Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226

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Overview

- Production of Ac-225/Bi-213
  - *Radiochemical separation from Th-229*
  - *Cyclotron process Ra-226(p,2n)Ac-225*

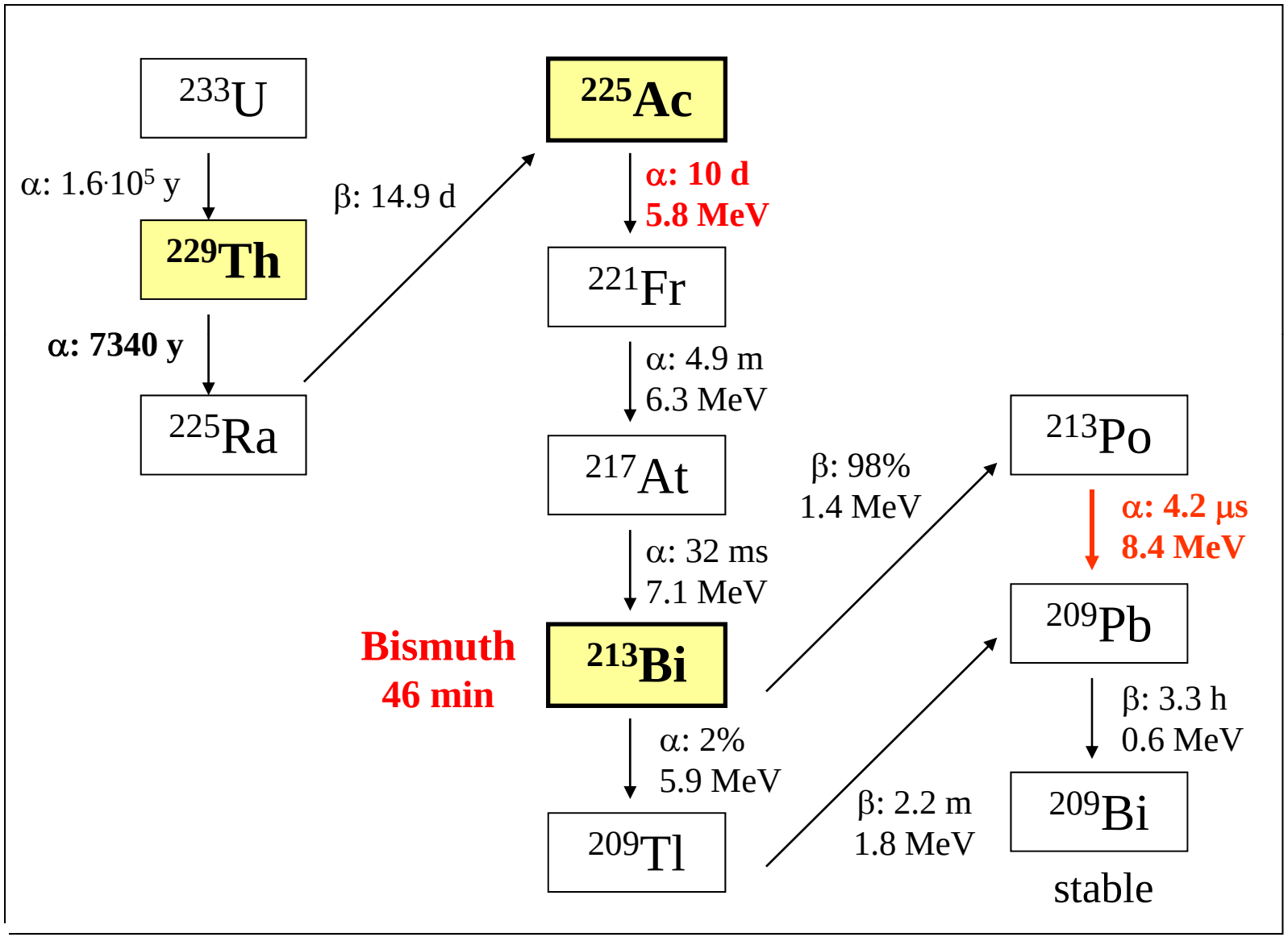
- *Synthesis of Bi-213-DTPA- and Bi-213-DOTA-conjugates*

- Production of U-230/Th-226
  - *Th-232(p,3n)Pa-230(β^+)U-230*
  - *Pa-231(p,2n)U-230*

- *Synthesis of Th-226-DTPA-conjugates*

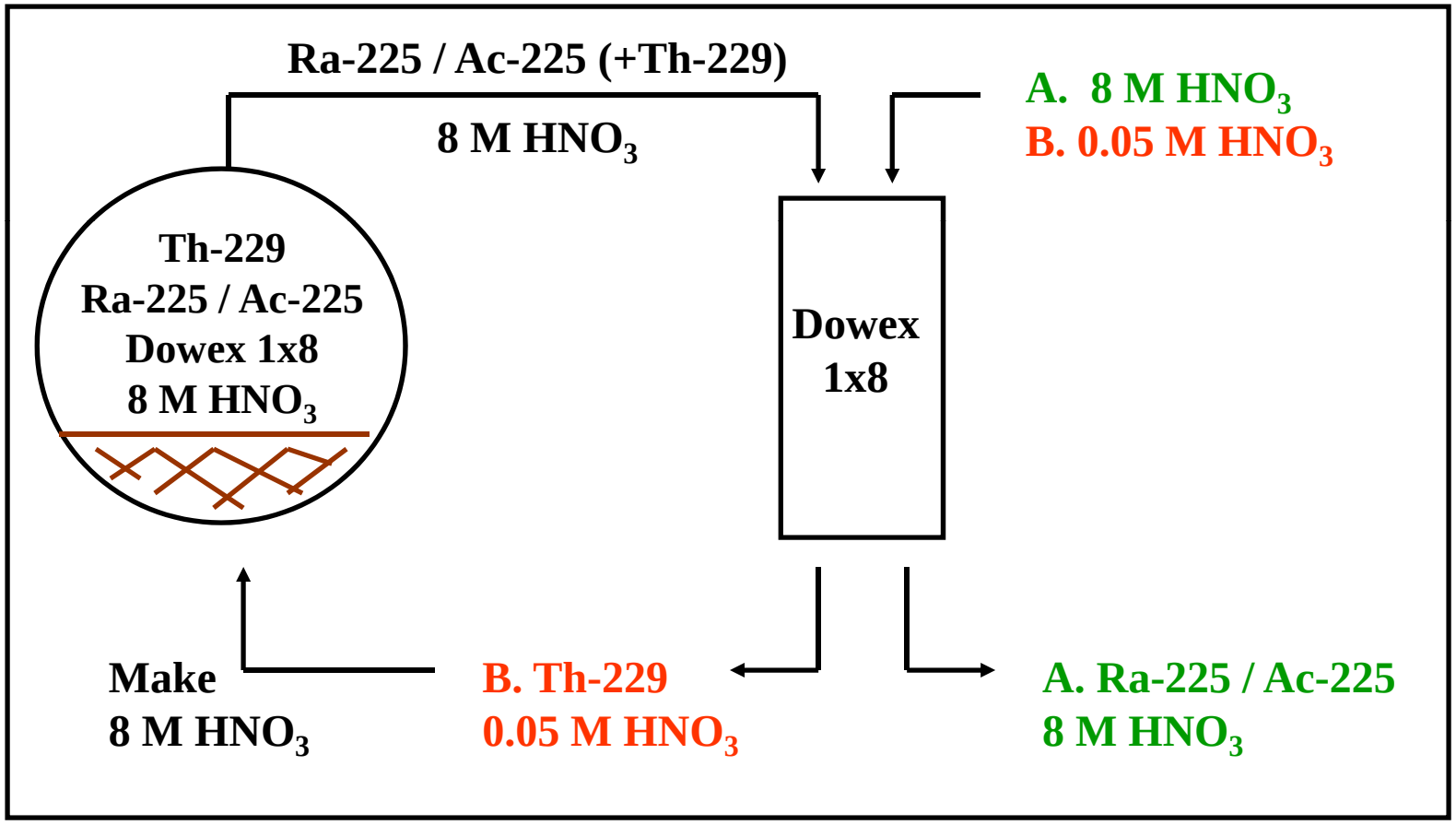
- *In vitro* comparison of Bi-213- *vs.* Th-226-CHXA-DTPA-HuM195

