Radiopharmaceutical Chemistry of Targeted Radiopharmaceutics

Synthesis of Astatine-211 labeled Radiopharmaceuticals at High Activities for Clinical Use

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Main Goal

To understand the problem of the synthesis of ^{211}At-labeled radiopharmaceuticals found at the high activities.

And to use this knowledge to overcome this problem to be able to make reliable high yields labeling for therapy.

Background Observations

Decreasing labeling efficiency as activities of alpha-particle increased (therefore radiation dose) likely related to radiolysis.

The impact of the radiolysis-mediated process produced by the α -particle over the labeling chemistry is much higher in comparison with typical β-emitters due to a deposition of energy in the solvent in a highly localized manner two orders of magnitude per unit volume higher than ^{90}Y or ^{131}I.

How was the problem addressed

Setup of a comprehensive study looking for a general pattern about the synthesis of ^{211}At-labeled radiopharmaceuticals at high activities analysing:

Effect of radiation dose (Gy) and dose rate (Gy)

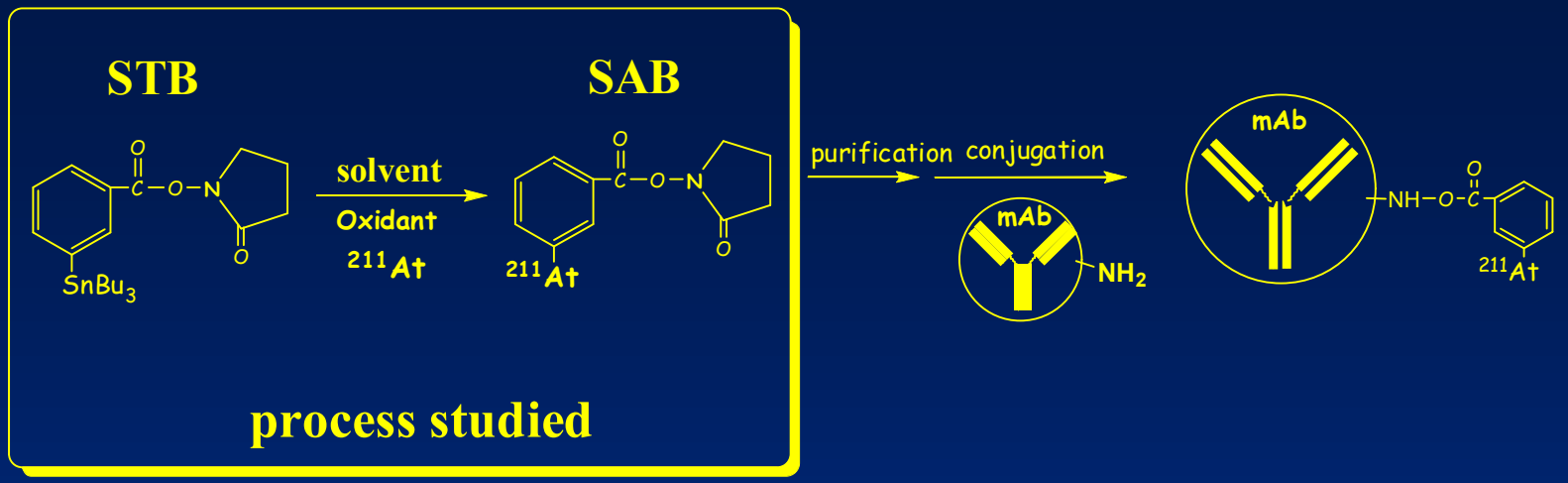
Effect of radiolysis-mediated process

In controlled experiments ⇩ **over**

- **Cold chemistry** : role of solvent and pH over the astatination precursors

- **Hot chemistry**
  - the labeling reaction: nature and yields of labeled product generated
  - over the radioisotope itself ? ,
    influence of the high radiation field over its chemical behavior ?

How the studies were carried out



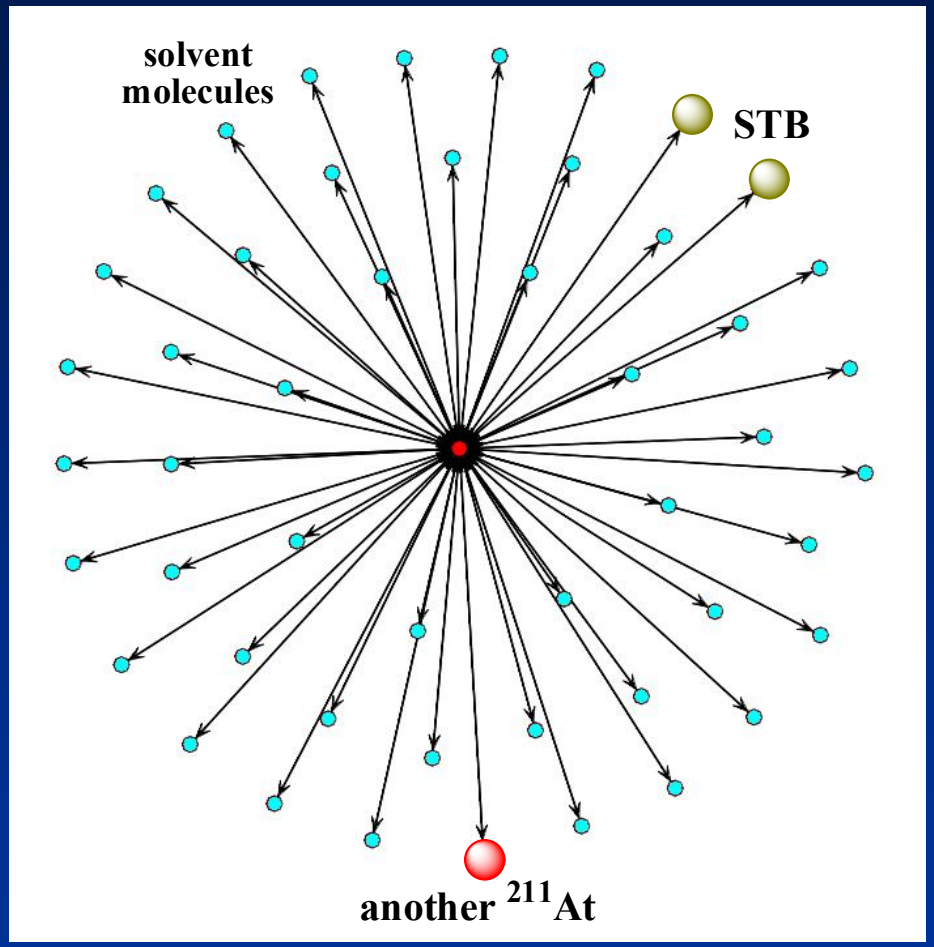
- Choosing STB as astatination precursor model, and SAB as astatinated model compounds
- Choosing chloroform, benzene and methanol as models of the solvent groups mostly used in the past to do astatination, halogenated, aromatics and alcohols.
- Setting up analytical techniques for analyzing STB, SAB and other astatine species
- Careful design of experiments to control radiation dose (Gy) or dose rate (Gy/s)
- Careful recording of activity, time and volume to calculate the radiation dose or dose rate
- Careful (and statistical) analysis of the information

