PRELIMINARY RESULTS PRISMAP PROJECT:

OPTIMIZED CYCLOTRON PRODUCTION OF ASTATINE: ACTIVITY BALANCE OF ASTATINE AND POLONIUM AFTER EXTRACTION CHROMATOGRAPHY

M. B. C. Sevenois, dr. L. Navarro, prof. dr. M. d’Huyvetter, prof. dr. P. Covens

Project supervisor: prof. dr. F. Haddad, prof. dr. C. Duchemin

VRIJE UNIVERSITEIT BRUSSEL

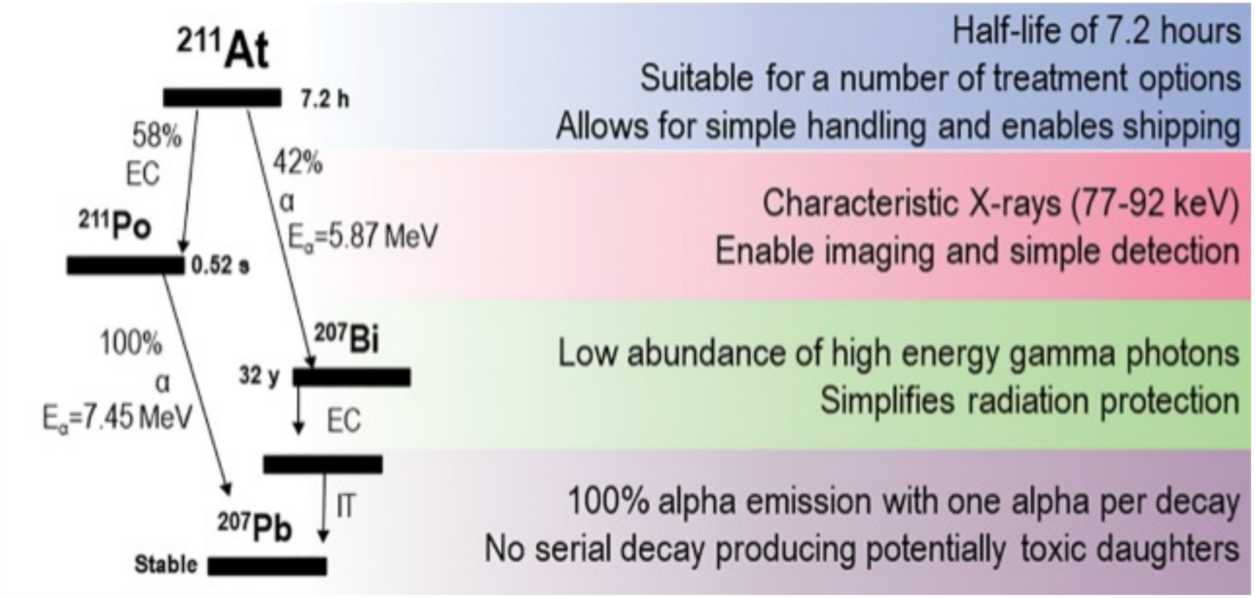
MOLECULAR IMAGING & THERAPY RESEARCH GROUP

Matthijs.bart.sevenois@vub.be

27 EU P Prismap

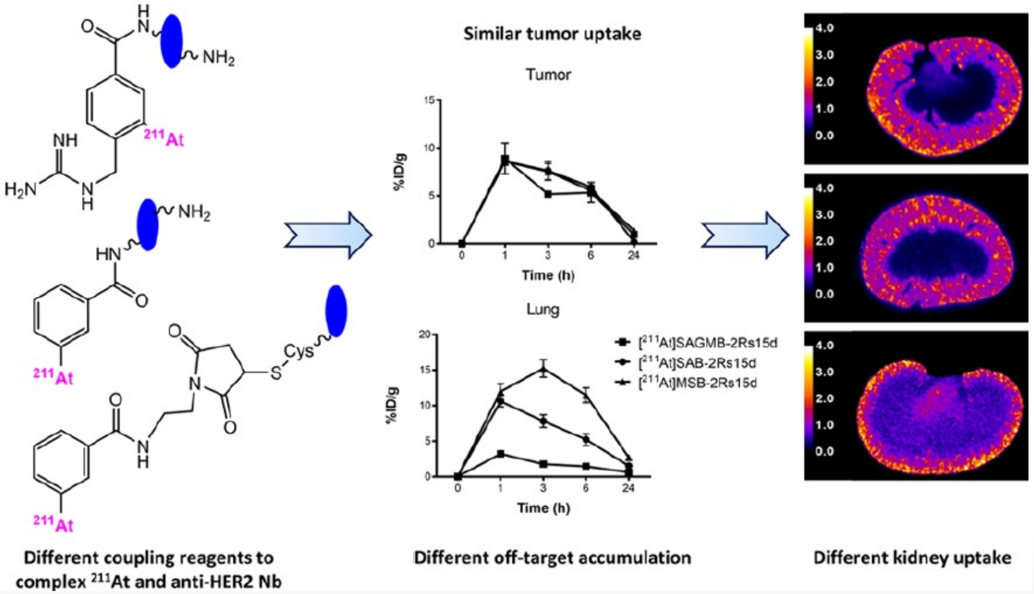
Table of contents

^{211}At as a promising radionuclide for TAT



Lindegren *et al, 2020*

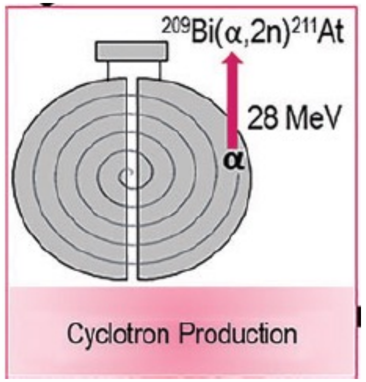
- Cyclotron produced & cost-effective
- Distribution
- Radiolabelling & conjugation



Dekempeneer *et al, 2019*

Drawback of ^{211}At: availibility

- Common method for production



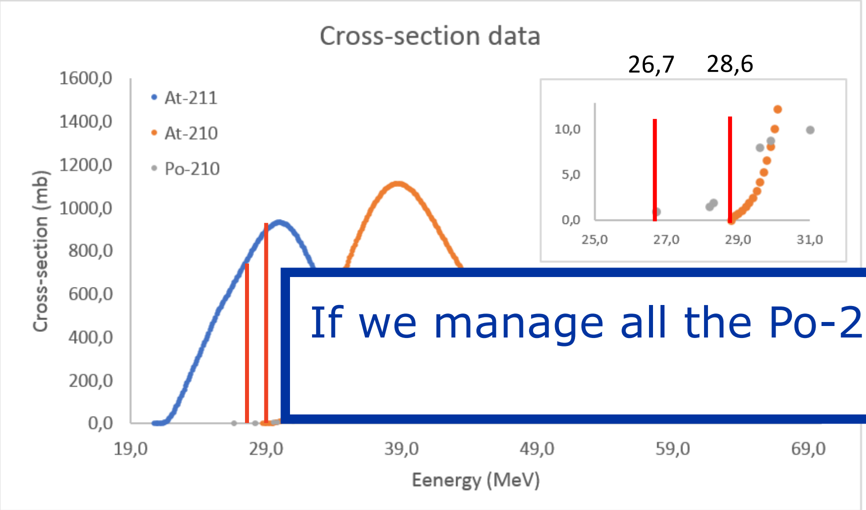
Lindegren *et al, 2020*

MC32 scandotronix, Copenhagen

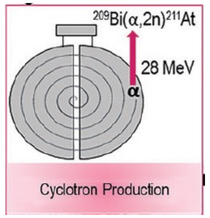
- Limited number of cyclotrons

- Production based on α-beam energy < 28,6 MeV

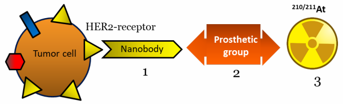
^{211}AT AND THE PRODUCTION CHALLENGE

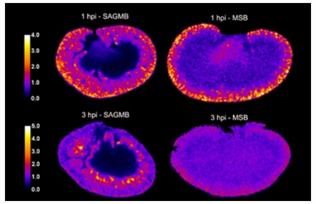


^{210}Po Source term



If we manage all the Po-210 in every step of the way, can we increase the production of At-211?



