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Towards reliable production of ^{225}Ac for medical applications:

Systematic analysis of the production of Fr, Ra and Ac beams.

CERN-INTC-2017-016 ; INTC-P-498

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08/02/2017

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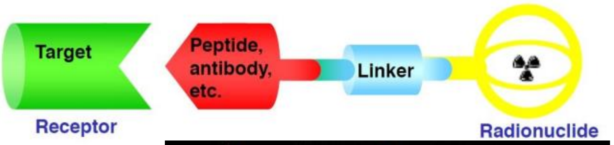
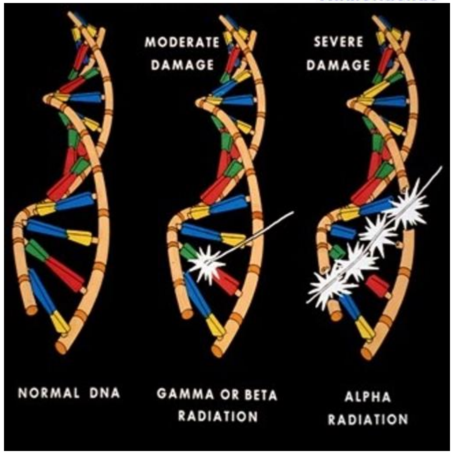
Outline

- Context
- Current ^{225}Ac production
- Yield and release curve characteristics
- Measurement techniques and approaches
- Conclusion
- Summary beam time request

Context

- Research on medical radioisotopes
- Targeted-Alpha-Therapy (TAT) has big potential
  - Linked to pharmaceutical drug





  - High Linear-Energy-Transfer (LET) value
  - 70-100 µm pathlength (2-3 cell diameters)
  - Double stranded-breaks in DNA
- Very efficient tumor cell killer
- **Applications:** recurrent brain tumor, recurrent ovarian cancer, myelogenous leukemia, metastatic melanoma, metastatic castration-resistant prostate cancer, …

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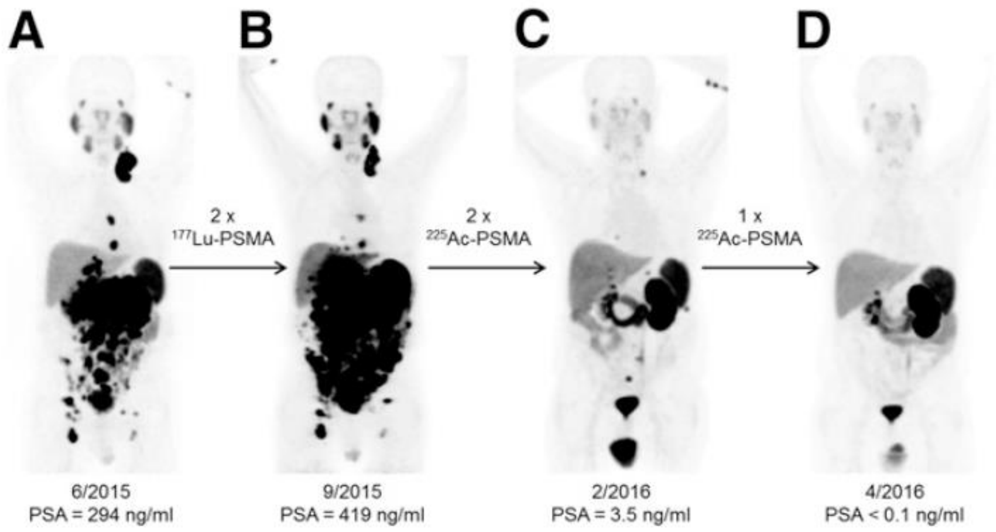
Context

- Very promising α-emitters: ^{225}Ac and daughter ^{213}Bi
- Successful early pre-clinical and clinical studies
    - Treatment of bladder cancer by TAT using ^{213}Bi
    - Phase I/II trials on acute myeloid leukemia
    - 2016: total remission of mCRPC-patient



Ga^{68}-PET/CT image of patients

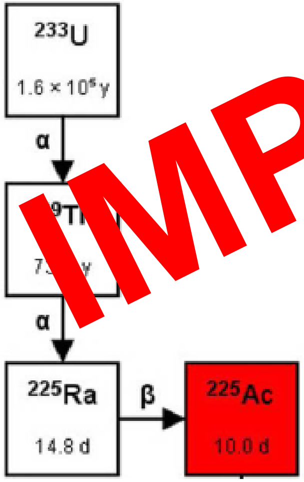
Progressive under conventional β-emitting ^{177}Lu therapy

Using ^{225}Ac: Prostate-Specific Antigen decline!!