$$D\ (Gy) = A_i(1 - e^{-\lambda t})\frac{1}{\lambda}\frac{1}{m}\Delta_i$$

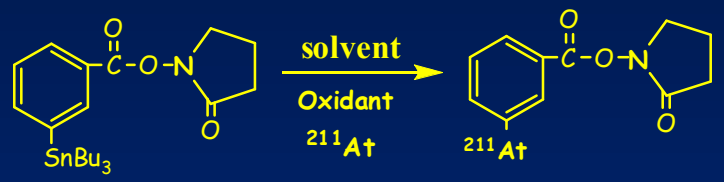
A_i: is the initial activity in MBq,
λ: is the decay constant for ^{211}At (s^{-1}),
t : is the exposure time in seconds,
m: the mass of the solution (g),
Δi: is the mean energy emitted per nuclear transition ($1.09\ 10^{-3}$ Gy·g/MBq·s)
Pozzi, Zalutsky, J.Nucl.Med 2005;46:700-706

Rationale

Why is the interaction of the α particle with the solvent so important ? :



STB **SAB**

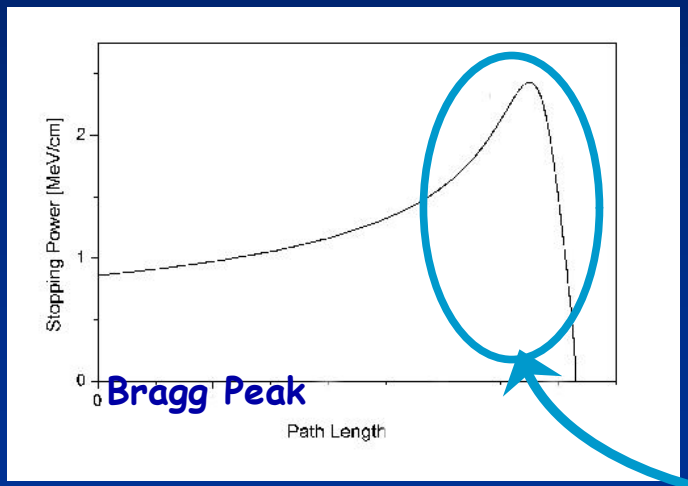


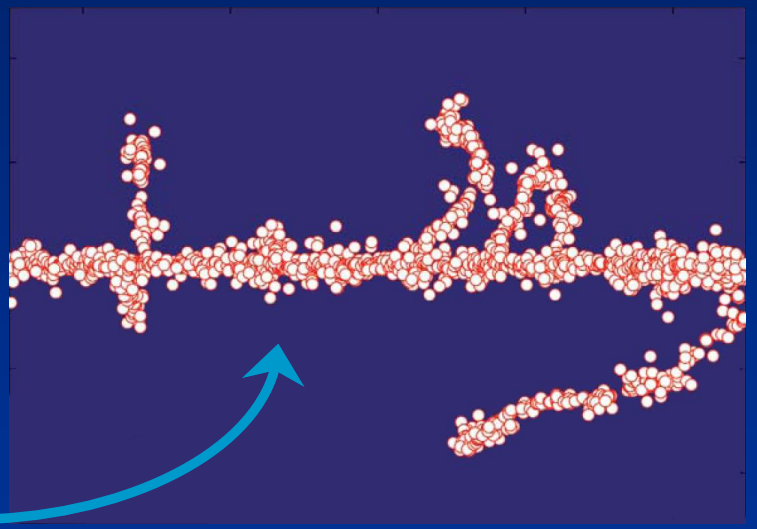
Prototypical SAB synthesis		
Amount of (μL or μg)	Number of molecules	ratio
500 μL MeOH	74.4 10^{20}	5.4 10^{9}
100 μg of STB	1.18 10^{20}	8.5 10^{7}
100 μg NCS (oxidant)	4.5 10^{20}	3.2 10^{8}
1 mCi ^{211}At (37 MBq)	1.38 10^{12}	1

⇨ >> probability of interaction with the solvent

Once interaction happens we have to keep in mind:

- LET_{α} >> LET_{β} : ^{211}At LET_{mean} ≈ 100 KeV/μm vs 0.22 for ^{90}Y (454 times higher).
- Bragg peak: Most of the energy will be delivered very packed in short distance (^{211}At mean range ~ 60 μm) , as a consequence:
  - It will produce <u>critical differences in radiolysis mechanism</u> for α-particle in comparison with β-particle (range 0.5 – 12 mm)
    - → spur overlapping and track formation
    - → radiolysis reactions do not dependent on dose rate or moderated by scavengers