The Ac-225/Bi-213 system



Step 1: Separation of Ra-225 + Ac-225 from Th-229

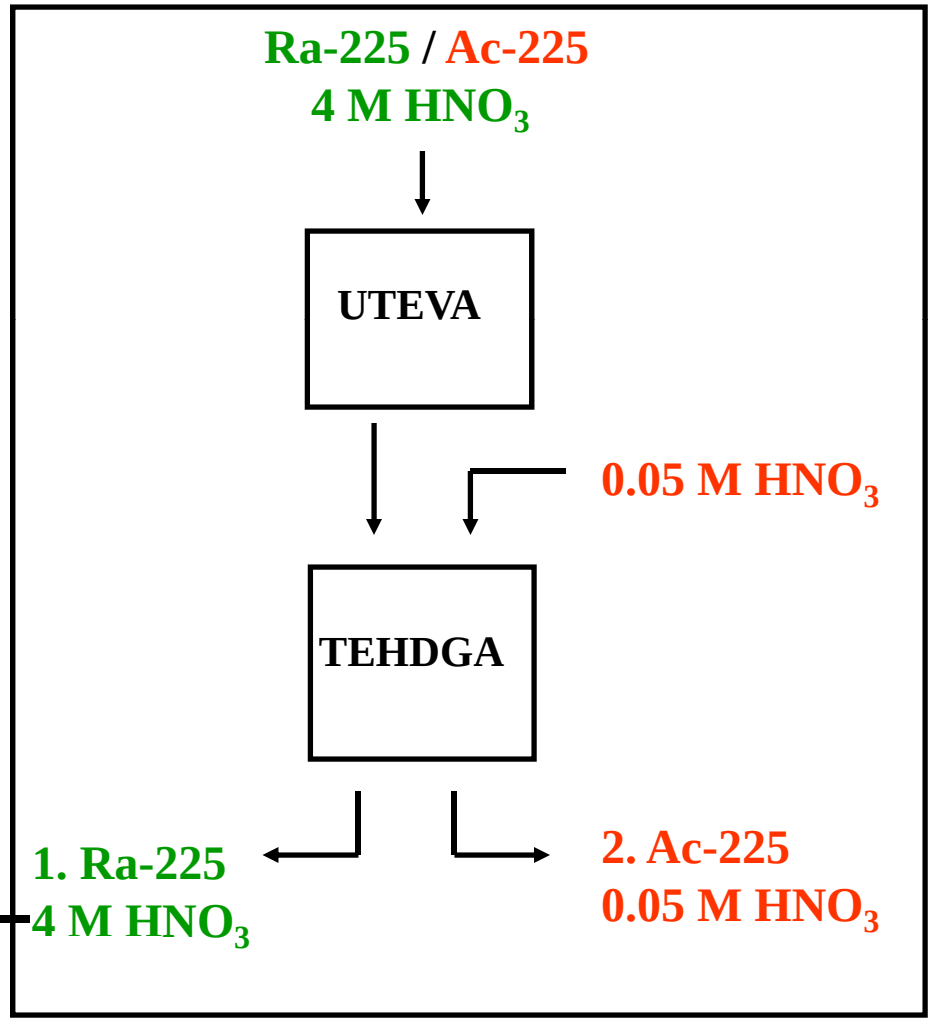
Anion exchange



C. Apostolidis et al., Anal Chem. 2005 Oct 1;77(19):6288-91

Step 2: Ra-225 / Ac-225 separation

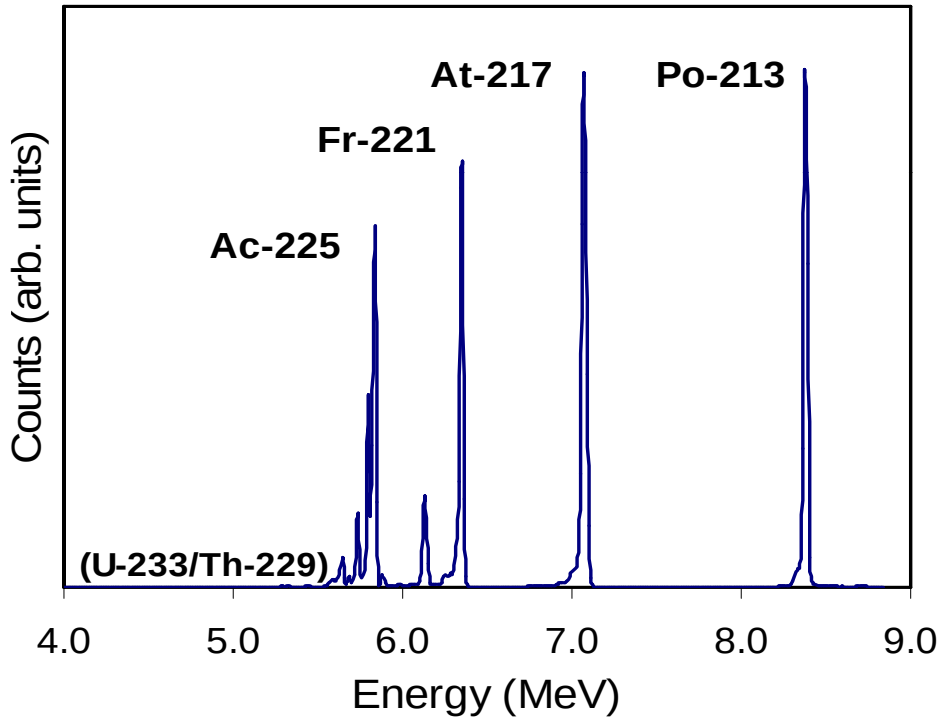
Extraction chromatography

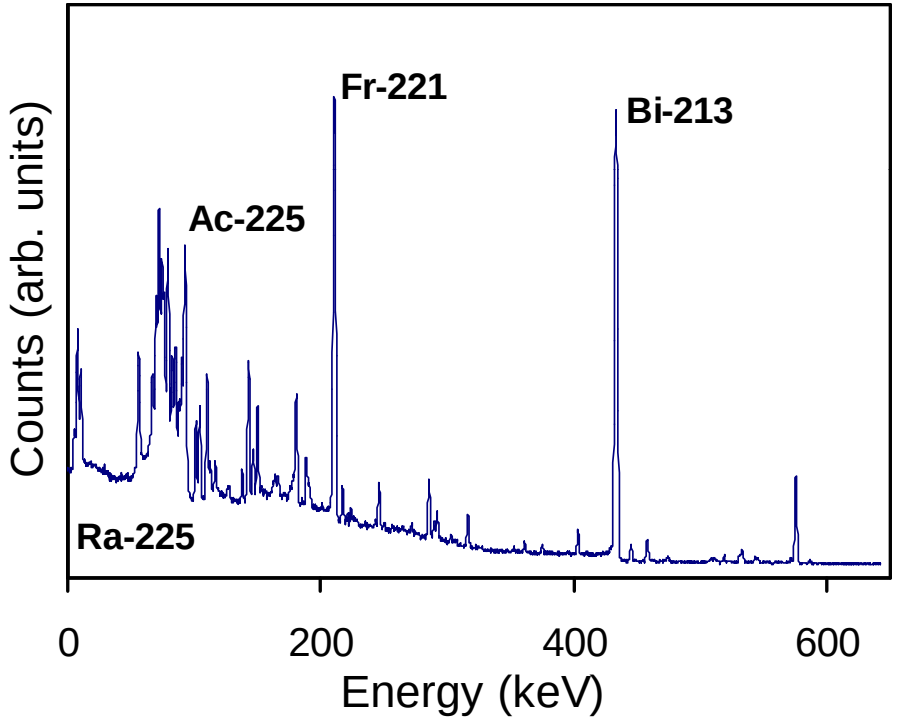


additional Ac-225 after approx. 3 weeks storage

B. Zielinska et al., Solv. Extr. Ion Ex. 2007;25(3):339-49

- Alpha- and Gamma-spectrometry
- ICP-MS



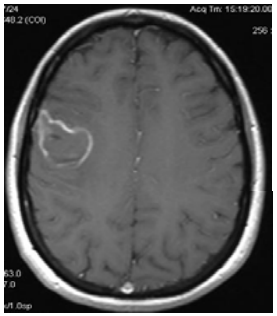


Ac-225 Product Characteristics

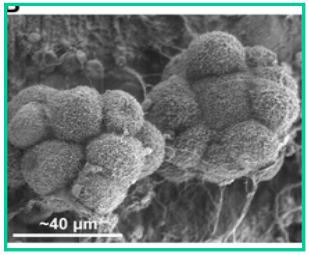
- Radiochemical purity > 99.98%
  [U-233+Th-229] / [Ac-225] < 90 ppm
  [Ra-225] / [Ac-225] < 20 ppm
- Other impurities: [Fe] < 0.3 µg per batch of dry Ac-225
- Overall yield of separation process: > 98%
- Batch sizes: ca. 35 mCi, 13 mCi, 6 mCi, 3 mCi
  => 55-60 mCi per production cycle
- Typically 6 production cycles per year in 9 week intervals
  => Total annual production: ca. 350 mCi
- Provided free-of-charge on basis of scientific collaborations