Kratochwil, C.,et al. (2016). 225Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. *Journal of Nuclear Medicine*, *57*(12), 1941–1944

^{225}Ac production

- Decay from ^{233}U
  - ^{232}Th(n,2*β) ➔ ^{233}U
  - Civil and military nuclear applications



- Proton irradiation of ^{226}Ra
  - ^{226}Ra(p,x) ➔ ^{225}Ac
  - $\sigma_{^{225}Ac} < \sigma_{^{227}Ac}$

IMPURITIES

- Proton irradiation of ^{232}Th
  - ^{232}Th(p,x) ➔ ^{225}Ac
  - $\sigma_{^{225}Ac} < \sigma_{^{227}Ac}$

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^{225}Ac production

- Limited availability of **pure** ^{225}Ac and ^{213}Bi
  - Big bottleneck for progressing research
- Big need from nuclear medicine:

mCRPC.

Nevertheless, the limited availability of ^{225}Ac is still a key challenge for its clinical translation, and this shortage has to be

situation, any extra peritoneal location of tumor cells.

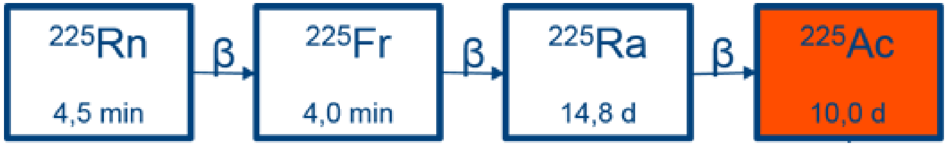
A major issue that may hamper wide implementation in the clinic and that needs to be simultaneously addressed is the availability of suitable α-particle emitters at a reasonable cost (43, 89). Otherwise, TAT will remain just a potentially effective treatment, or a very rarely implemented option.

pharmacokinetics have been established for all types of malig

Element selective and mass-pure production

➔ **ISOL-technique**

➔ ^{225}Ac, ^{225}Ra, ^{225}Fr



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Elgqvist, J., Frost, S., Pouget, J.-P., & Albertsson, P. (2014). The Potential and Hurdles of Targeted Alpha Therapy – Clinical Trials and Beyond. *Frontiers in Oncology*, *3*(January), 324

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Yield and release curve characteristics

Fr	218 - g	1.0 ms	SC	4.3E+03*	UC_x
Fr	219 - g	20 ms	SC	8.9E+03*	UC_x
Fr	220 - g	27.4 s	SC	6.0E+08*	ThC_x
Fr	220 - g	27.4 s	SC	3.8E+07*	UC_x
Fr	221 - g	4.9 m	SC	8.9E+08*	ThC_x
Fr	221 - g	4.9 m	SC	2.8E+07*	UC_x
Fr	222 - g	14.2 m	SC	1.2E+09*	ThC_x
Fr	222 - g	14.2 m	SC	1.0E+07*	UC_x
Fr	223 - g	21.8 m	SC	1.2E+09*	ThC_x
Fr	224 - g	3.33 m	SC	4.7E+09*	ThC_x
Fr	224 - g	3.33 m	SC	1.4E+06*	UC_x
Fr	225 - g	4.0			
Fr	226 - g	49			
Fr	226 - g	49			
Fr	227 - g	2.4			
Fr	228 - g	38			
Fr	228 - g	38			