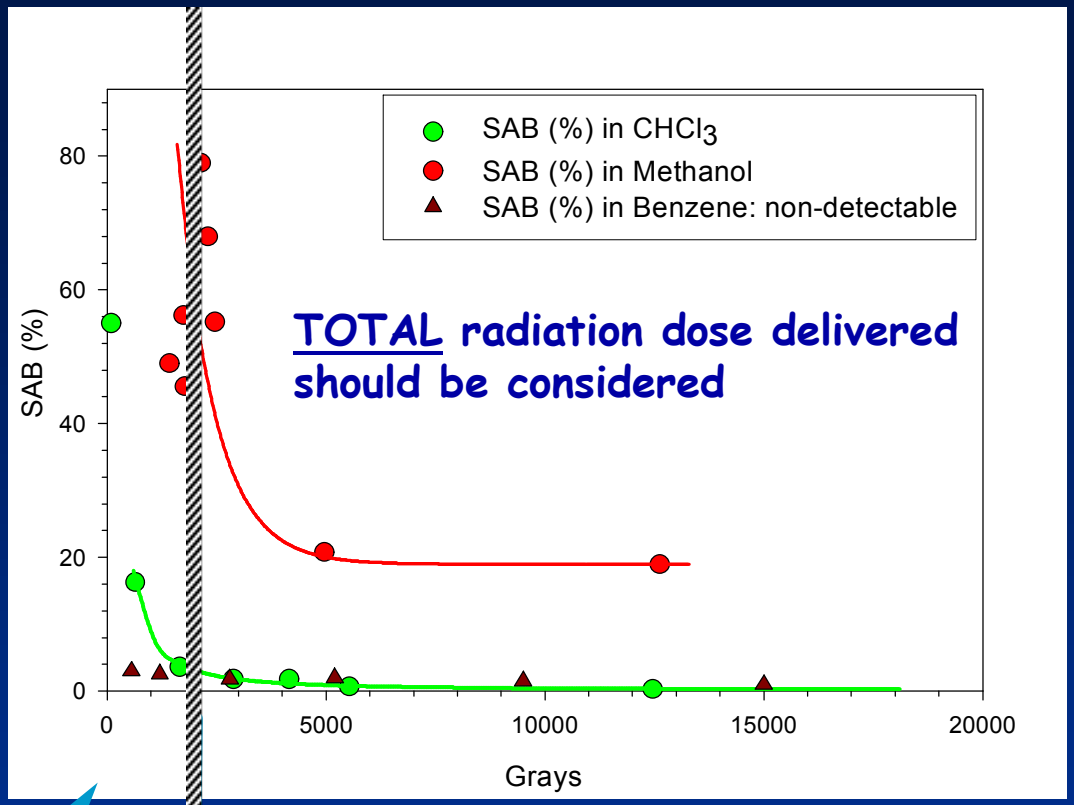


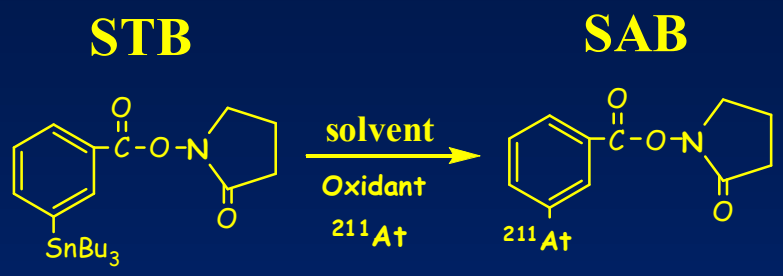


Around 60-70% of the energy is delivered at the end of the range

⇨ **It will modulate reactions at high activities (hence high radiation dose)**

Synthesis of SAB from reaction between STB and ^{211}At in 3 solvents





Aproximately 2000 Gy can be considered the limit between research and labeling for therapy (fc. of rxn time, volume, solvent density; generally < 5-10 mCi)

Pozzi, Zalutsky, J.Nucl.Med 2005;46:1393-1400

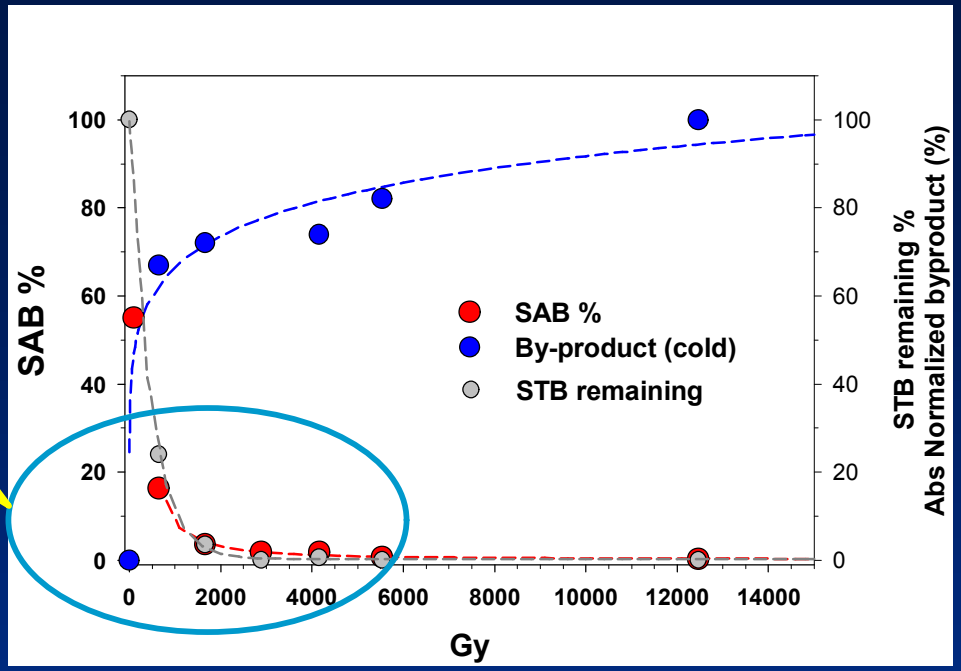
SAB synthesis yield decreased as activity increased (hence dose):

- **Benzene**: useless as solvent for SAB synthesis at almost any activity
- **$CHCl_3$**: useless for therapy labeling
- **MeOH**: therapy labeling might not work (depending on reactions yields, purification steps, etc)

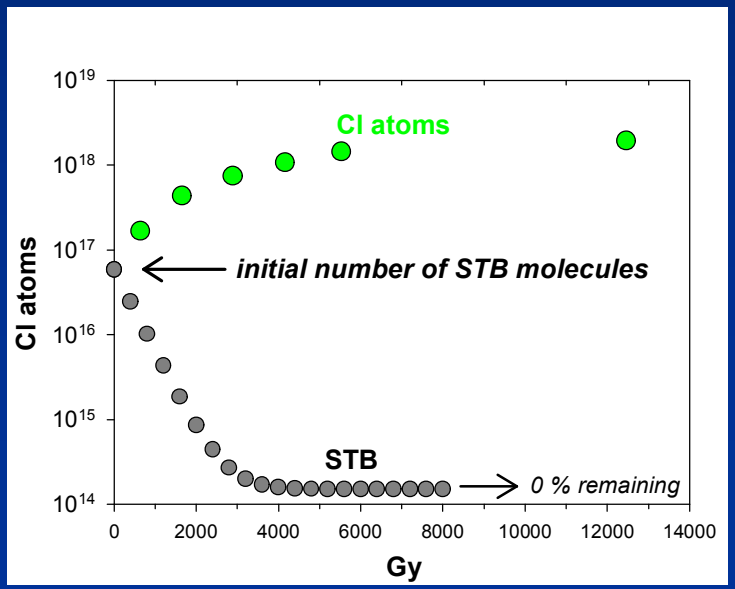
Why ?