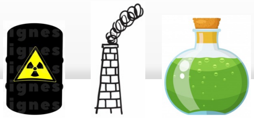


Dekempeneer *et al*, 2019

Processing labelling Toxicity studies

- ^{210}Po as the daughter of ^{210}At
- Directly produced ^{209}Bi(α,x)^{210}Po

waste issues **Dosimetry issues**



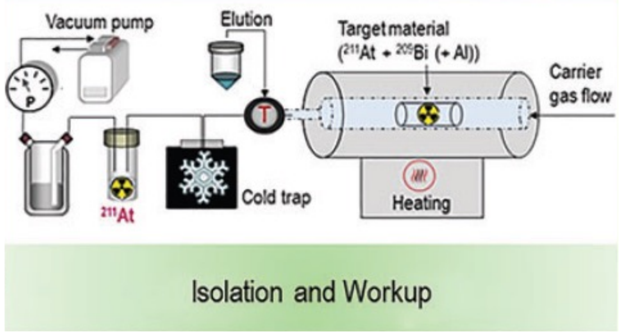
VRIJE UNIVERSITEIT BRUSSEL

PRISMAP project work packages

- WP 1: target characterization and influence of production methods
- WP 2: Analysis of activity balance during target processing and labelling
- WP 3: Analysis of biodistribution of $^{211/210}At$ labelled sdAbs

Table of contents

Target processing



Lindegren *et al*, 2020

Tereshatov *et al*, 2022

- Common method of extraction: dry distillation
  - Oven > Bp astatine (380°C)
  - Cold trap
  - Chloroform/methanol

- Novel technique: radiochemical separation by extraction chromatography (Burns et al, 2020)
  - Advantages
    - Cheaper alternative
    - Absence of radioactive gasses
    - Simple setup allows easy sampling for activity balance of radionuclides

Procedure

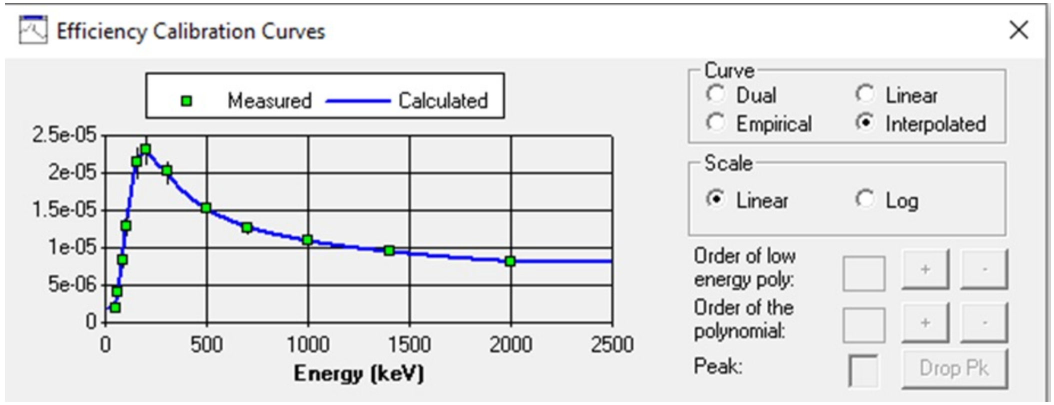
1. Characterization of target $^{211}At/^{210}At$
2. Dissolve target using customized in-house dissolution unit
   - Measure fractions of dissolved target $^{211}At/^{210}At/^{210}Po$
3. Extraction chromatography
   - Measure collected fractions $^{211}At/^{210}At/^{210}Po$
4. Target characterization after dissolution