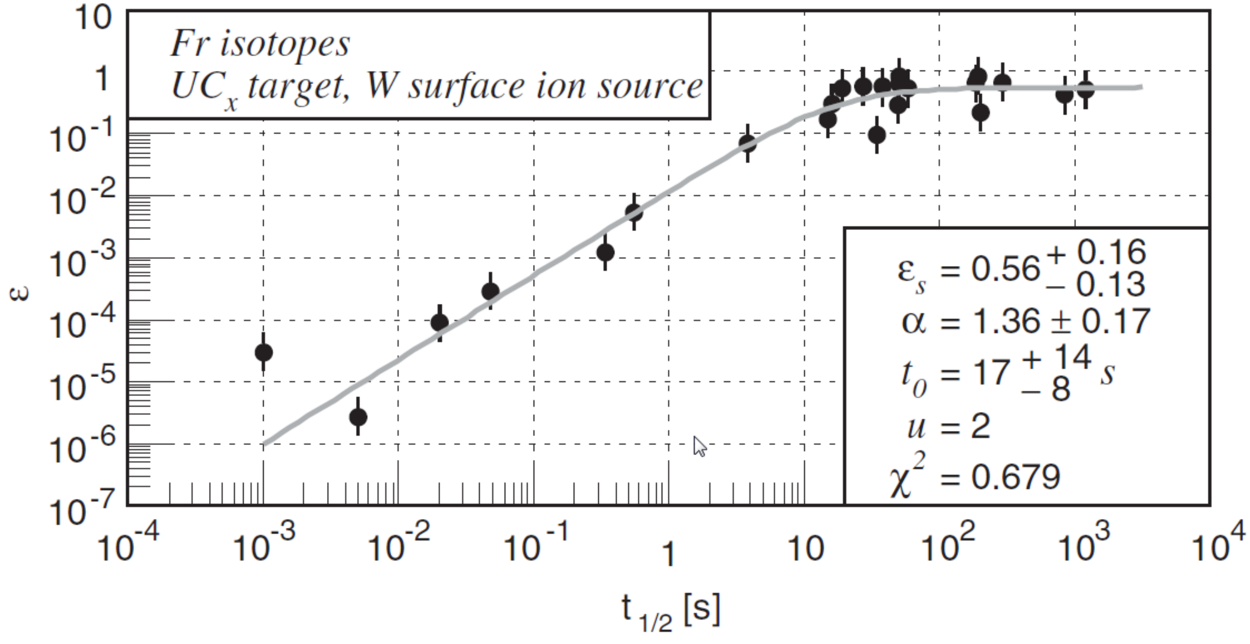
Ra	214 - g	2.46 s	SC	9.2E+06*	ThC_x
Ra	214 - g	2.46 s	SC	9.0E+06*	UC_x
Ra	220 - g	18 ms	SC	2.4E+05*	ThC_x
Ra	220 - g	18 ms	SC	1.7E+05*	UC_x
Ra	221 - g	28 s	SC	3.5E+09*	ThC_x
Ra	221 - g	28 s	SC	3.7E+07*	UC_x
Ra	222 - g	38.0 s	SC	1.3E+09*	ThC_x
Ra	222 - g	38.0 s	SC	3.3E+07*	UC_x
Ra	224 - g	3.66 d	SC	6.0E+08*	UC_x
Ra	225 - g	14.9 d	SC	2.6E+08*	ThC_x
Ra	226 - g	1600 y	SC	1.1E+08*	UC_x
Ra	228 - g	5.75 y	SC	1.8E+07*	UC_x

http://test-isolde-yields.web.cern.ch/test-isolde-yields/radium_isotopes.html

Yield and release curve characteristics

- Optimization of ^{225}Ac collection
  - Yield (^{225}Ac, ^{225}Ra, ^{225}Fr)
  - Release curve (^{225}Ac, ^{225}Ra, ^{225}Fr)

$$\varepsilon_{total} = \varepsilon_{diffusion} * \varepsilon_{effusion} * \varepsilon_{transport} * \boldsymbol{\varepsilon_{ionsource}}$$