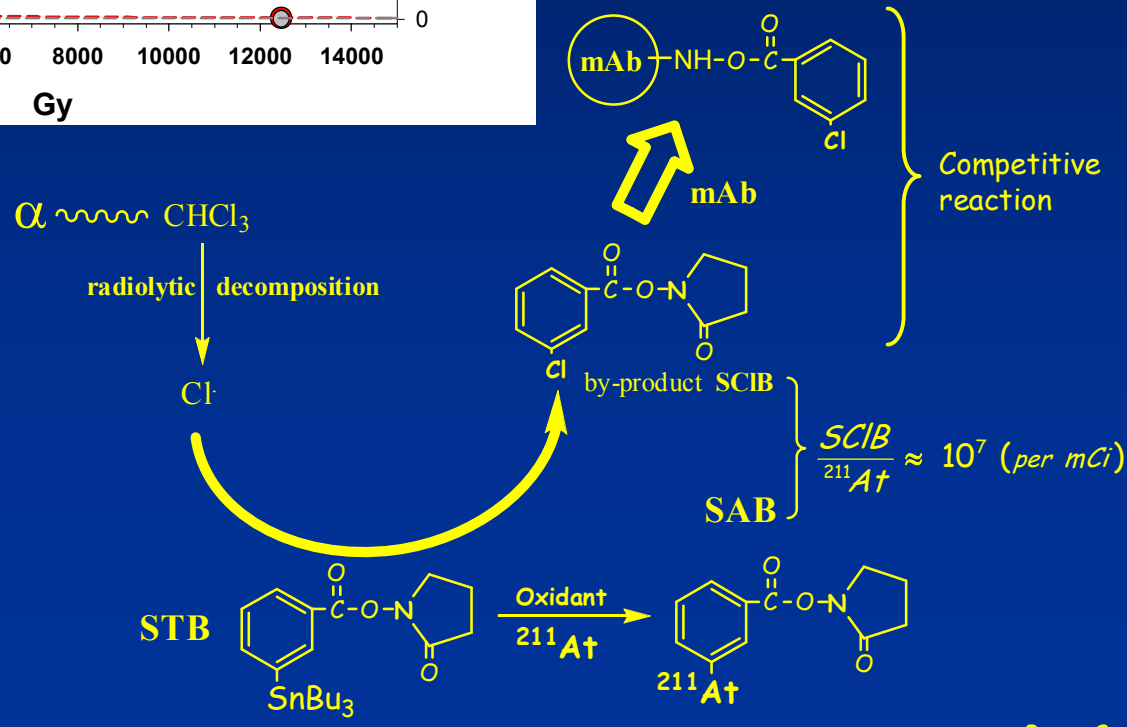
Why does the SAB synthesis reaction in CHCl3 fail?

Strong and fast depletion of the astatination precursor

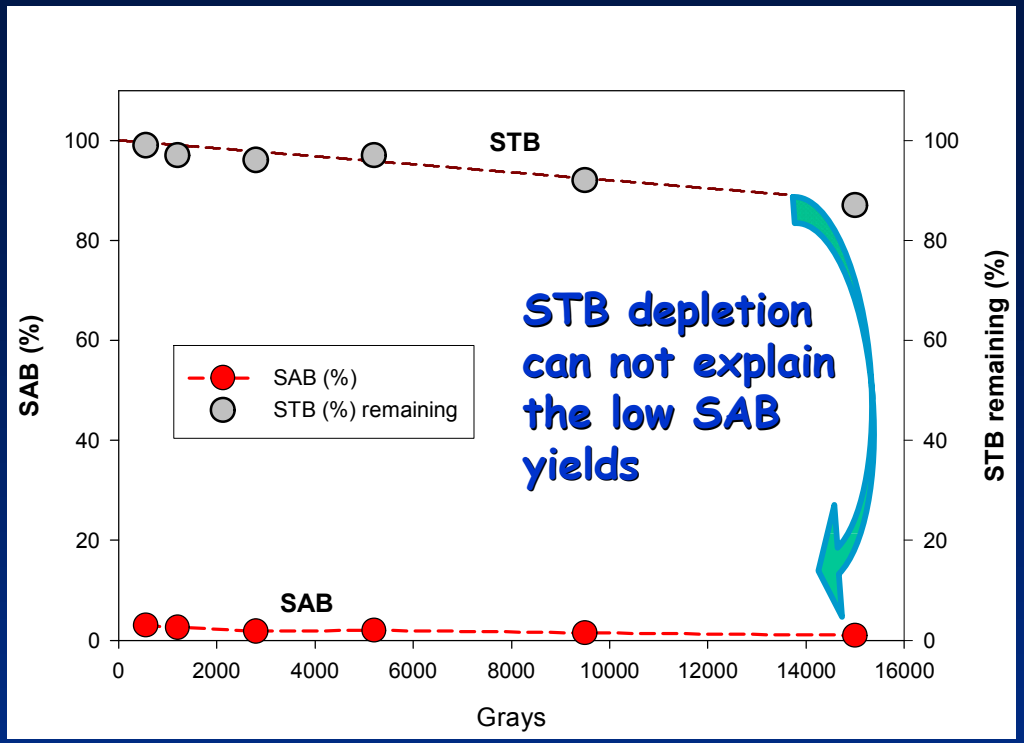


Pozzi, Zalutsky,
J.Nucl.Med 2005;46:700-706
J.Nucl.Med 2005;46:1393-1400

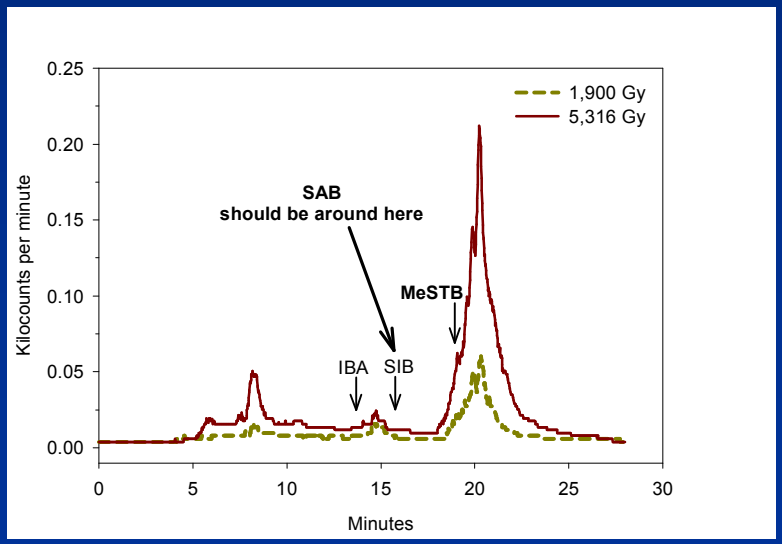




Why does the SAB synthesis reaction in Benzene fail?