Characterization of target

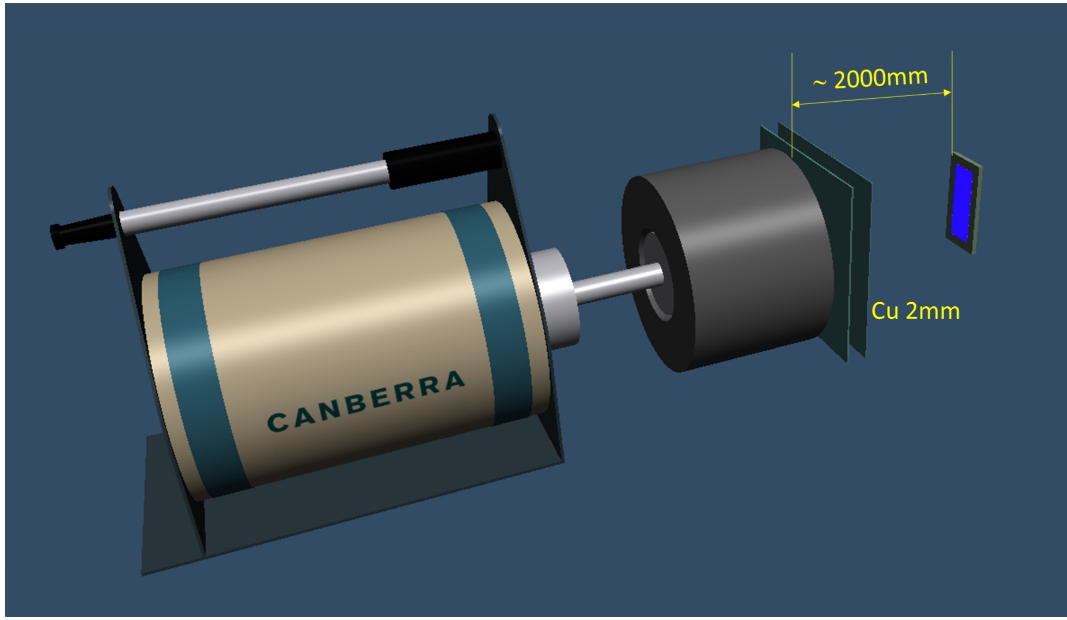
HPGe detector with ISOCS

for $^{211}At/^{210}At$ determination

- Monte Carlo based
- Geometry specific

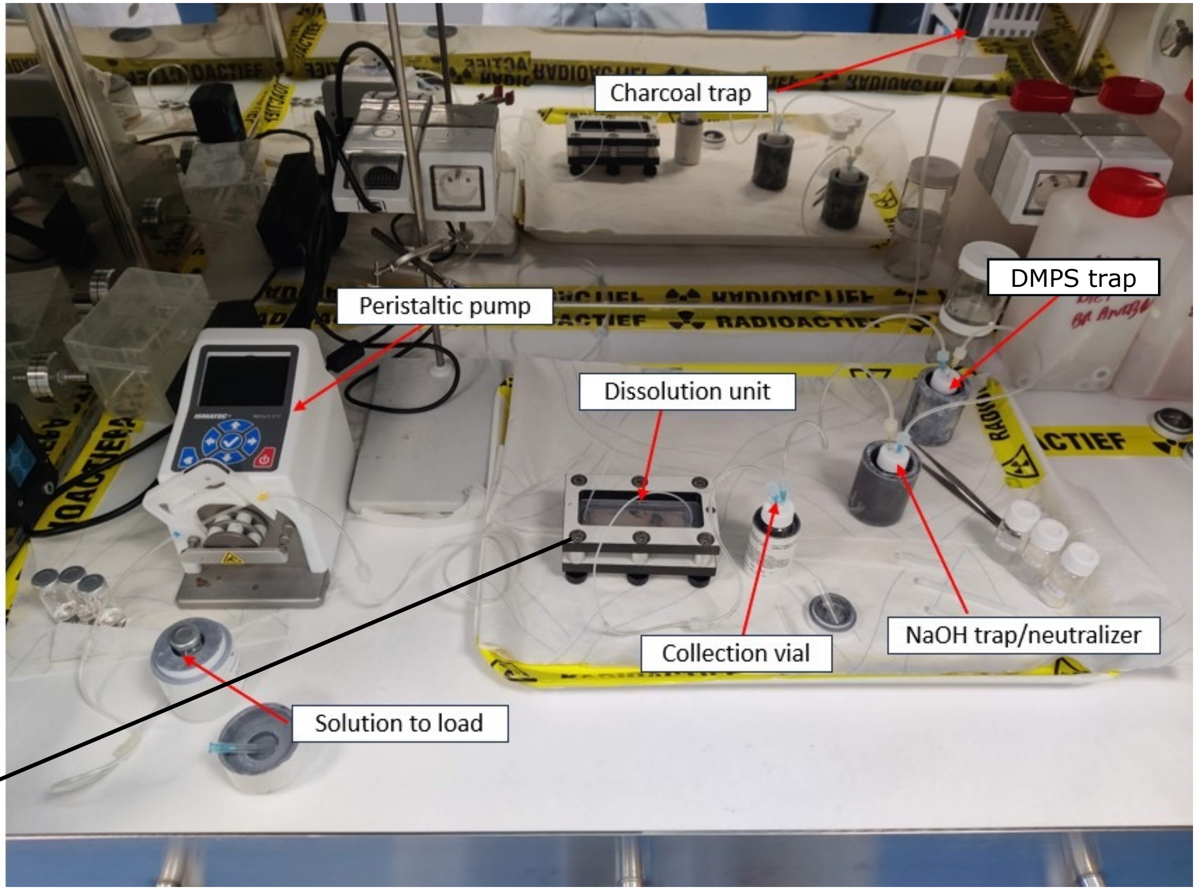


Mirion technologies, 2023

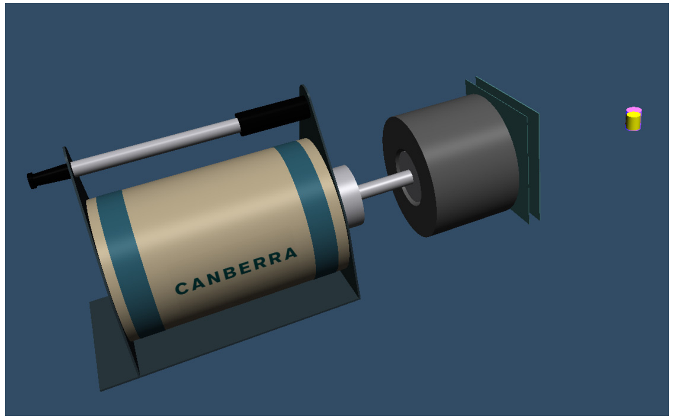


Dissolution of target

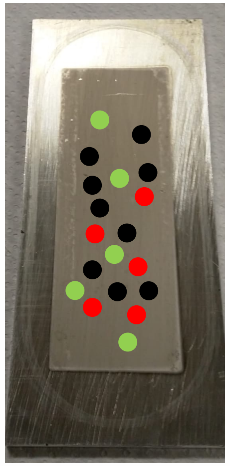
- Setup:
  - Peristaltic pump – controlled flow
    - 6 M HNO_3
  - Customized in-house built dissolution unit
    - Thin window allows small film of liquid
  - NaOH trap
  - DMPS trap
  - Charcoal trap



Dissolution of target



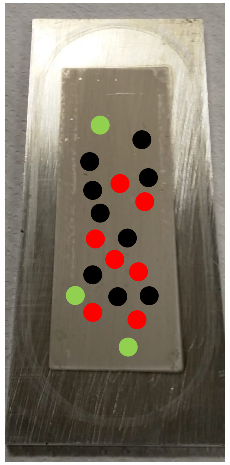
At Arronax



^{211}At: 7,2h
^{210}At: 8,1h
^{210}Po: 138d

9h

At MITH before dissolution



^{211}At
^{210}At
^{210}Po

Dissolved target (B6M)

^{211}At/^{210}At by HPGe

Sampling

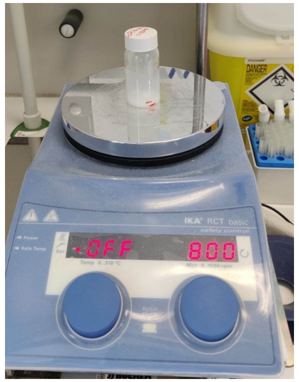
7 days

^{210}Po by LSC

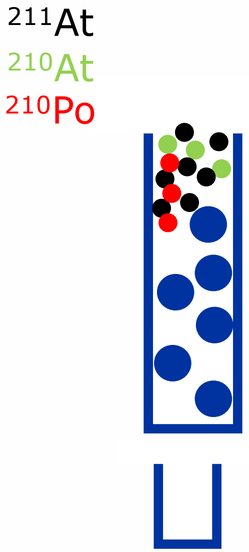
B6M

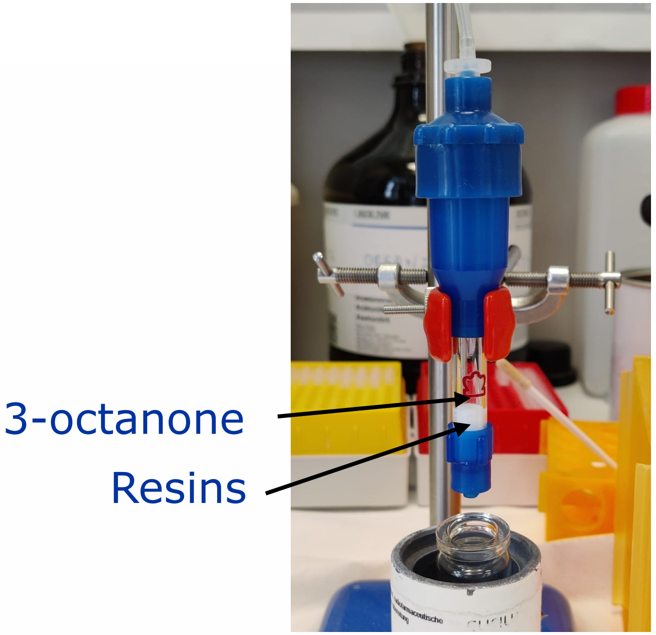
Hidex triathler

Extraction chromatography



- Based on impregnated resins (Amberchrom CG300M) with 3-octanone
- Extraction chromatography recipe
  1. Load the dissolved target
  2. Rinse with 2 M HNO_3
  3. Flush with H_2O
  4. Elute with EtOH