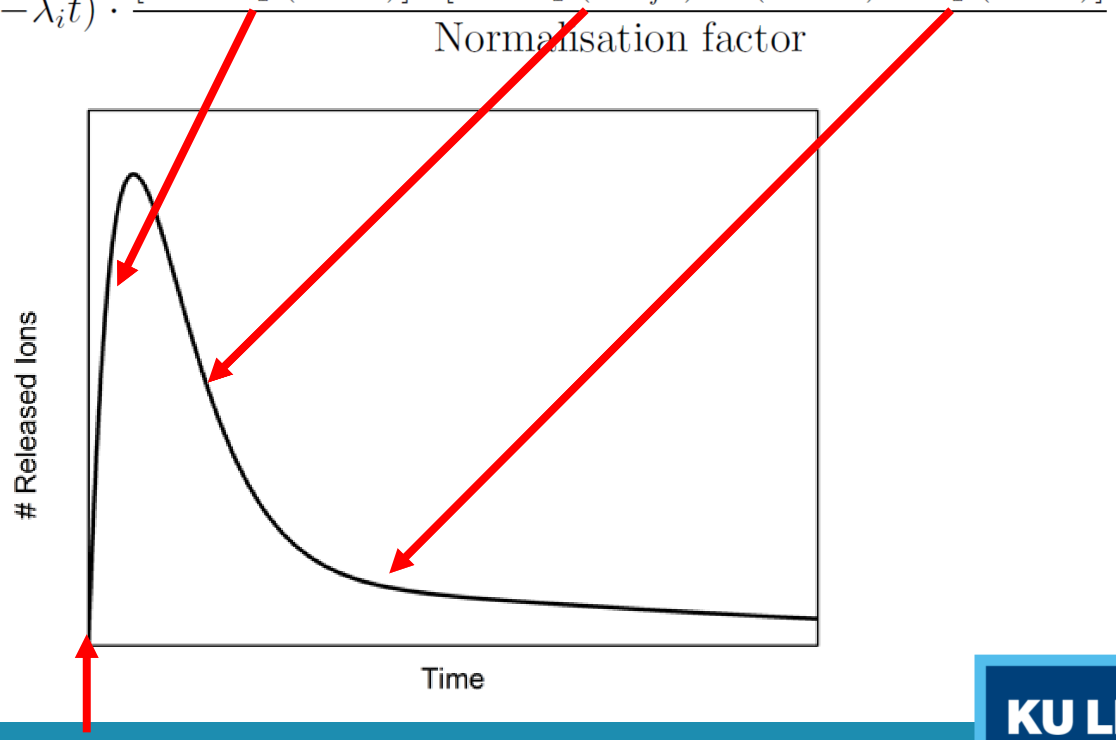


Lukić, S., Gevaert, F., Kelić, A., Ricciardi, M. V., Schmidt, K. H., & Yordanov, O. (2006). Systematic comparison of ISOLDE-SC yields with calculated in-target production rates. *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, *565*(2), 784–800.

Yield and release curve characteristics

- Optimization of ^{225}Ac collection
  - Yield (^{225}Ac, ^{225}Ra, ^{225}Fr)
  - Release curve (^{225}Ac, ^{225}Ra, ^{225}Fr)

$$P_i(t, \lambda_i) = \exp(-\lambda_i t) \cdot \frac{[1 - \exp(-\lambda_r t)] \cdot [\alpha \cdot \exp(-\lambda_f t) + (1-\alpha) \cdot \exp(-\lambda_s t)]}{\text{Normalisation factor}}$$



Proton impact on target

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Measurement techniques and approaches

- Release curve for accurate yield measurements
  - Faster without precision loss
  - Eliminate half life
  - Eliminate secondary production

- Release curve
  - ➔ ^{205,207,220,221,222,227}Fr
  - ➔ ^{214,220,221,222,227}Ra

- Integrated yield measurement
  - Longer half life scale
  - ➔ $^{218,219,223-226,228}$Fr
  - ➔ $^{219,223-226,228}$Ra

Measurement techniques and approaches

- **α**-emitters: **Windmill** setup (**KU Leuven**)

On-line

➔ $^{205,207,218\text{-}221}$Fr

➔ $^{214,219\text{-}222}$Ra

Off-line

➔ ^{223,224,226}Ra (800kBq)

IC from **NPL**

- **β**-emitters: **Tape station** (**ISOLDE**)

On-line

➔ $^{222\text{-}228}$Fr

➔ ^{227}Ra

- Off-line collection (**Windmill**)