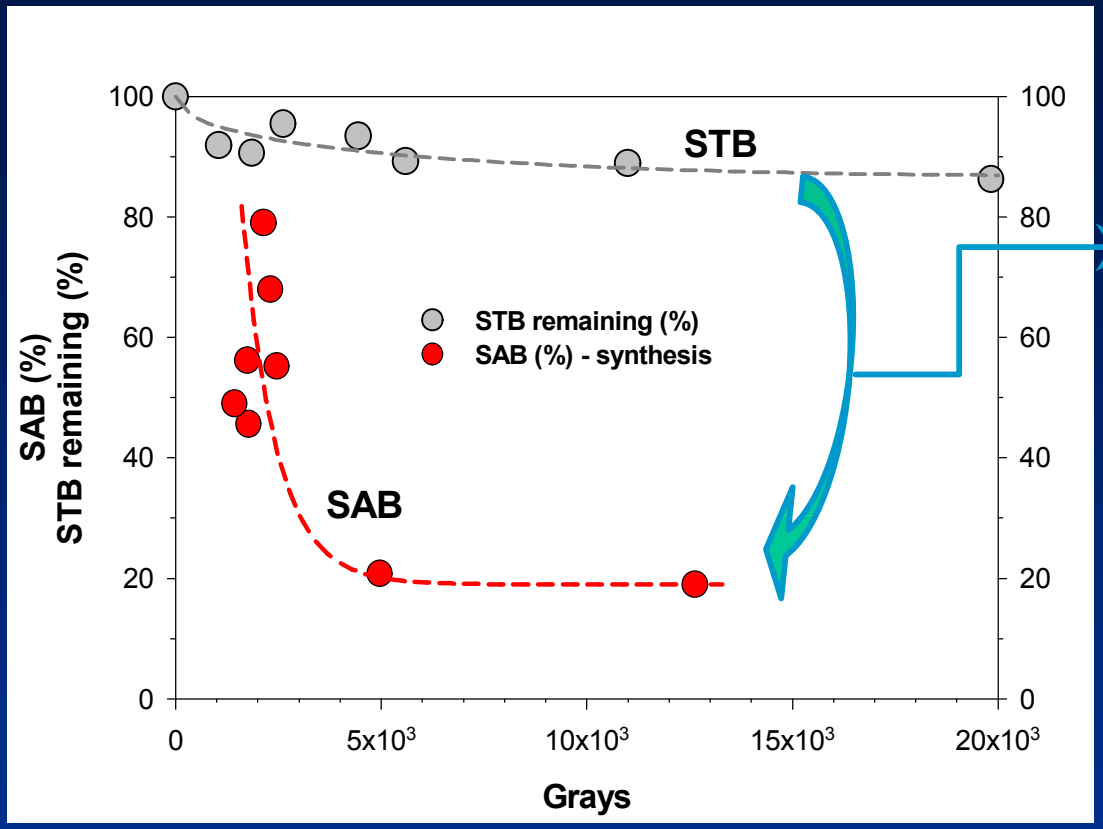
- SAB can not be synthesized at any radiation dose
- Benzene has a radical production yield << than aliphatic compounds but is not radiation inert
- Background: phenyl radicals are scavenged very efficiently by iodine to produce iodobenzene → we might expect a similar behavior with astatine



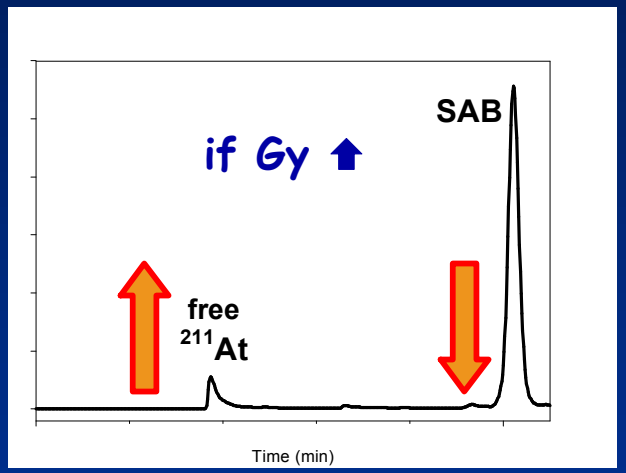
- Astatination reaction in benzene resulted in the formation of very lipophilic species at yields generally greater than 90%.
- This astatine "capture" might explain the failing of SAB synthesis in benzene

Pozzi, Zalutsky, J.Nucl.Med 2005;46:700-706
J.Nucl.Med 2005;46:1393-1400

Why does the SAB synthesis reaction in MeOH fail ?



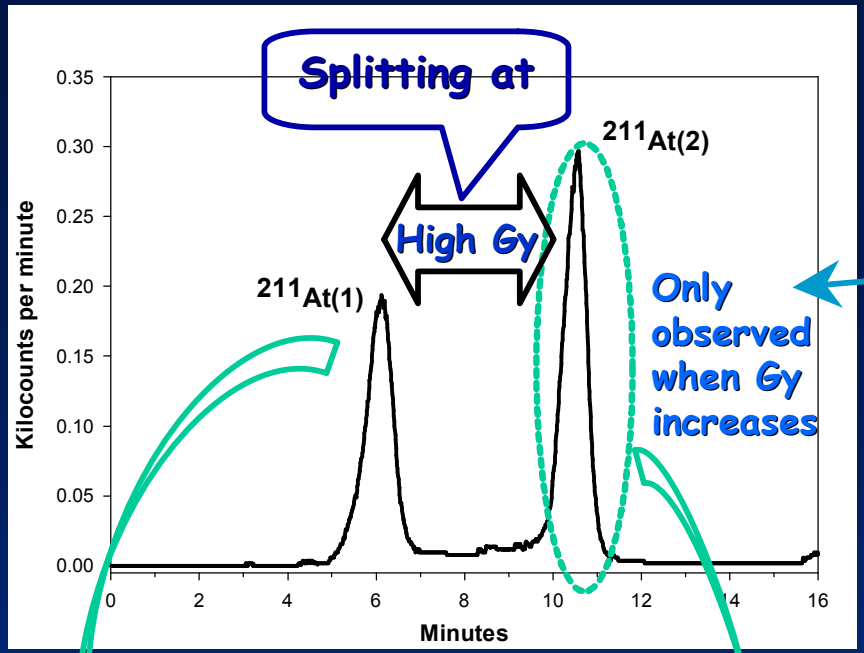
The STB depletion can NOT explain the decreased SAB synthesis