Current partners of ITU

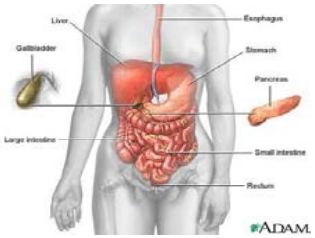
MSTA, Sydney
(*Melanoma*)



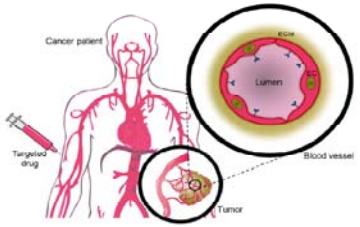
UH Basel
(*Glioma, Prostate*)



Univ. Gothenburg
(*Ovarian*)

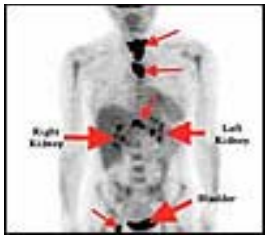


TU München
(*Gastric, Bladder*)

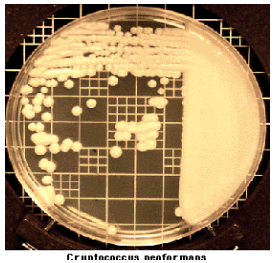


ETH, Zürich
(*Anti-Vascular Therapy*)

ITU
α-emitting
isotopes

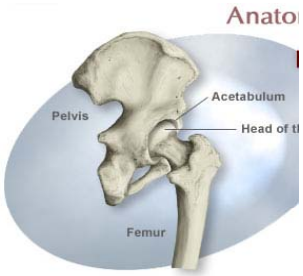


Johns Hopkins, Baltimore
(*Breast Cancer*)

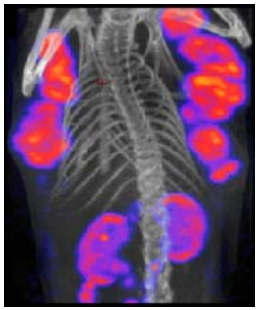


Albert Einstein College, NY
(*Infectious Diseases*)

?



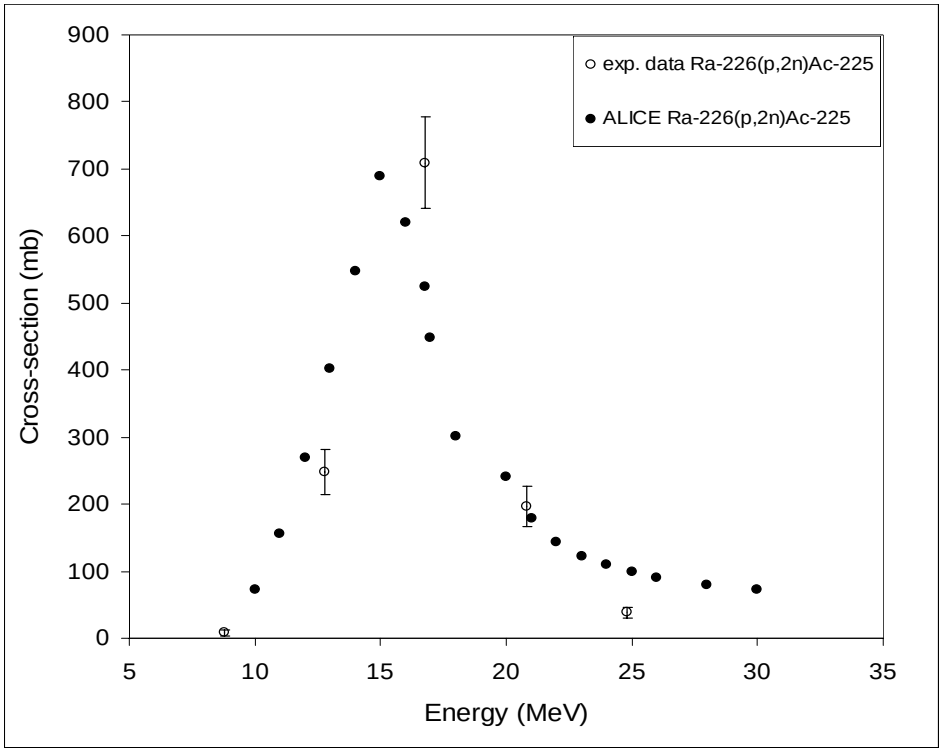
INSERM, Nantes
(*Multiple myeloma*)

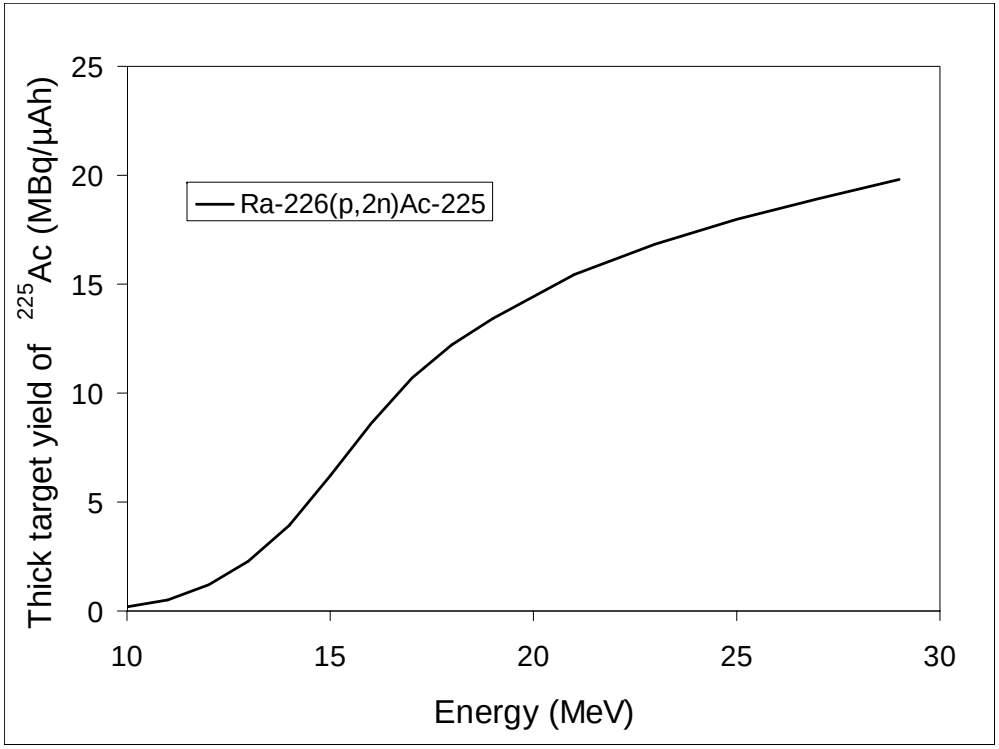


PSI, Villigen
(*Folates*)