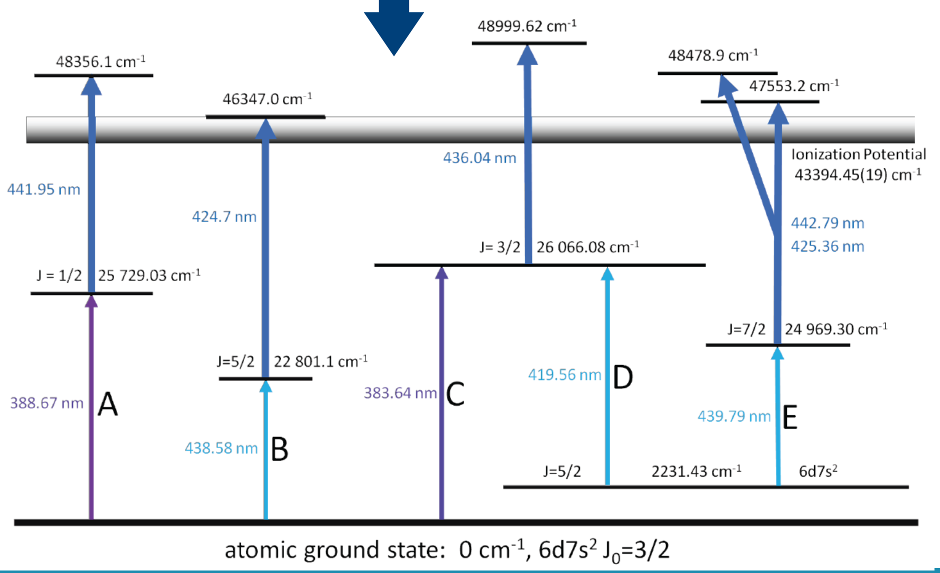
➔ ^{225,228}Ra (0,1-1kBq): primary counting methods at **NPL**

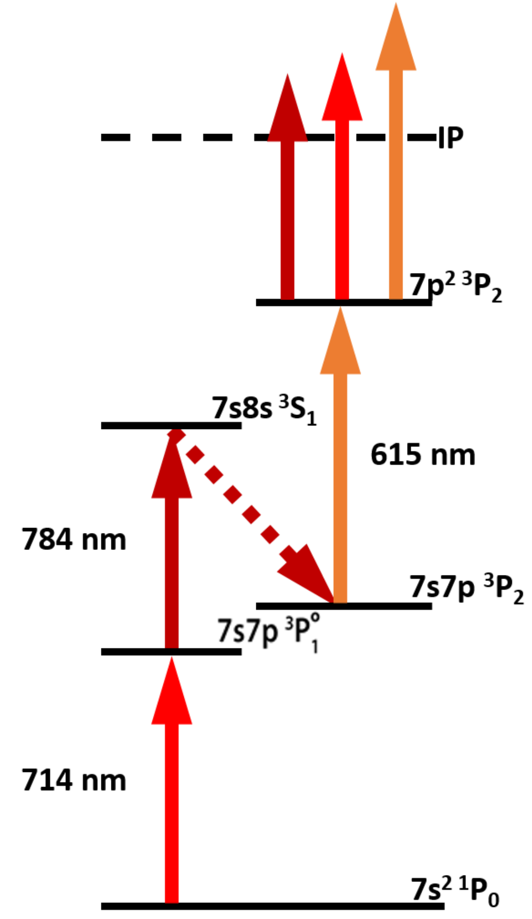
➔ ^{225}Ac

https://fys.kuleuven.be/iks/ns/images/windmill.png/view

Measurement techniques and approaches

- Ion Sources:
  - Fr: Ta surface ion source
  - Ra: Resonant laser ionization
  - Ac: Resonant laser ionization





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Conclusion

- ISOL offers solution to lack of pure isotope samples
- 3 routes: - **^{225}Ac**

  - ^{225}Ra

  - ^{225}Fr

- Release curve is needed for fast and accurate yield

- Request **6 shifts**: proper and systematic measurements
  - 3 on fresh target
  - 3 on end-of-life target