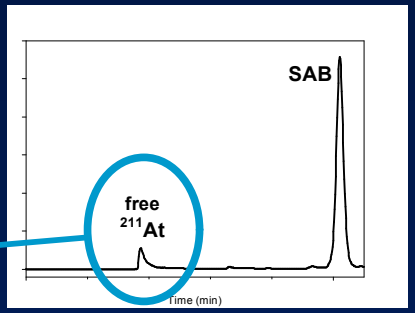
Pozzi, Zalutsky, J.Nucl.Med 2005;46:700-706 J.Nucl.Med 2005;46:1393-1400

Can the ^{211}At be itself the main source of problems ?

- We do know ^{211}At is not trapped in other astatinated compounds (as in benzene), only free astatine and SAB are observed on the HPLC's analysis

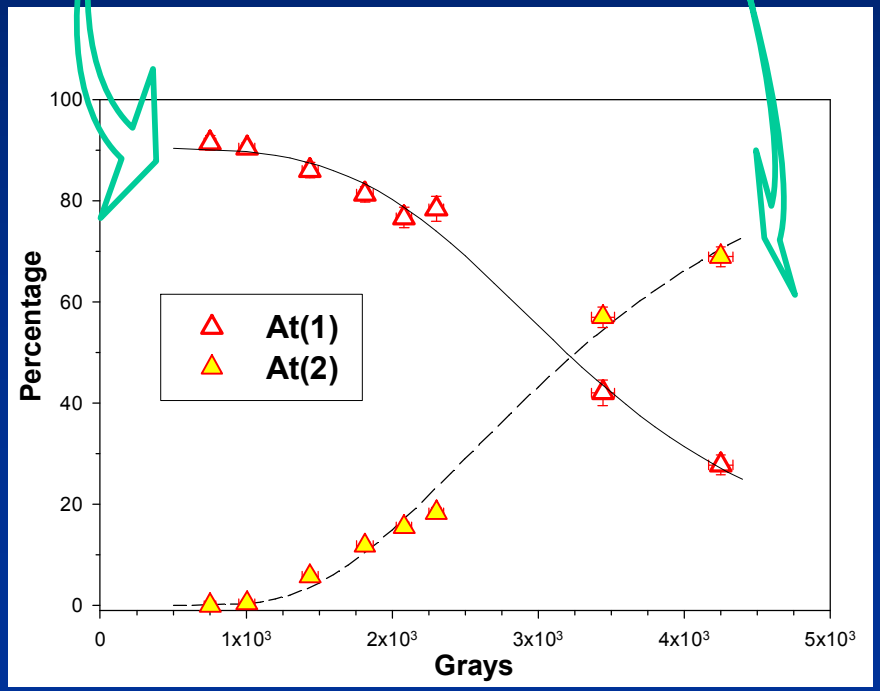


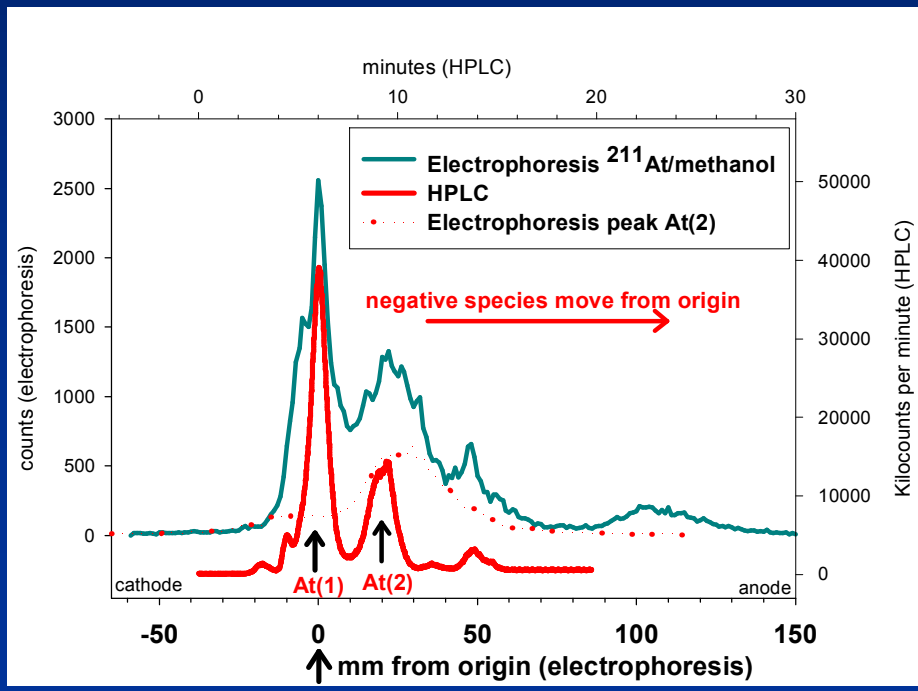
Changing HPLC conditions the splitting can be observed



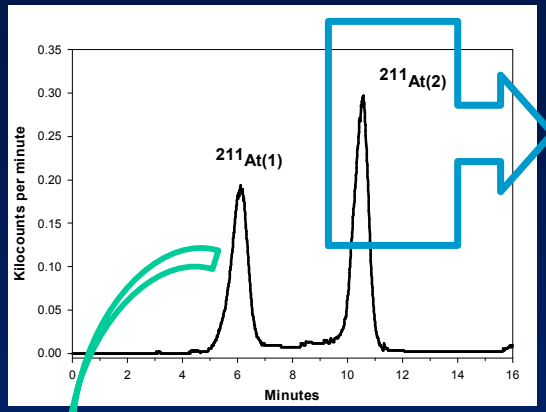
- As the radiation dose increased the HPLC for free astatine splits
- At low radiation dose free astatine is seen as only 1 peak (At(1))