Extraction chromatography

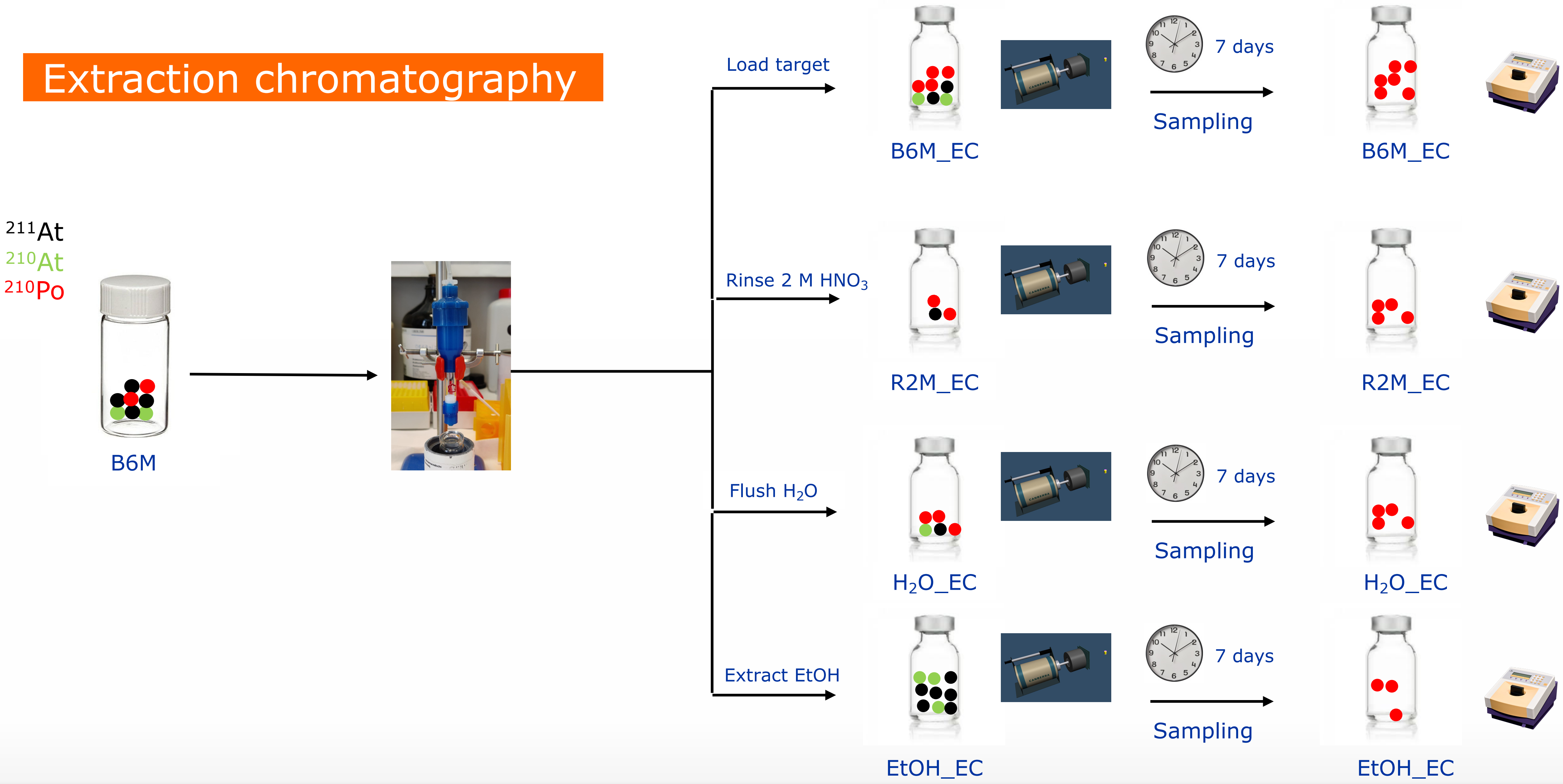
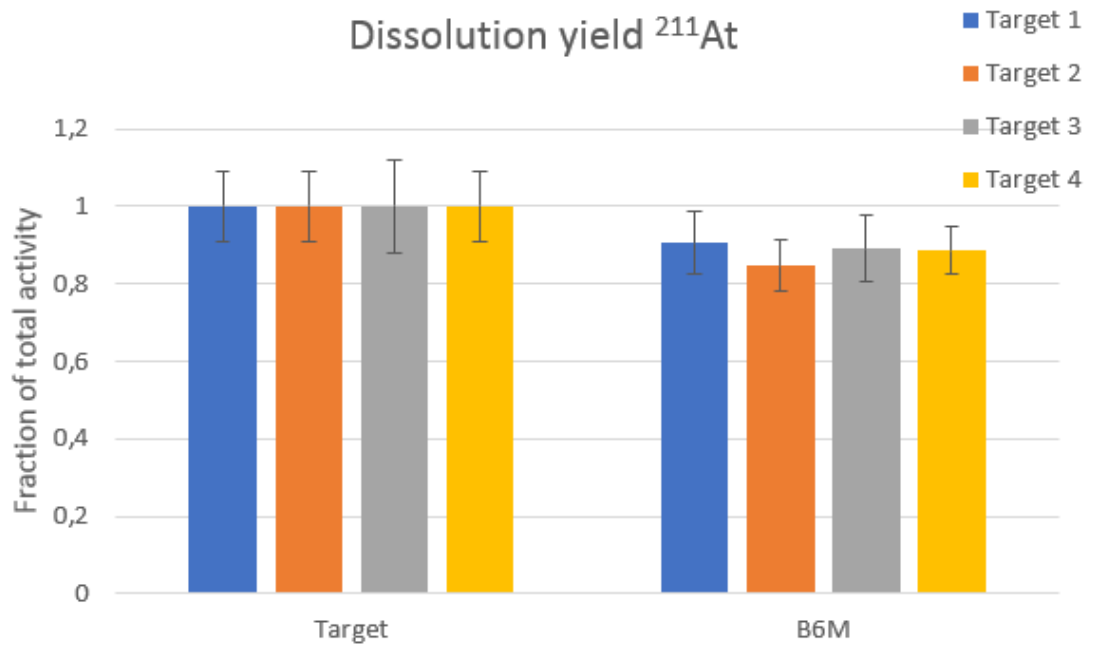
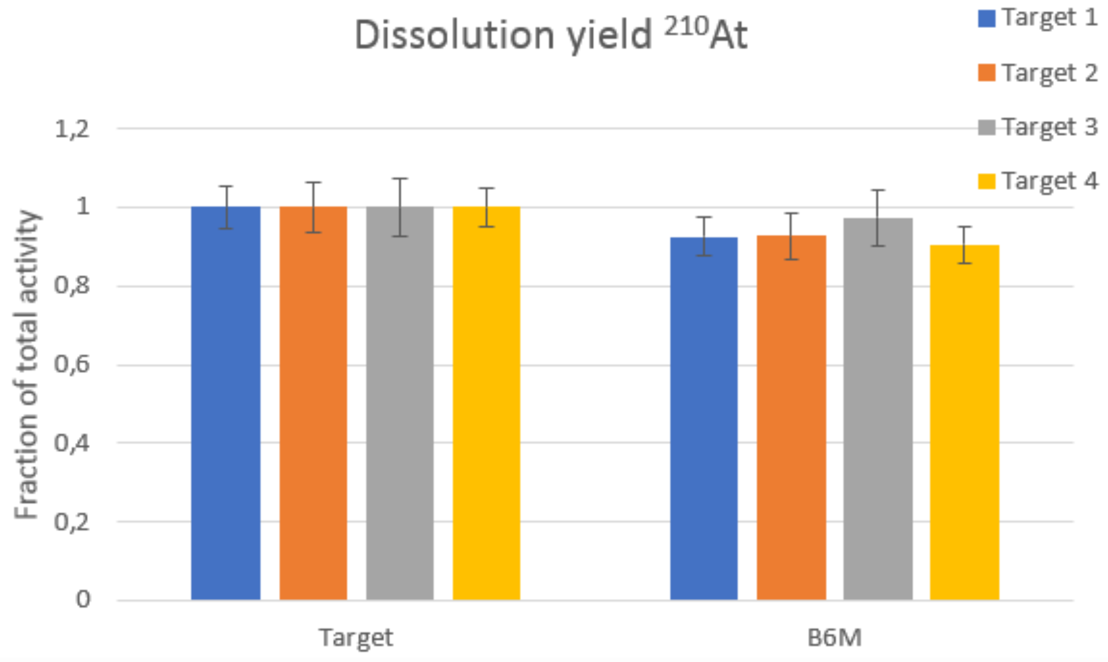