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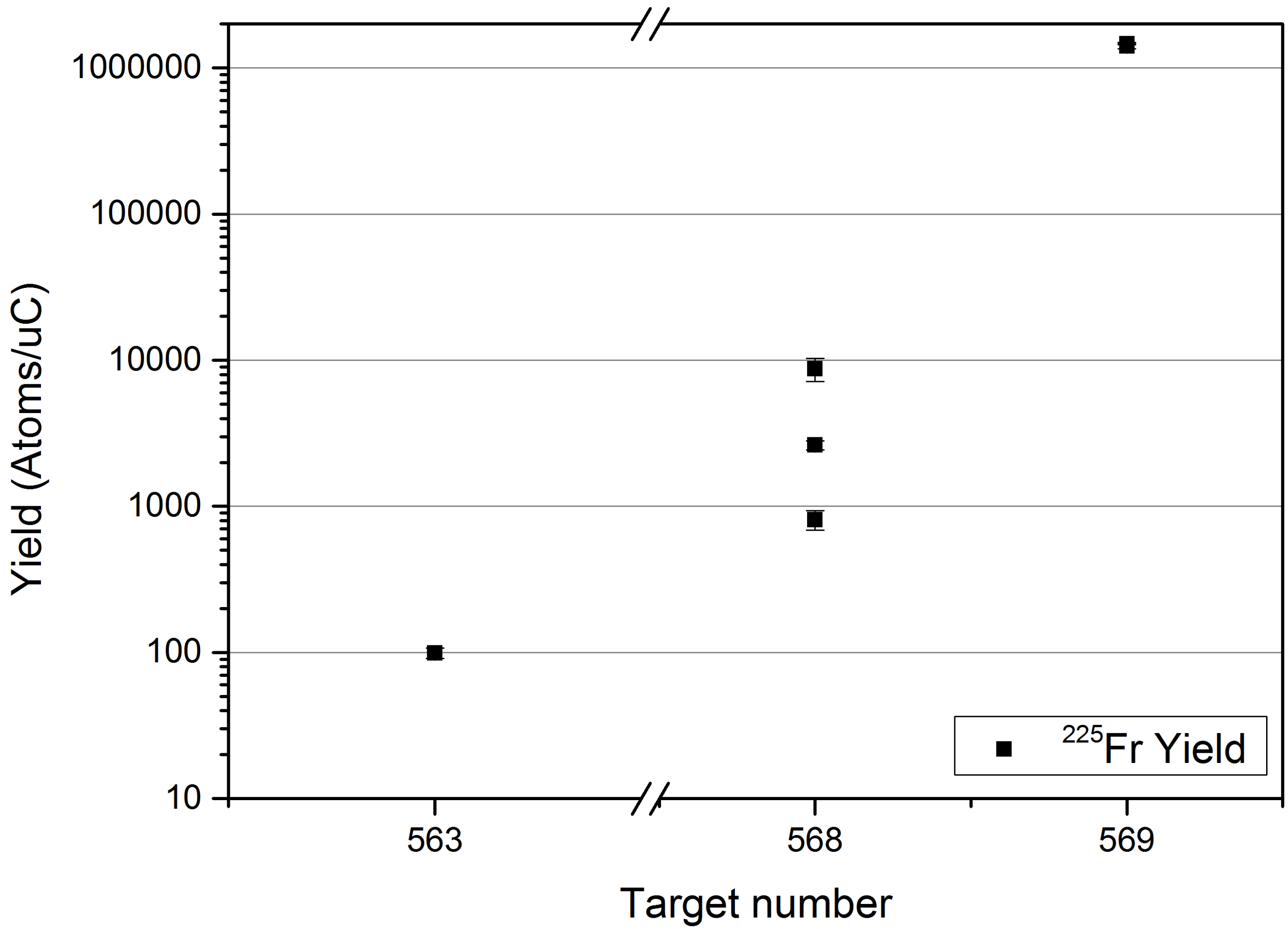
Summary beam time request

Isotope	Target	Ion Source	# shifts
$^{205,207,218-228}Fr$	UC_x	Ta	3+3
$^{214,219-228}Ra$	UC_x	Laser	
^{225}Ac	UC_x	Laser	RILIS-development

Back-up slides

LOI 2015



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