At(2) showed to be a negative species





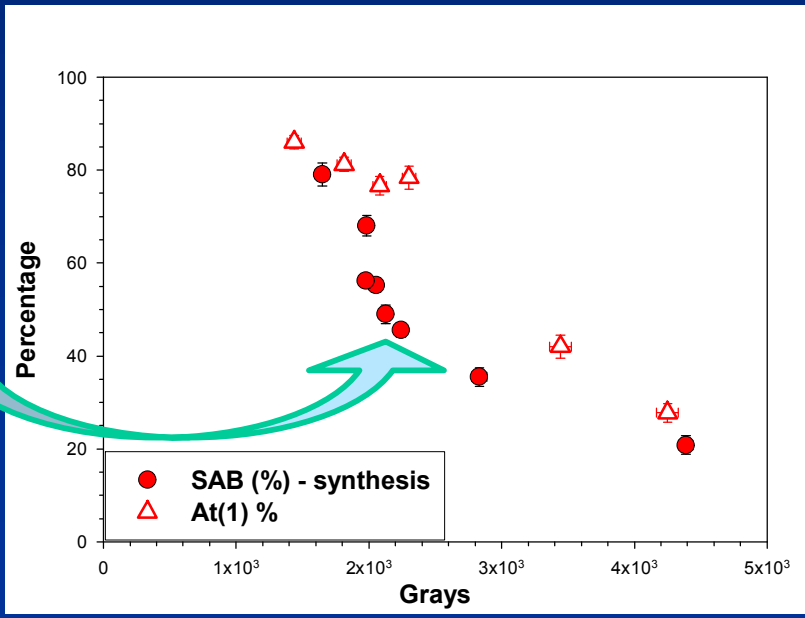
What is the meaning of the emergence of astatine form At(2):



- is an indication of radiolysis-induced problems
- it increases when the dose increased (correlation)
- it is not reactive toward electrophilic astatination reactions: high yields of SAB synthesis can only be obtained when At(2) is not present or in very low amounts
- At(2) is a reduced form of astatine, probably astatide (At-)
  - At(1) $\xrightarrow{\text{sodium sulfite}}$ At(2) almost completely
  - retention time of At(2) nearly identical to that of $^{131}I^-$ (INa)
  - At(2) is an anionic species (electrophoresis)

What is the meaning of the astatine form At(1):

- Observed as the only peak only at low Gy, as Gy increased its amount decreases
- Is a neutral form of astatine, reactive towards electrophilic astatination reactions
- The **At(1) declines accounts for the decline in labeling** yields at elevated radiation dose
- Its chemical form?: speculative, might be a neutral form or At^+ stabilized by a complex with the solvent (complex formation between methanol and I)



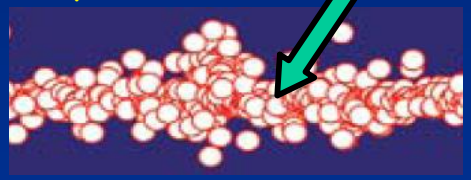
- We do know that:
  - high radiaton dose delivered to the MeOH will produce At(2)
  - the emergence of At(2) will produce low astination yields
  - is a negative, reduced species, astatide the most probably

But **WHY** is At(2) produced by the high Gy ?

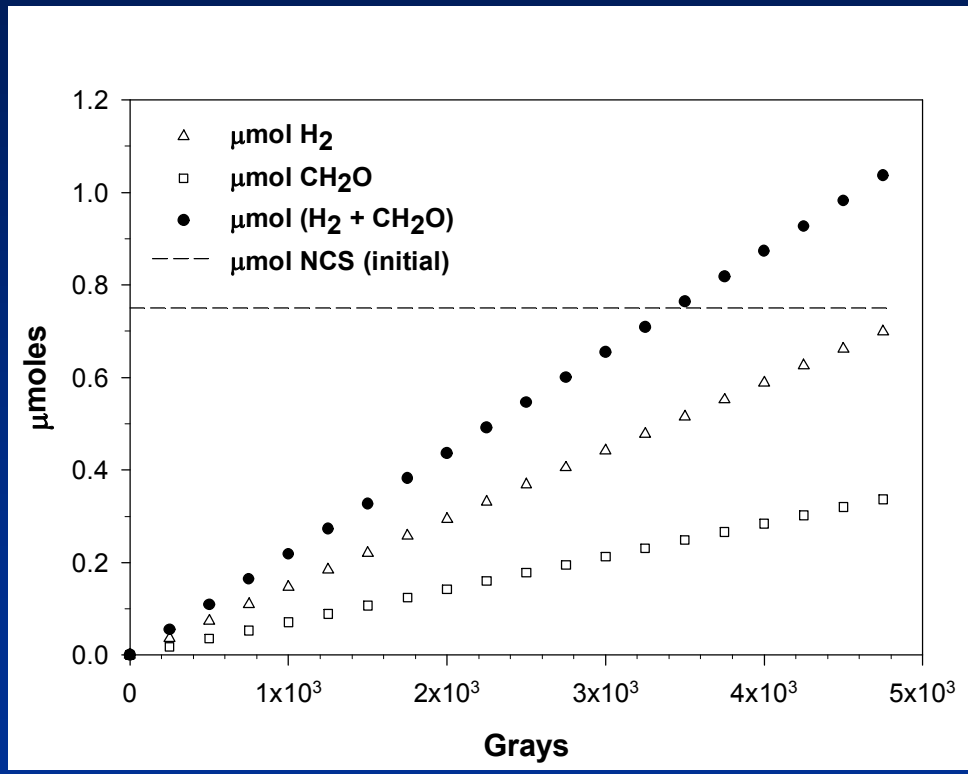
⇩

- With higher LET radiation, the yield of molecular products is increased while the yield of radicals that can be scavenged is decreased, reflecting an increase in intraspur reactions at the expense of radical escape from the spur .