Table of contents

Activity balance results astatine

	Dissolution yield (%)
^{211}At	85-90
^{210}At	90-98



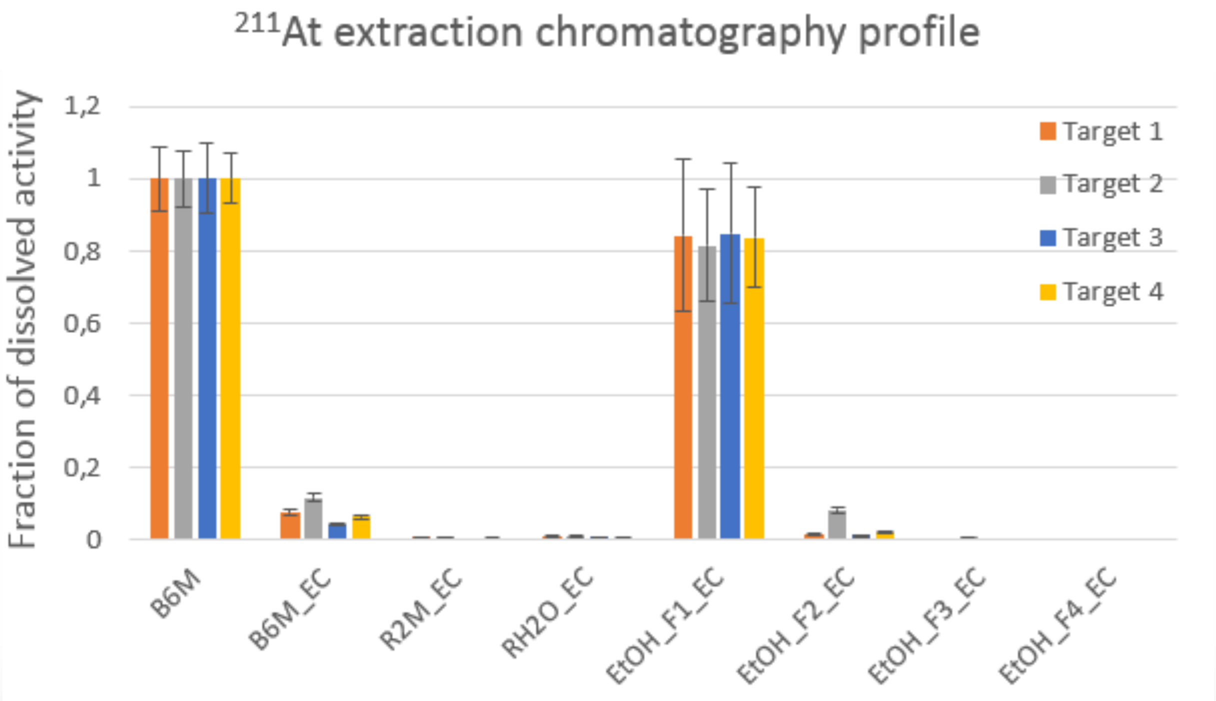


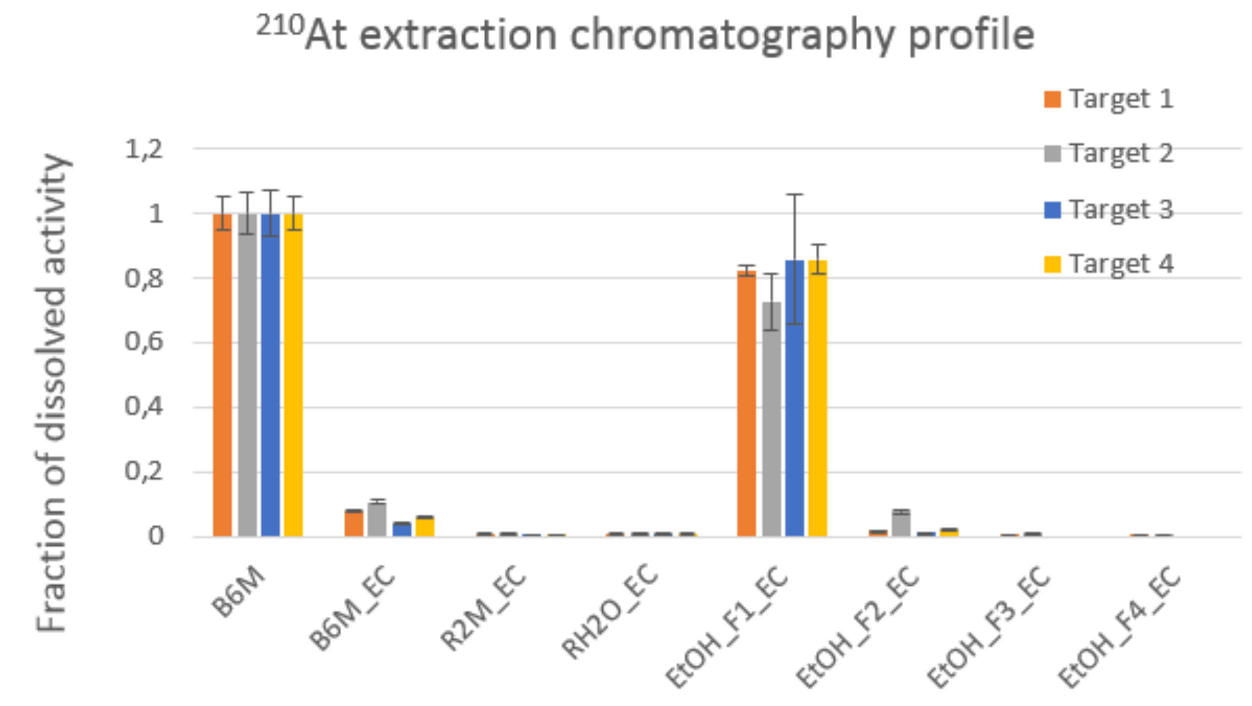
VRIJE UNIVERSITEIT BRUSSEL

MOLECULAR IMAGING & THERAPY RESEARCH GROUP

Activity balance astatine

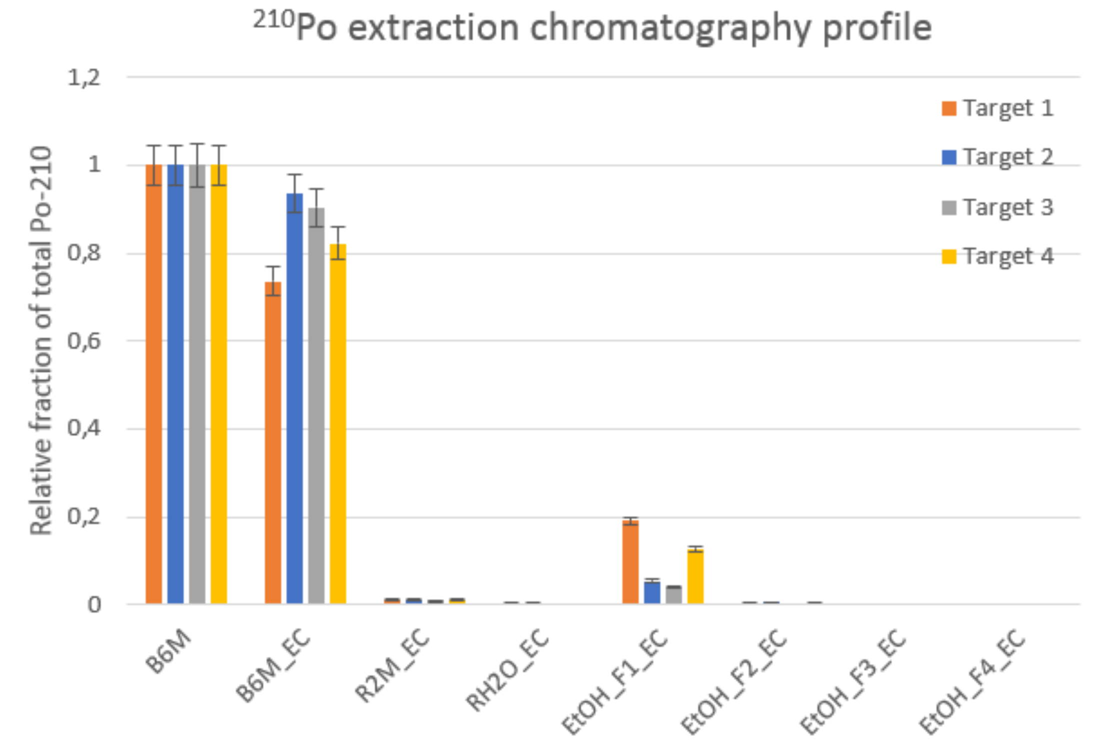
	Dissolution yield (%)	Extraction yield (%)	Overall yield (%)
^{211}At	85-90	82-85	69-76
^{210}At	90-98	72-85	65-83