Cyclotron production of Ac-225

Ra-226(p,2n)Ac-225



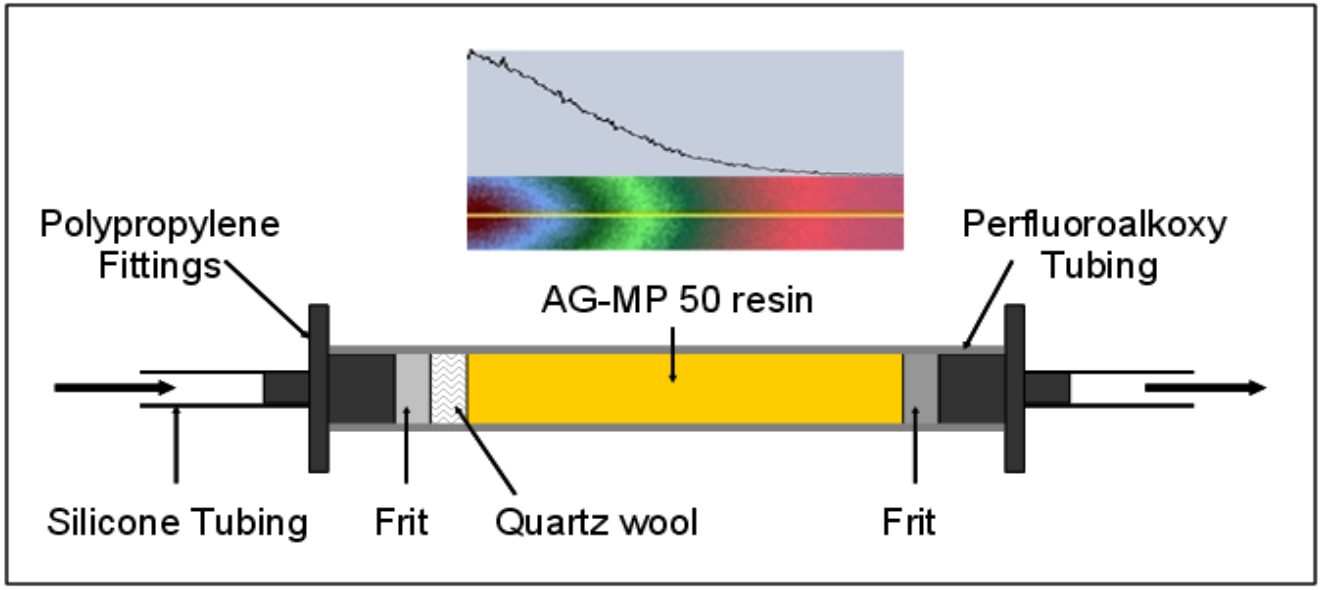


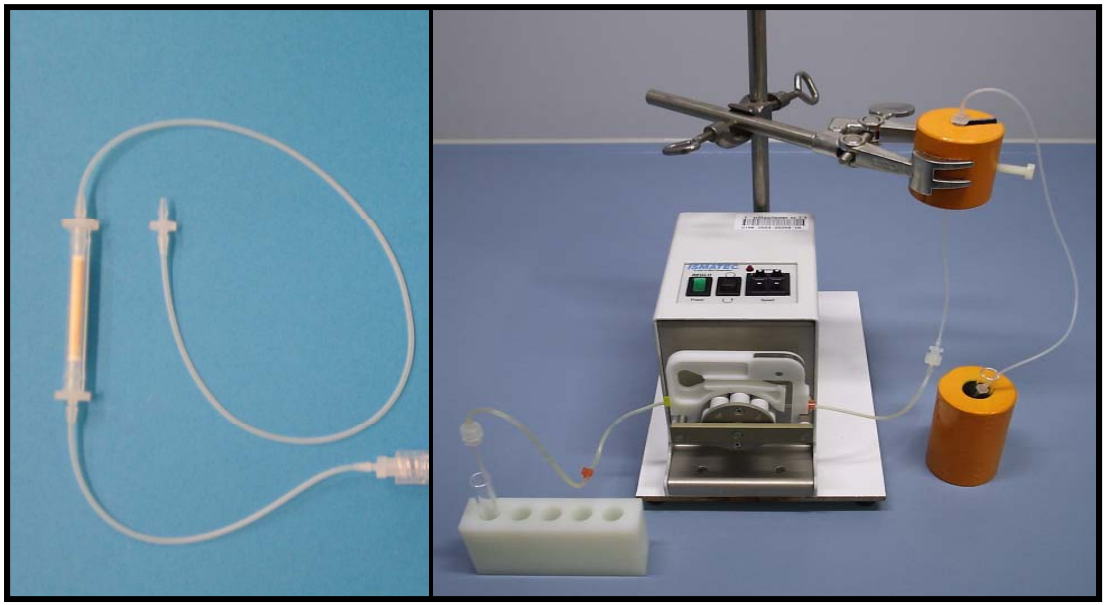
- Max. cross-section: 7.1e2 ± 68 mb at 16.8 MeV proton energy
- Thick target yield: 18 MBq/µAh at 25 MeV
  => 20 h of irradiation with 50 µA yield 18 GBq (486 mCi) Ac-225

=> Basis for widespread clinical application

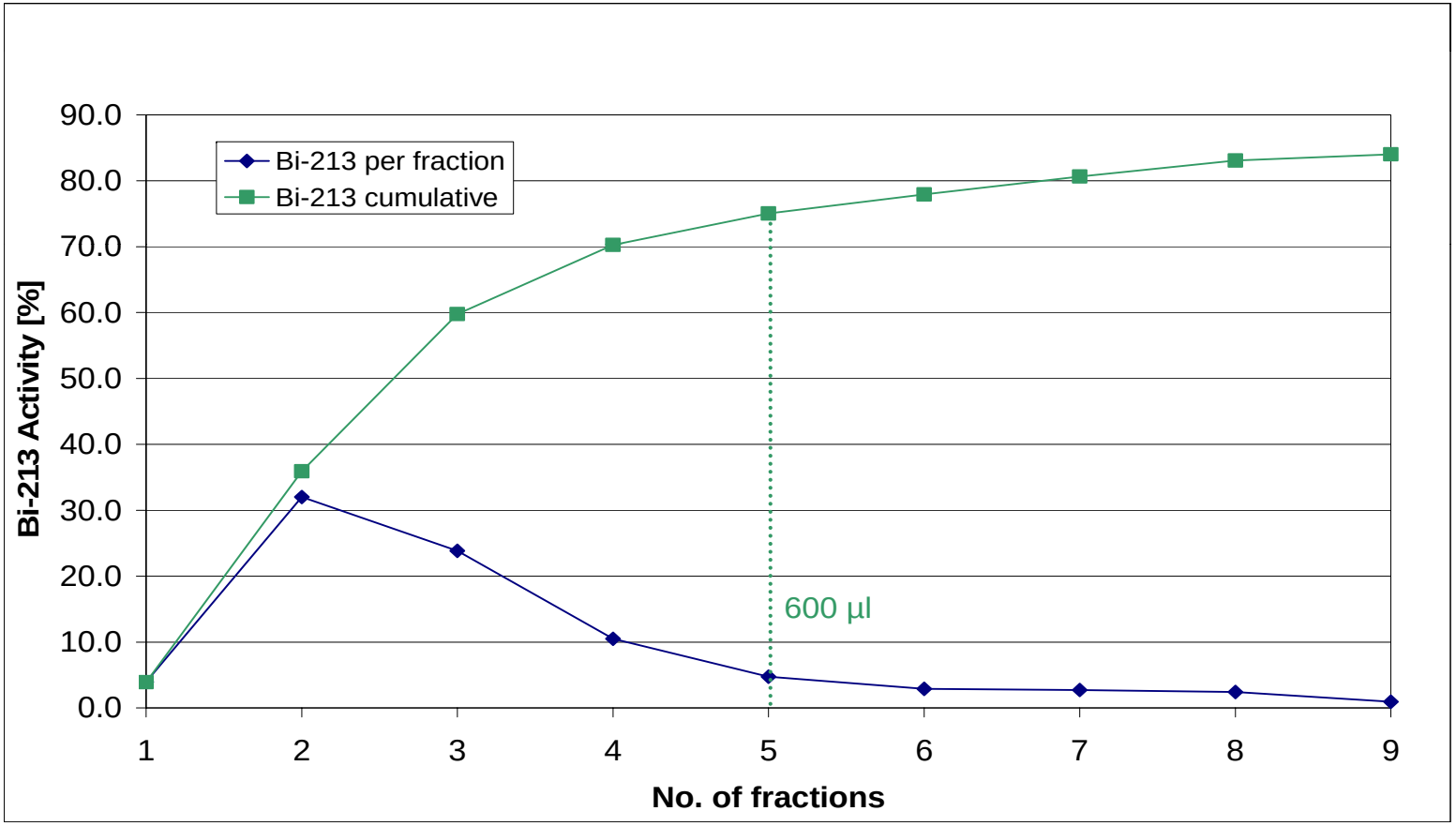
C. Apostolidis et al., Appl. Rad. Isot. 2005;62(3):383-7.