Reducing species formation increases inside spur and tracks



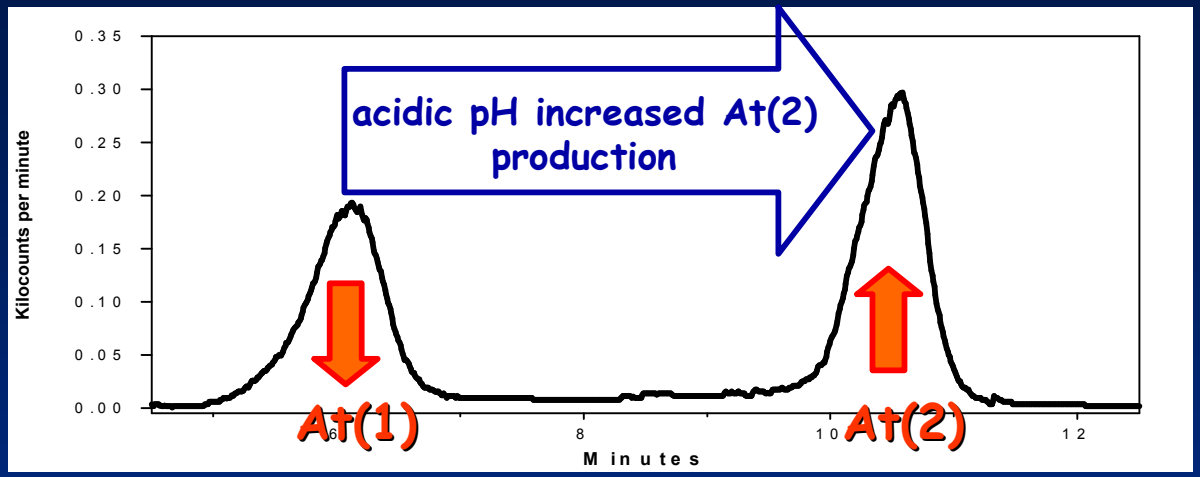
- Interradical reactions occurring in the spur can yield hydrogen and formaldehyde. Thus, as the radiation dose increases, the production of these reducing species also may increase.



- Pozzi, Zalutsky, J.Nucl.Med 2005;46:1393-1400
- Spink JW, Woods RJ. Introduction to Radiation Chemistry. 2nd ed. New York, NY: Wiley; 1976: 410-417.
- Baxendale JH, Wardman P. The Radiolysis of Methanol: Product Yields, Rate Constants, and Spectroscopic Parameters of Intermediates. Washington, DC: National Bureau of Standards; 1975:1-26. Table 2.1.1. Report NSRDS-NBS 54

We do find a radiation-dose dependence for amounts of SAB, At(1) and At(2)

Is there a pH-dependence for astatination reaction either ?



Pozzi, Zalutsky, J.Nucl.Med 2007;48:1190-1196

At low radiation dose (Gy), where At(2) is not observed, if pH is lowered At(2) increases and may even become the main peak.

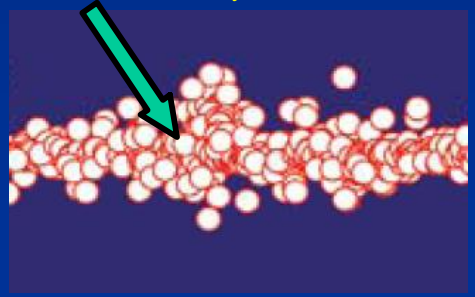
At(1) —(if pH ⇩ / is transformed in)→ At(2)

Is there a relatioship between pH-dependence and radiation dose ?

- in methanol, radiation renders the spur more acidic than the bulk because of the formation of $CH3OH_2^+$
- acidic pH increases the production of reducing species in methanol

Baxendale JH, Wardman P. Washington, DC: National Bureau of Standards; 1975:1-26. Report NSRDS-NBS 54.

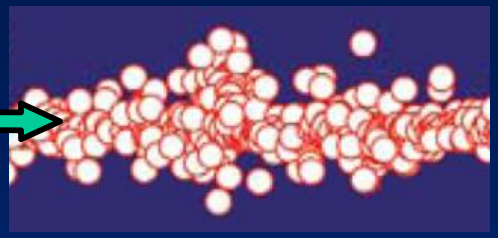
lower pH inside the spur and tracks



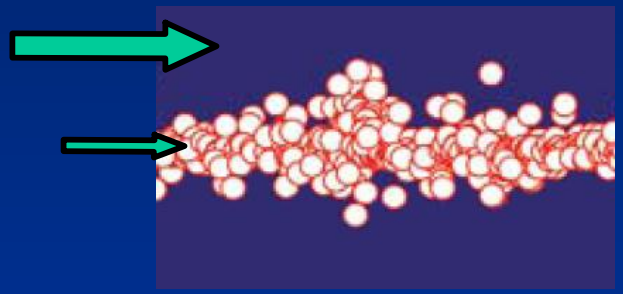
➢ At non-acid added condition the sequence of events leading to an increasing At(2) production might be:

⇑ Gy → more acidic spurs → more reducing species → more At(2)

will mainly happen inside the spur/tracks



➢ At acid added condition the sequence of events leading to an increasing At(2) radiolysis-mediated-reactions now might also happen in the bulk:



The consequence will be an increased At(2) production at comparative lower radiation dose → you will run into problems at lower activities

⇒ **Working in MeOH at acidic condition might be counterproductive**

Main Final Conclusions

(1) Astatine chemistry critically depends on the solvent where the reaction is carried out.

On benzene and chloroform high reactions yields at high activities can not be obtained

(2) Astatine chemistry at low activities (research) and high activities (therapy) might be very different → because of radiolysis

(3) Methanol is up to day the best solvent found to do astatination at high activities

High SAB synthesis yield at high activities can not be obtained on reliable fashion

Recommended procedure:

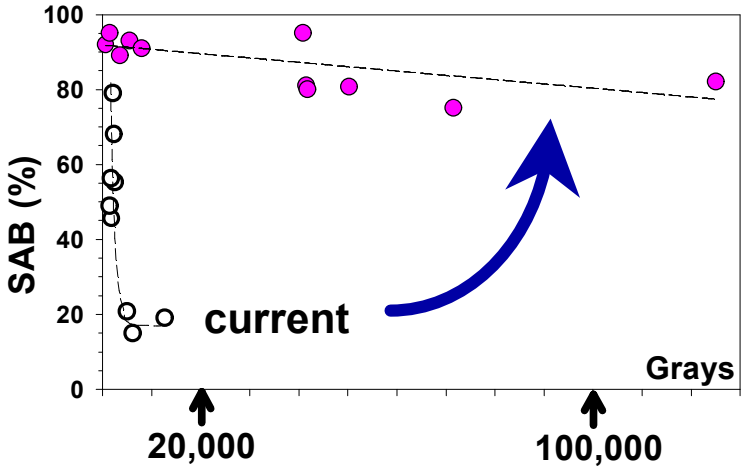
- radiation dose should be kept below 1500 Gy ("safe zone")
- equivalent to 20 min reaction in 500 µl with 370-480 MBq ^{211}At (10-12.97 mCi)
- working in 4 parallel reaction vessels 900 MBq (24.3 mCi) SAB from 1375 MBq (37.16) of ^{211}At (66% radiochemical yield).

(4) Total radiation dose delivered to the solvent

(5) Acid addition is unnecessary at high activitie

(6) Problems in methanol are independent of the

(7) Problems in methanol at > 1500 Gy can be s



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Thank you for your attention

Acknowledgements

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