Activity balance polonium

- > 95 % of ^{210}Po formed before EC in waste
- ^{210}Po in EtOH fraction: mainly due to ^{210}At but 95% confidence interval includes even 0 Bq ^{210}Po



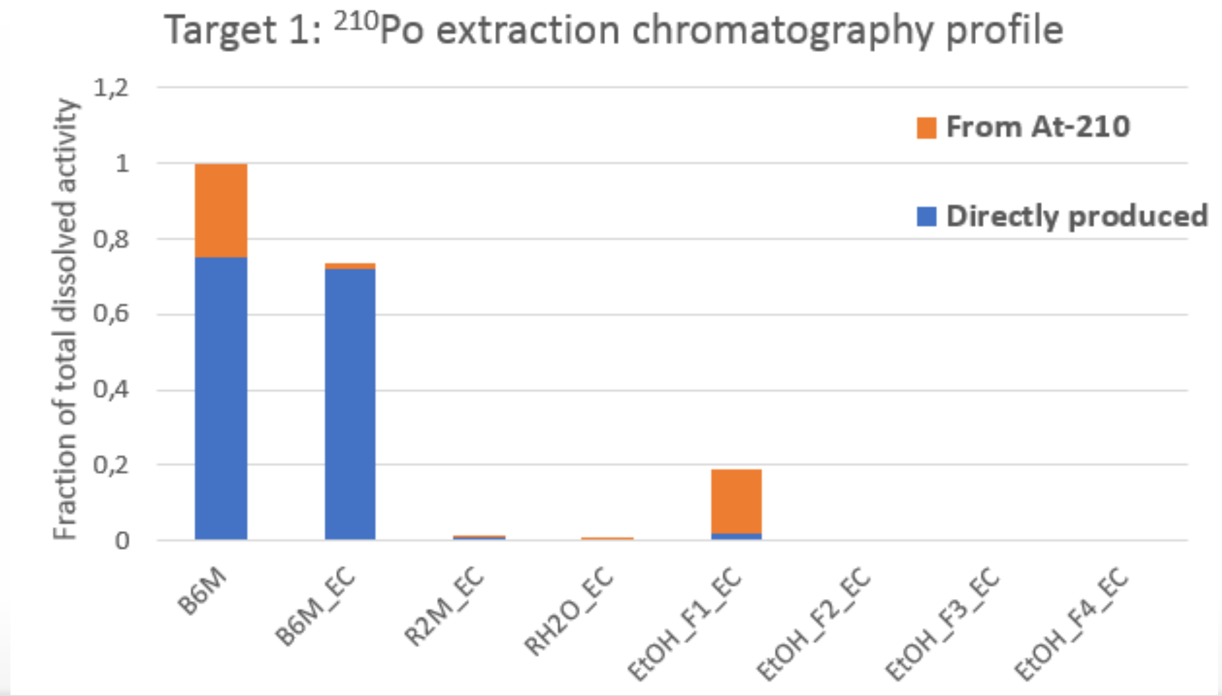
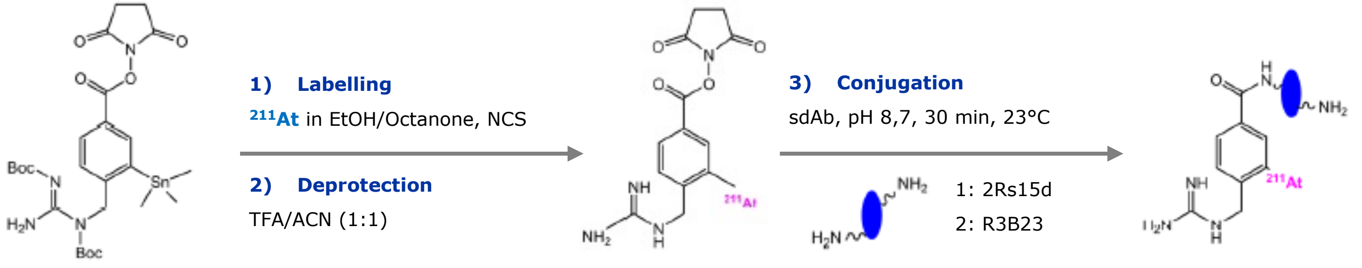


Table of contents

CHEMISTRY

- **[^{211}At]GAMB-sdAb prod.**
  - Future biodistribution study
  - GAMB linker selected (better stability)
  - Preliminary results



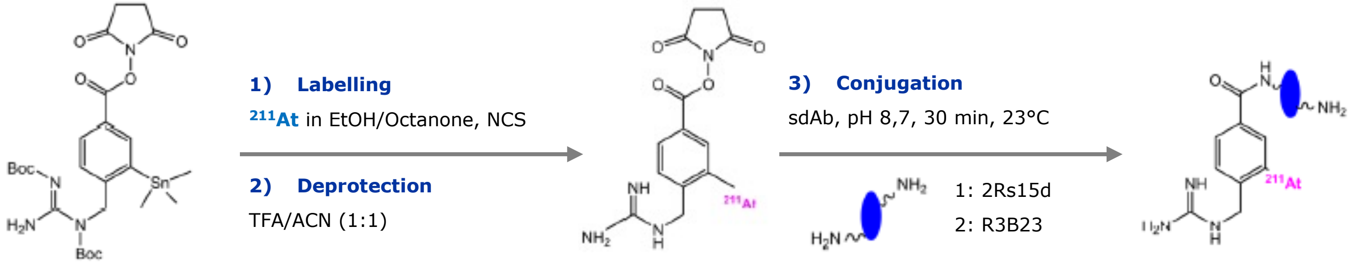
SGMTB-Boc$_2$ → **^{221}At-SAGMB** → **^{221}At-GAMB-sdAb**

Cond.	Target 1	Target 2		Target 3		Target 4
LAB.	92,3%	93,5%	97,2%	94,3%	/	90,0%
DEP.	97,3%	98,0%	98,1%	97,2%	/	98,5%
SAGMB yield	**47,5%**	**48,3%**	**61,8%**	**89,4%**	**92,1%**	**85,4%**
CONJ. (2Rs15d)	38,20%	57,0%	52,0%	/	/	/
CONJ. (R3B23)	/	50,6%	48,7%	/	/	/

Last process optimization to be confirmed during the next targets!

