average Yield of the $^{89}Y(p,n)^{89}Zr$ nuclear reaction [MBq/uAh] |
|---|---|---|---|---|---|
| 3 | 20 | 500 | 9.8 | 529.5 | 8.83 |
| 3 | 30 | 500 | 9.8 | 791.7 | 8.79 |
| 2.1 | 30 | 400 | 11.6 | 973.4 | 15.45 |
| 1.5 | 20 | 400 | 11.6 | 445 | 14.83 |
| 3 | 30 | 400 | 11.6 | 1400 | 15.56 |
| 3.5 | 30 | 400 | 11.6 | 1398 | 13.31 |
| 6.28 | 25 | 400 | 11.6 | 2364 | 15.06 |

# CONCLUSIONS

Production of $^{89}Zr$ with C 18/9 and COSTIS STS is possible**.** It is necessary to wait at least 4 hours before measuring the activity and decay correct in order to calculate the $^{89}Zr$ activity at the end of cyclotron production. Degrading the proton beam to **10 MeV** produces radionuclidically pure $^{89}Zr$ with yields of **9 MBq/µAh**. Whilst this is enough for pre-clinical use, the yield is not enough for either clinical use or commercial supply. Using thinner beam degraders (Nb 0.4 mm) to increase the proton beam energy (**11.6 MeV**) increases the yield (**15.5 MBq/µAh**) and does not affect purity of the product.

# REFERENCES


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# Thank you for attention!

**ACKNOWLEDGMENTS:**

Many thanks to

S. Preusche and M. Walther from HZDR Dresden

Ch. Marshall and S. Paisey from PETIC.