ITU standard Ac-225/Bi-213 Generator

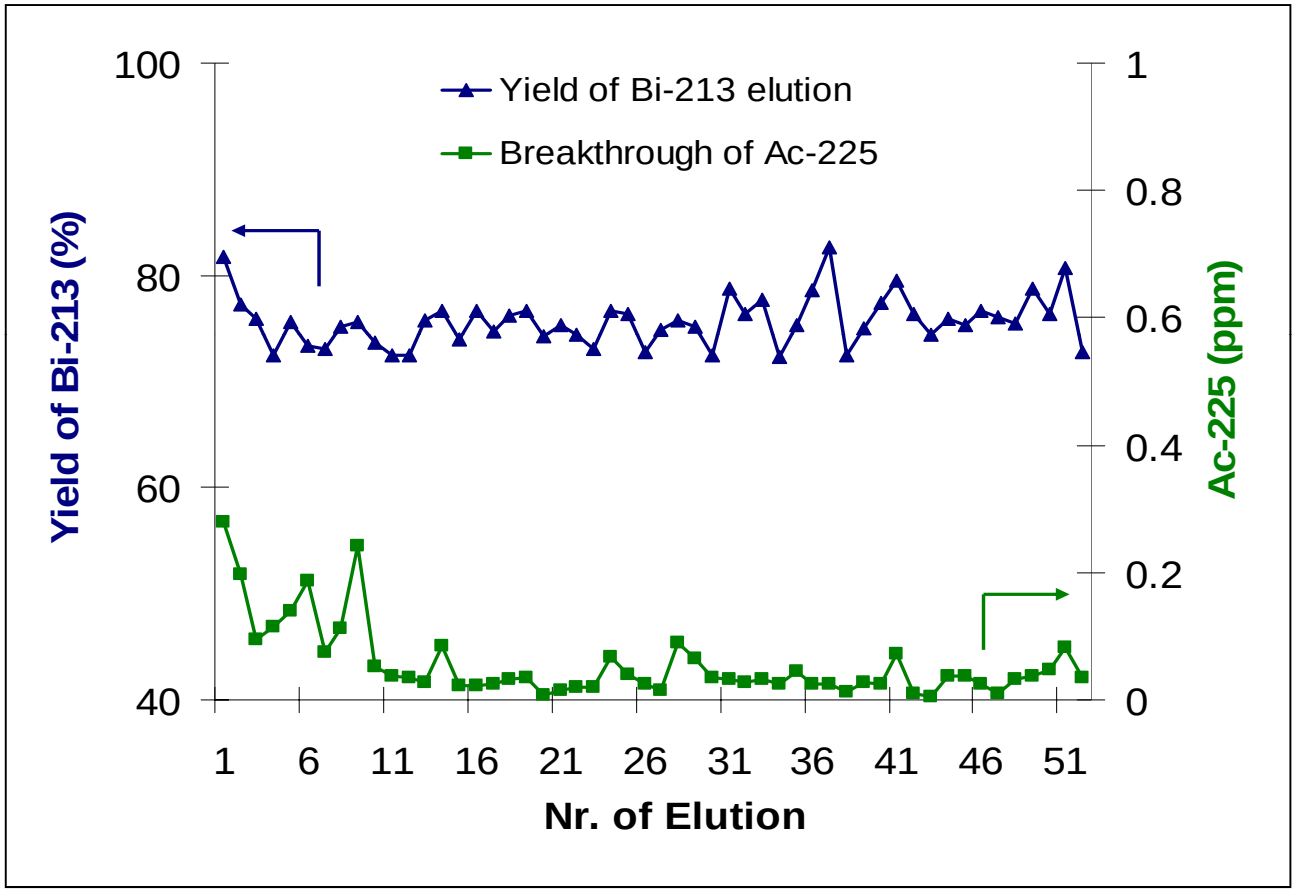




Elution profile using 0.1 M HCl/0.1 M NaI



Bi-213 yield and Ac-225 breakthrough



- Typical elution volume: 0.6 ml 0.1 M HCl/0.1 M NaI
- Bi-213 yield: 75 ± 10%
- Breakthrough of Ac-225 parent: < 0.2 ppm (59±60 ppb)

timescale

0 min

5 min

8 min

Elution of Ac-225/Bi-213-generator (e.g. 30 mCi Bi-213)

600µl 0.1 M NaJ / 0.1 M HCl into

60 µl 2 M Na_2CO_3 (metal-free) and

50 µl 20% ascorbic acid ==> pH 8.5

Microwave assissted synthesis of Bi-213-DOTA-Substance P

(e.g. Biotage Initiator)