CHEMISTRY

- **[^{211}At]GAMB-sdAb prod.**



SGMTB-Boc$_2$ → ^{211}At-SAGMB → ^{211}At-GAMB-sdAb

❑ Preliminary conclusion:

- **Significant improvement in the yield of the ^{211}At-SAGMB linker** (> 80%) despite the chemical limitations associated with the presence of octanone in the medium
- Development of an evaporation method aimed at **eliminating the octanone** before coupling the ^{211}At-SAGMB linker to the protein
- **Conjugation processes validated** (> 40%) on selected VHH (anti-HER2 VHH 2Rs15d / non-targeted VHH R3B23)
- **Best chemistry results** so far with this extraction method (no comparable result in literature yet)

❑ Perspectives:

- Validation robustness **chemistry** with ^{211}At in EtOH/octanone
- Optimization evaporation process of the octanone to prevent any residues before conjugation on protein
- Evaluation of ^{211}At-SAGMB linker labelling involving **a whole source of astatine** produced by this method

} 3 targets (chemistry)
1 mock run

Table of contents

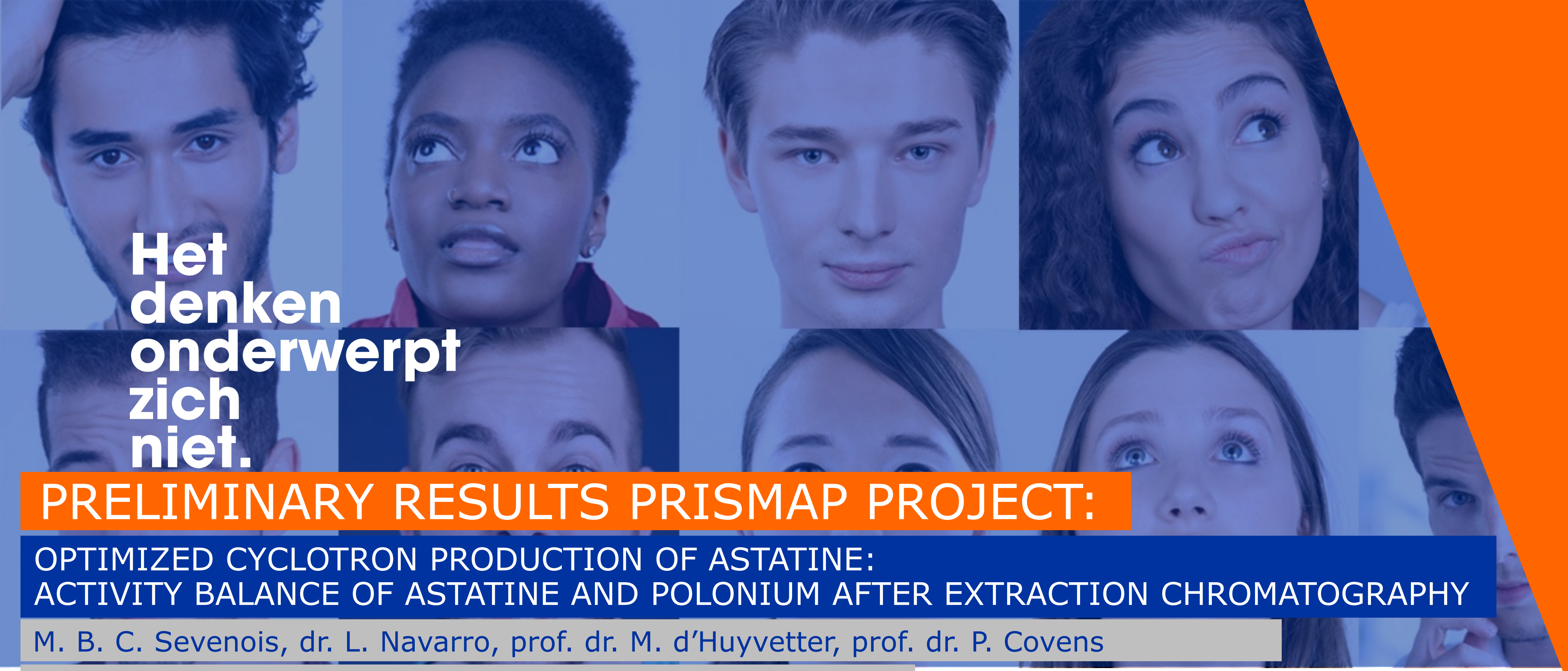
- Introduction: ^{211}At as a promising radionuclide for TAT
- Procedure of target processing
- Activity balances of astatine and polonium
- Radiolabelling and –conjugation
- Conclusion & future prospects

Conclusion & future prospects

- DC **> 70% overall yield** are obtained using extraction chromatography
- Current procedure allows maximal separation of $^{211/210}At$ and ^{210}Po
- Can we manage the produced Po-210 during target processing, to potentially increase the production of At-211?
- ^{210}At will be the main contributer of ^{210}Po internal activity for a relative high $^{210}At/^{211}At$ ratio (10^{-3})
- Patient injected activity of 100 MBq would lead to max ingrowth of < 500 Bq ^{210}Po

Future prospects

- Optimize radiolabelling and –conjugation strategy
- Start of biodistribution studies for low and high ratio of $^{210}At/^{211}At$
- Model biokinetics of ^{210}Po after IV administration of $^{211/210}At$ radiolabelled sdAbs



PRELIMINARY RESULTS PRISMAP PROJECT:

OPTIMIZED CYCLOTRON PRODUCTION OF ASTATINE: ACTIVITY BALANCE OF ASTATINE AND POLONIUM AFTER EXTRACTION CHROMATOGRAPHY

M. B. C. Sevenois, dr. L. Navarro, prof. dr. M. d'Huyvetter, prof. dr. P. Covens

Project supervisor: prof. dr. F. Haddad, prof. dr. C. Duchemin

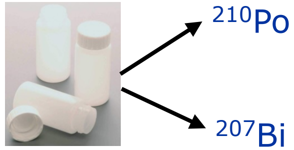
VRIJE UNIVERSITEIT BRUSSEL

MOLECULAR IMAGING & THERAPY RESEARCH GROUP

Matthijs.bart.sevenois@vub.be

27 EU P Prismap

LSC as modality for ^{210}Po detection



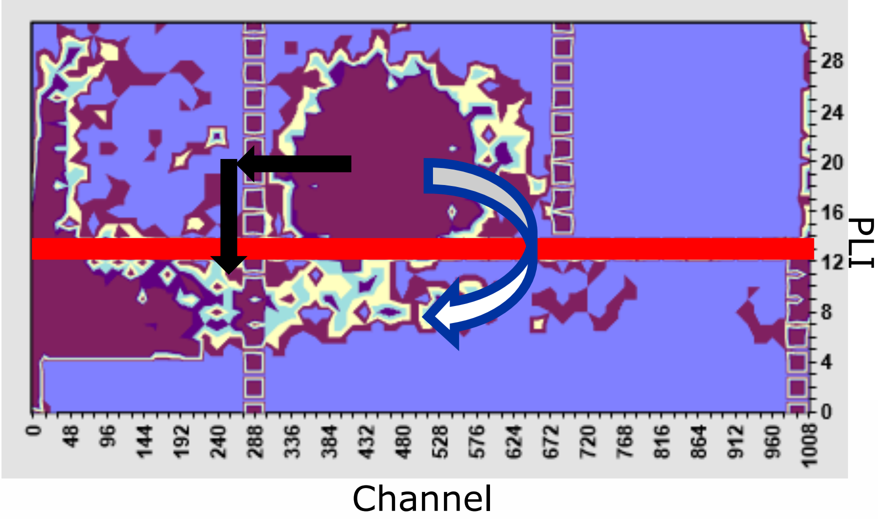
Advantages:

- 4ϖ geometry detection
- Sample capacity
- Fast

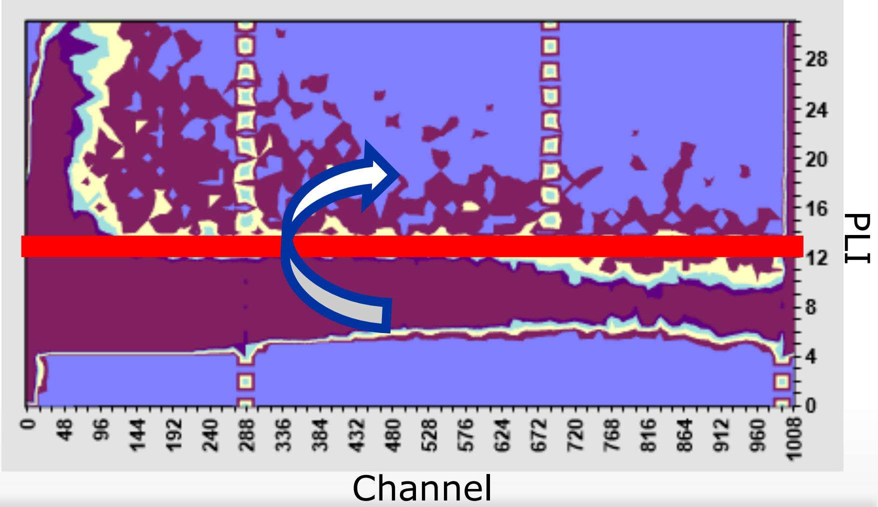
Disadvantage

- Sensitive to quenching
- Calibration for every matrix

^{210}Po spectrum



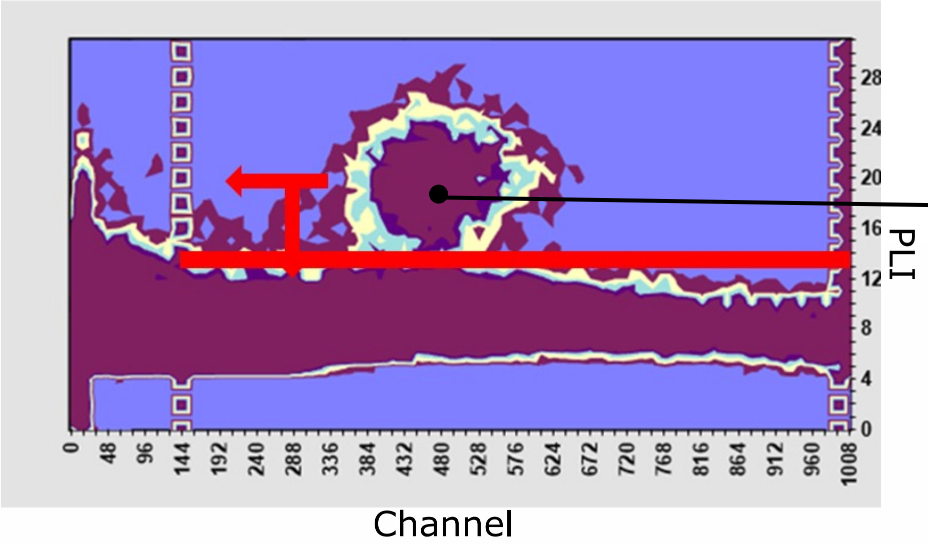
^{207}Bi spectrum

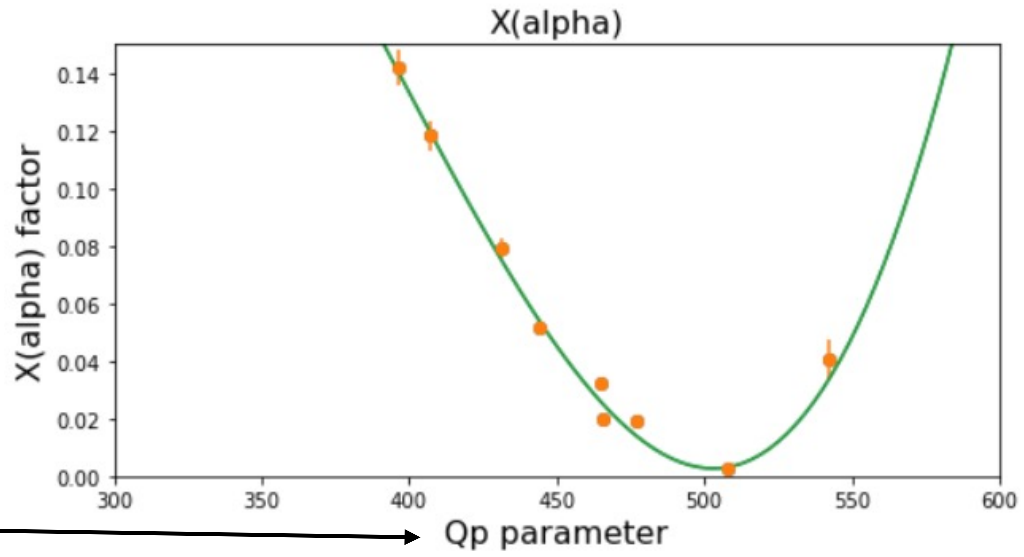


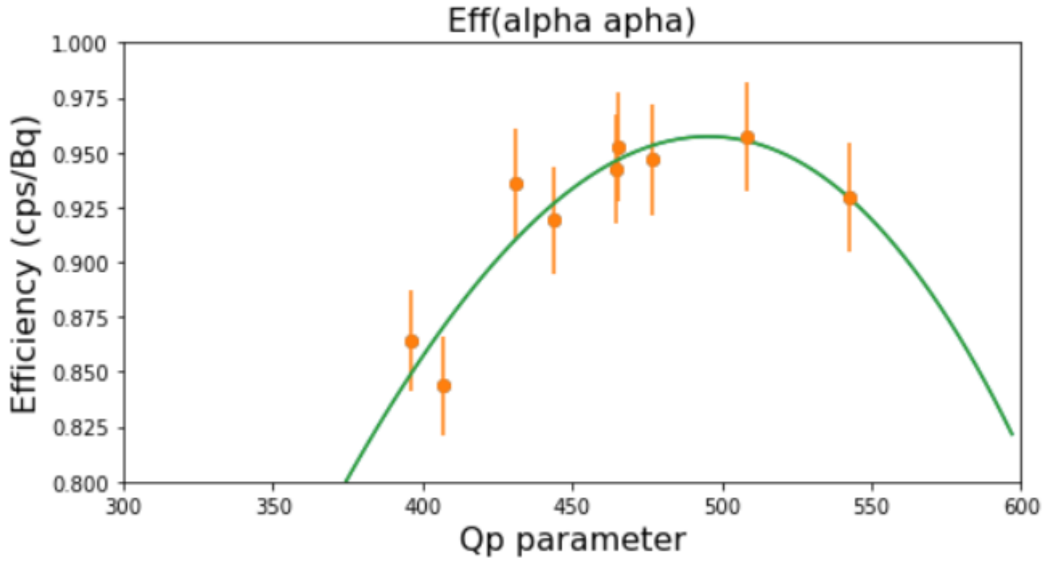
- Alpha/beta separation recipe:
  - Determine the pulse length index (PLI)
  - Determine optimal ROI
  - Determine efficiency and spill-over matrix
    - For every sample matrix

LSC as modality for ^{210}Po detection

^{211}At spectrum







- Generate efficiency and spill-over curves
  - Set of different molarity HNO_3

Overview of target activities

- Irradiation time: 2h
- Average beam current: 15 µA

Target 1		Target 2		Target 3		Target 4	
Direct ^{210}Po (%)	Total ^{210}Po	Direct ^{210}Po (%)	Indirect ^{210}Po	Direct ^{210}Po (%)	Indirect ^{210}Po	Direct ^{210}Po (%)	Total ^{210}Po
74,9	4960 ± 225	92,1	2425 ± 111	95,3	1778 ± 87	79,2	6146 ± 273

EOB	Target 1	Target 2	Target 3	Target 4
^{211}At (MBq)	687 ± 62	739 ± 66	657 ± 80	783 ± 70

VRIJE UNIVERSITEIT BRUSSEL