30 µg DOTA-Substance P

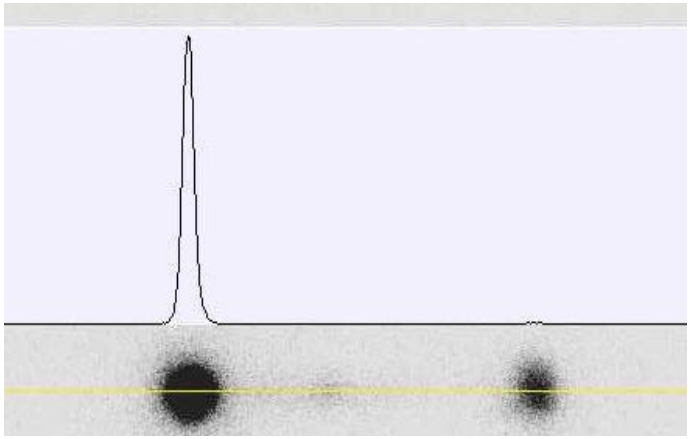
heating 5 min at 100°C

controlled cooling to 40°C

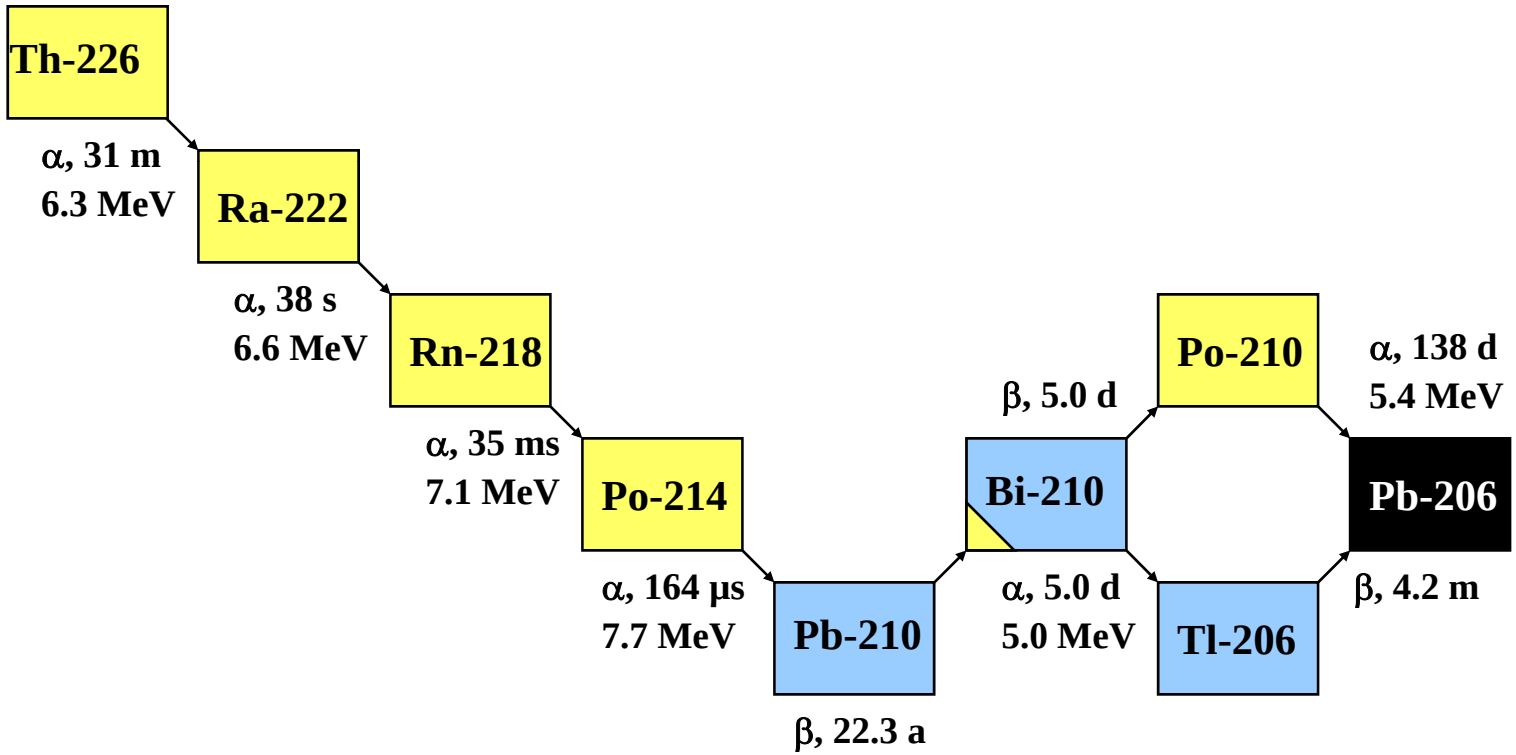
control with ITLC or Radio-HPLC

Radiochemical purity > 98%

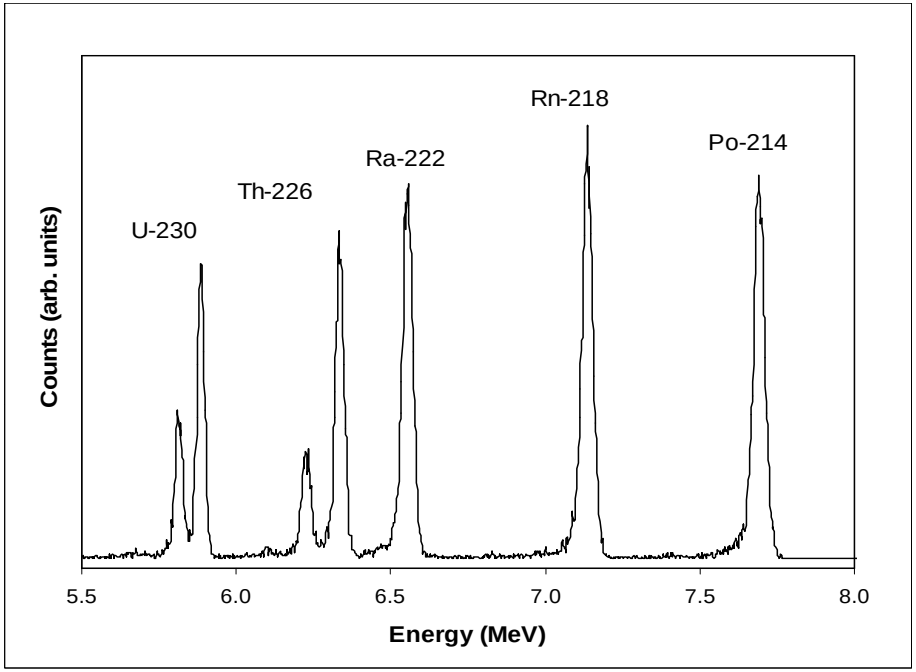
Specific activity up to 25 MBq/µg SP

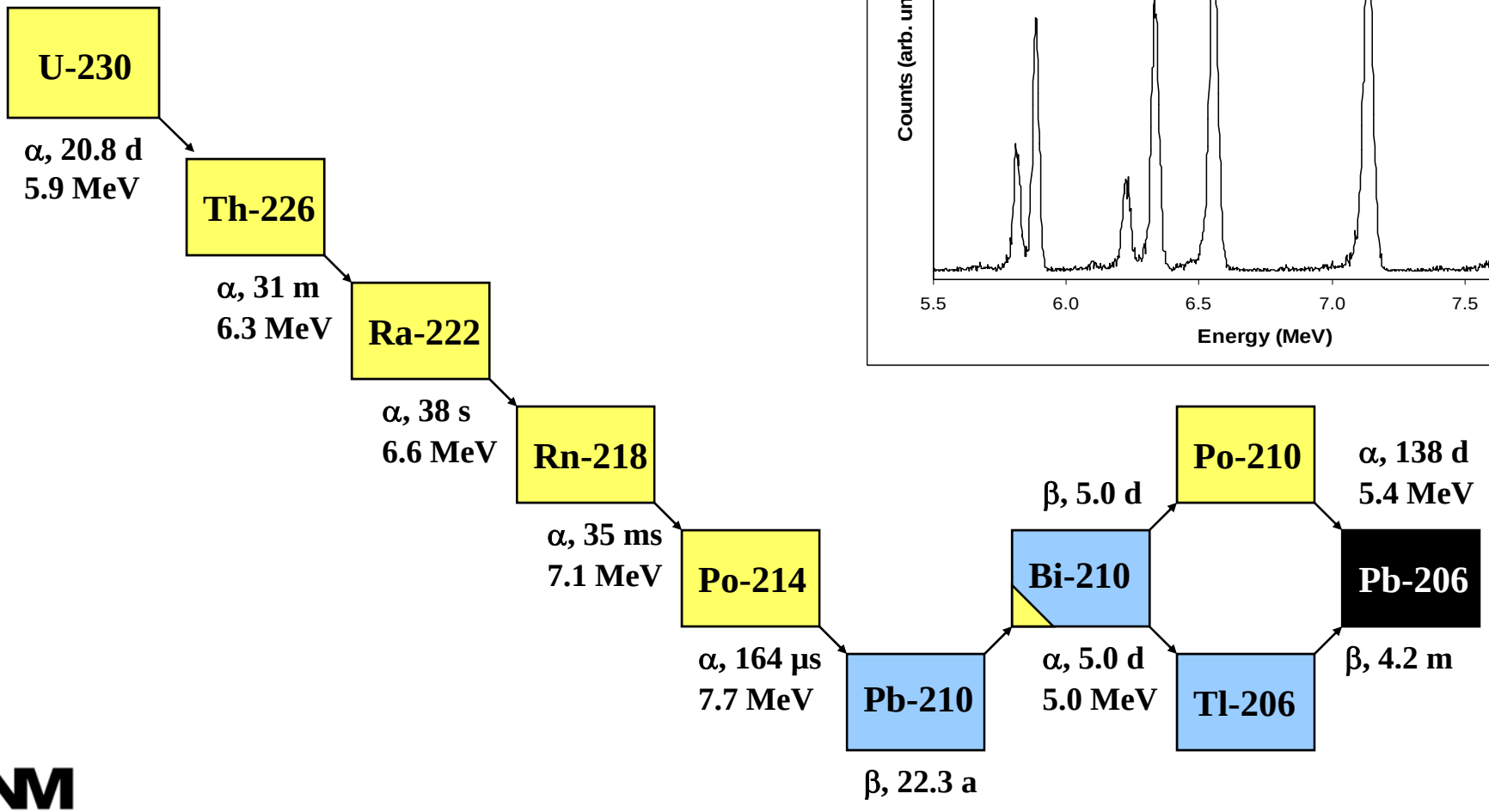


U-230/Th-226 decay scheme



U-230/Th-226 decay scheme





The U-230 / Th-226 system

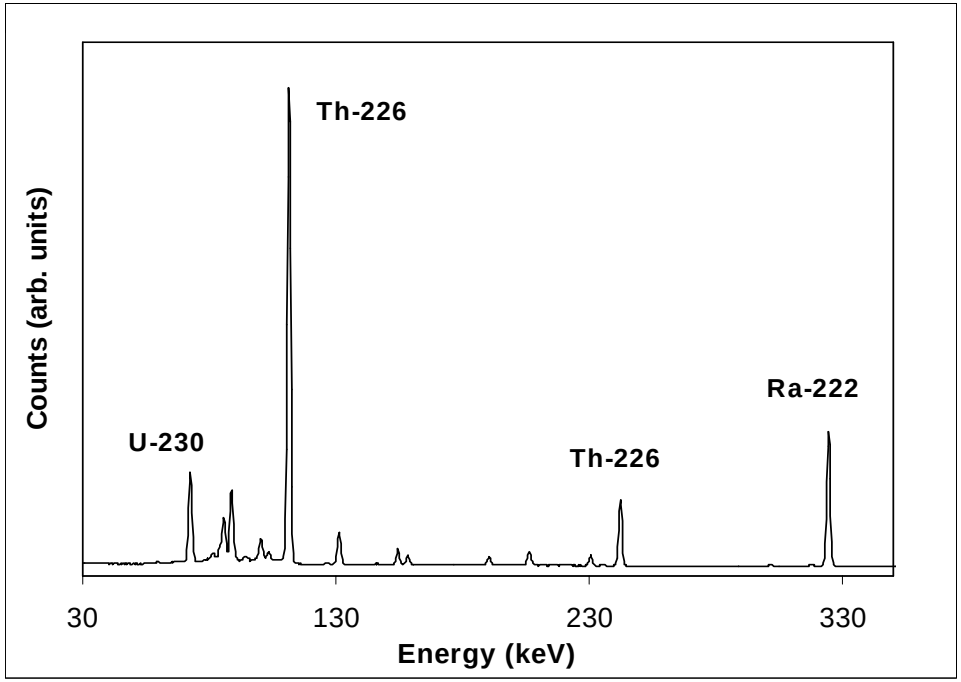
- parent nuclide U-230: $t_{1/2}$= 20.8 days
  => long generator lifetime

- Th-226 emits cascade of 4 alpha-particles of 27.7 MeV cumulative energy
  => high cytotoxicity

- half-life of daughter nuclides: 164 µs - 38 s
  => translocation from target site limited

- tetravalent Th(IV) forms very stable complexes
  => straightforward labelling protocols
  => high *in vivo* stability

- gamma emissions of Th-226 suitable for
  in vivo imaging (111 kev, 3.3%),
  but no high energy gamma emissions



The U-230 / Th-226 system

- limitation: Th-226: $t_{1/2}$= 31 min
  => rapid targeting required:
  loco-regional applications
  fast diffusible carriers (peptides)
  pre-targeting approaches

Direct application of U-230 as *in vivo* generator:

- U-230 emits cascade of 5 alpha-particles of 33.6 MeV cumulative energy
  => high cytotoxicity

- challenges: U-230: $t_{1/2}$= 20.8 days
  => stable targeting required: suitable chelate?

- first daughter nuclide: Th-226: $t_{1/2}$= 31 min
  => control of translocation from target site crucial
  => fate of Th-226 controls complete decay chain

Production of U-230 / Th-226

2 cyclotron driven processes available

- Proton irradiation of natural ^{232}Th

  $^{232}Th(p,3n)^{230}Pa$ (8.4% β^-, 17.4 d) ^{230}U

  => max. 2.8% ^{230}U-activity from ^{230}Pa after 28 days (indirect production)

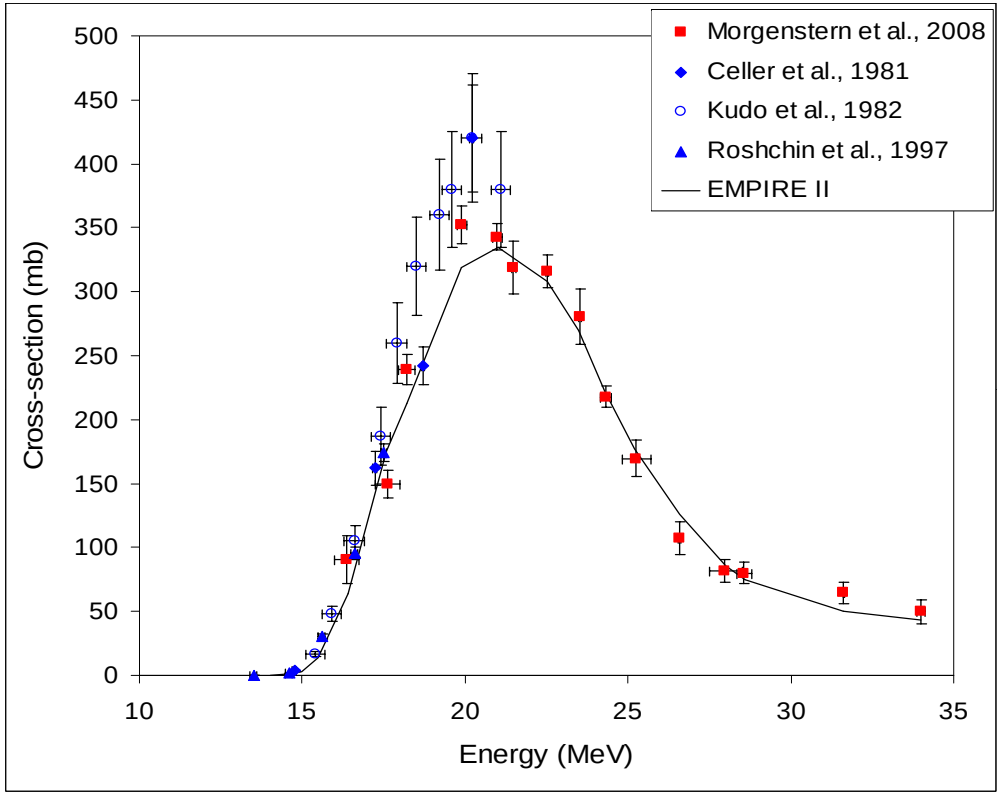
- Proton irradiation of ^{231}Pa

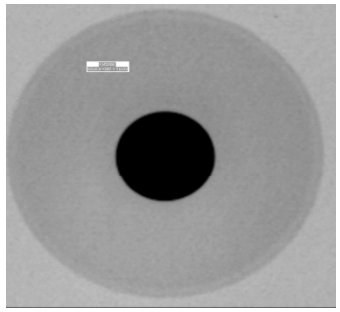
  $^{231}Pa(p,2n)^{230}U$

=> Direct production

Production of ^{230}U through proton irradiation of ^{232}Th

^{232}Th(p,3n)^{230}Pa(β^-)^{230}U





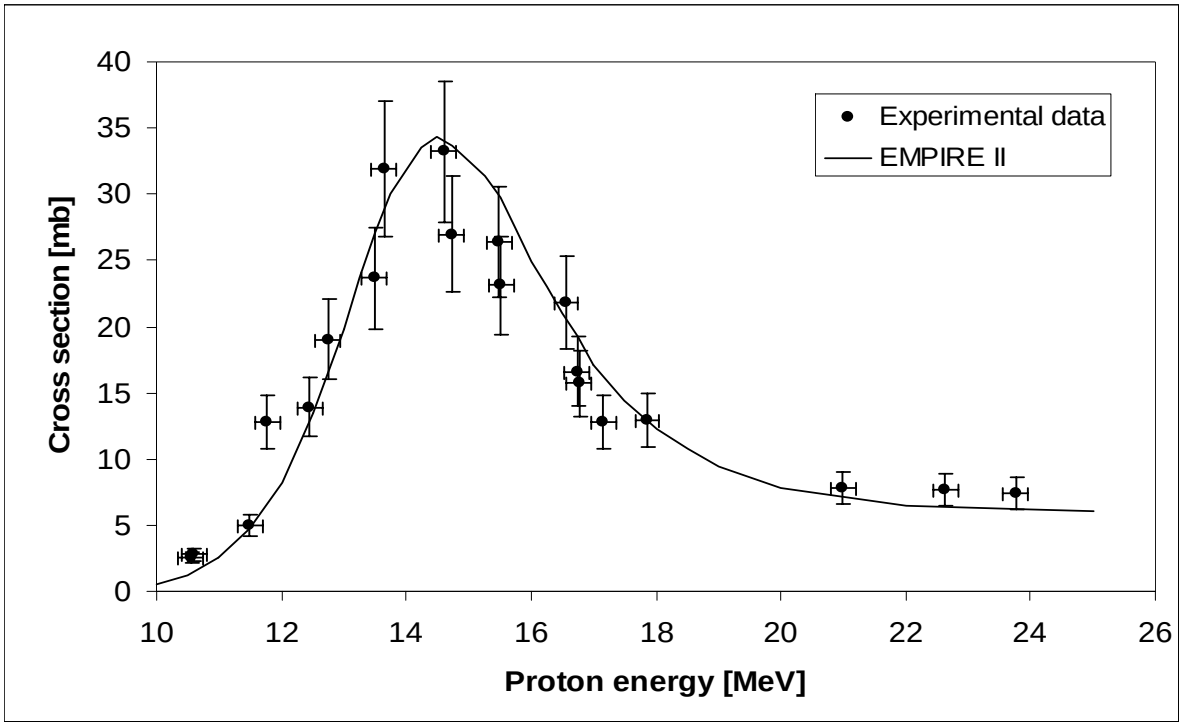
X-ray image of Th-232 metal disc in Al envelope

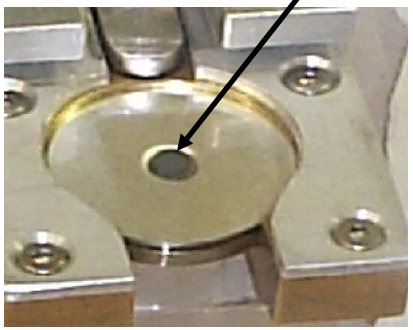
Th-232 target and water cooled high current target holder

+ simple irradiation of low radioactive Th-232 metal
+ isotopically pure U-230 product
- only moderately effective (approx. 0.24 MBq/µAh for thick targets)
- co-production of fission products (Th-232(p,f))

A. Morgenstern et al., Appl. Rad. Isotop. 2008

Production of ^{230}U through proton irradiation of ^{231}Pa
^{231}Pa(p,2n)^{230}U



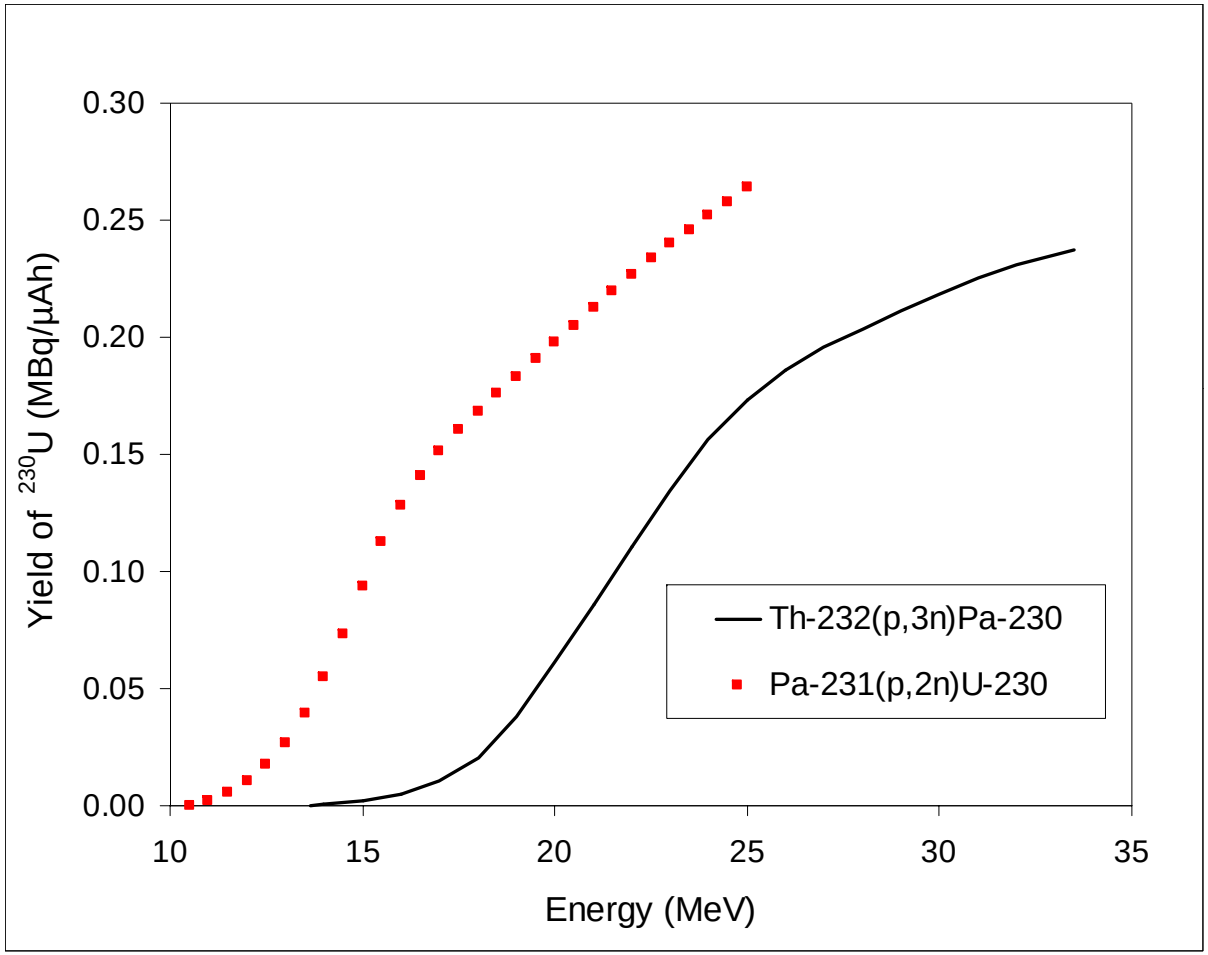


Pa pellet in silver envelope

+ irradiation of relatively long-lived ^{231}Pa ($T_{1/2}$ = 32760 years)
  => simple production and handling of targets
+ target material Pa-oxide or metal
  => mechanically stable and insoluble in water
+ comparable U-230 yields (approx. 0.25 MBq/µAh for thick targets)

A. Morgenstern et al., Anal. Chem. 2008

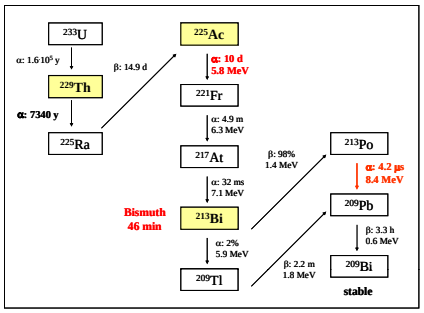
Thick target yields



Yield of U-230 from $^{232}Th(p,3n)^{230}Pa(\beta^-)^{230}U$ is calculated on day 28 after EOB (2.8 % of Pa-230 activity)

In vitro comparison, experimental conditions

Single alpha emitter Bi-213 vs. alpha cascade emitter Th-226

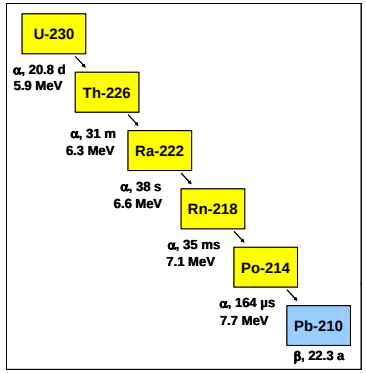


Bi-213 ($t_{1/2}$ = 46 min):

1 alpha particle
E = 8.4 MeV

Th-226 ($t_{1/2}$ = 31 min):

Rapid cascade of
4 alpha particles
E_{tot} = 27.7 MeV



- CHXA-DTPA-HuM195 (anti-CD33) labelled with Bi-213 or Th-226 at identical specific activities (23 - 230 kBq/µg)
- Activity concentrations: 2.25 to 225 kBq/ml
- Cell lines: sensitive HL-60 (CD33 +/+) as well as HL-60 (CD33 +/+) cell lines resistant to beta-radiation, gamma-radiation or chemotherapy
- Cell death and apoptosis measured by flowcytometry

Summary

- ITU produces ca. 350 mCi high purity Ac-225 from Th-229 annually
- Available free-of-charge to partner institutes as Ac-225/Bi-213 generator or dry Ac-nitrate, -chloride
- Cyclotron driven process for scale-up of Ac-225 production is available for commercial application
- Two cyclotron driven processes for production of novel alpha emitters U-230/Th-226 available
- The alpha cascade emitter Th-226 is more cytotoxic than Bi-213 *in vitro*
- *In vivo* comparison of Th-226 and Bi-213 ongoing in a bladder carcinoma mouse model (*B. Pfost et al., ISRTRD/ALPHA Session1: Clinical & Pre-clinical Studies, Sunday, June 14, 12:57 PM*)

Acknowledgements

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Thank you for your attention!