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Challenges in medical radionuclides production

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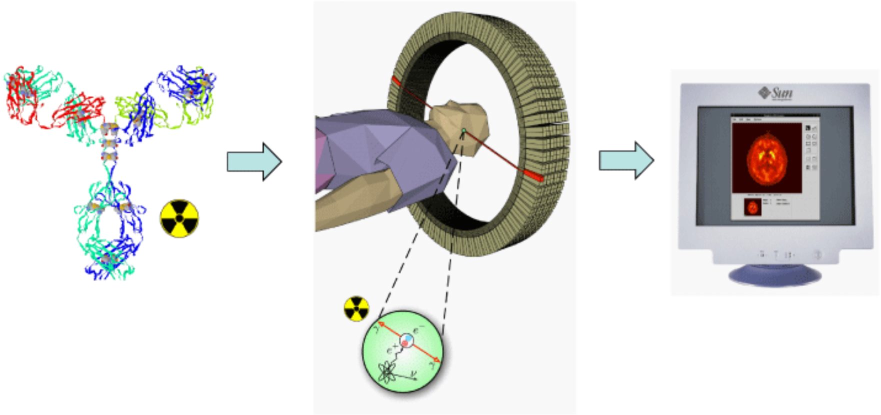
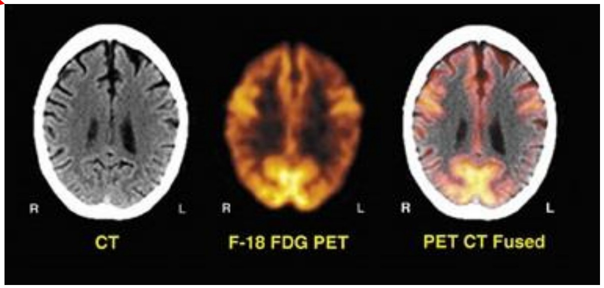
Functional diagnostics

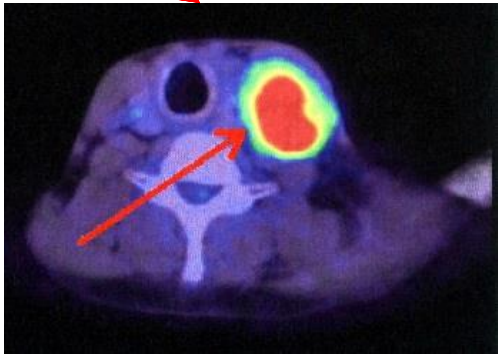
Compounds with γ (SPECT) or β^+ (PET) emitters

Ca 90 % of all radiopharmaceuticals

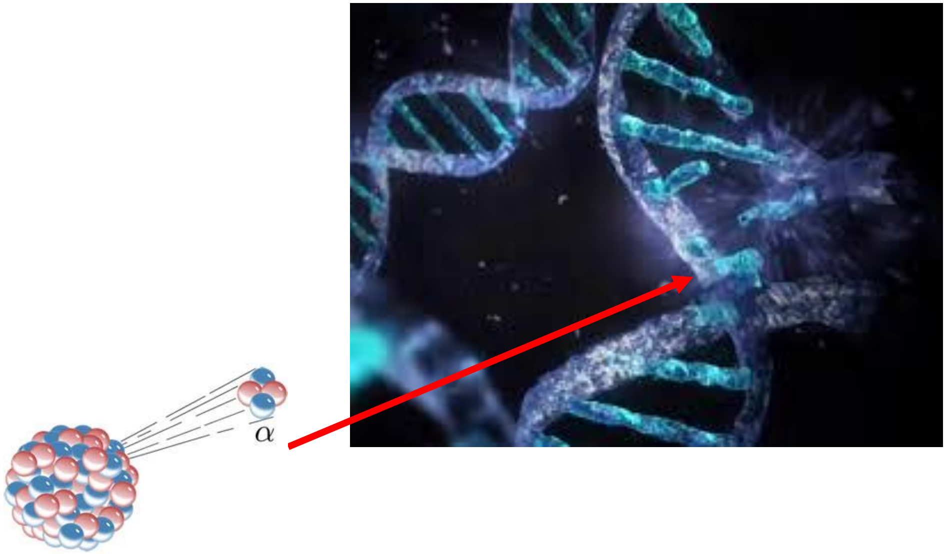
Combination with CT, MR (anatomy)







Targeted Radionuclide Therapy

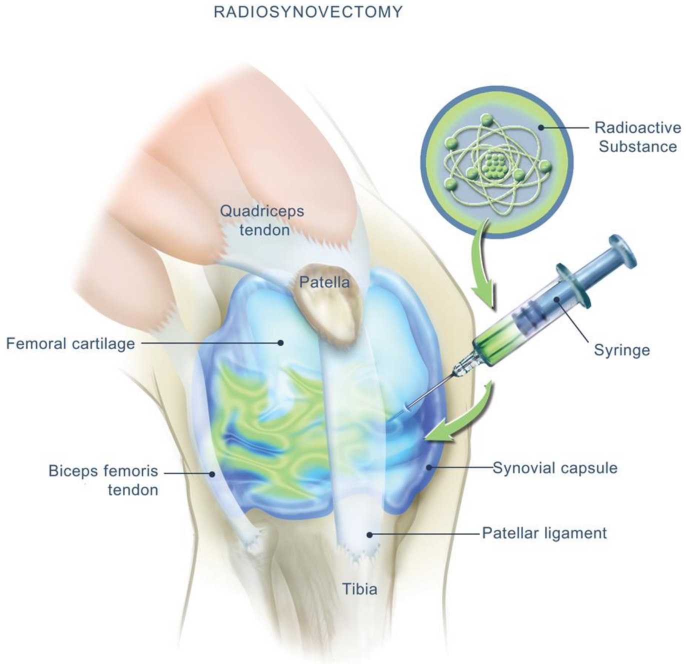


An α-particle inducing DNA double strand breaks

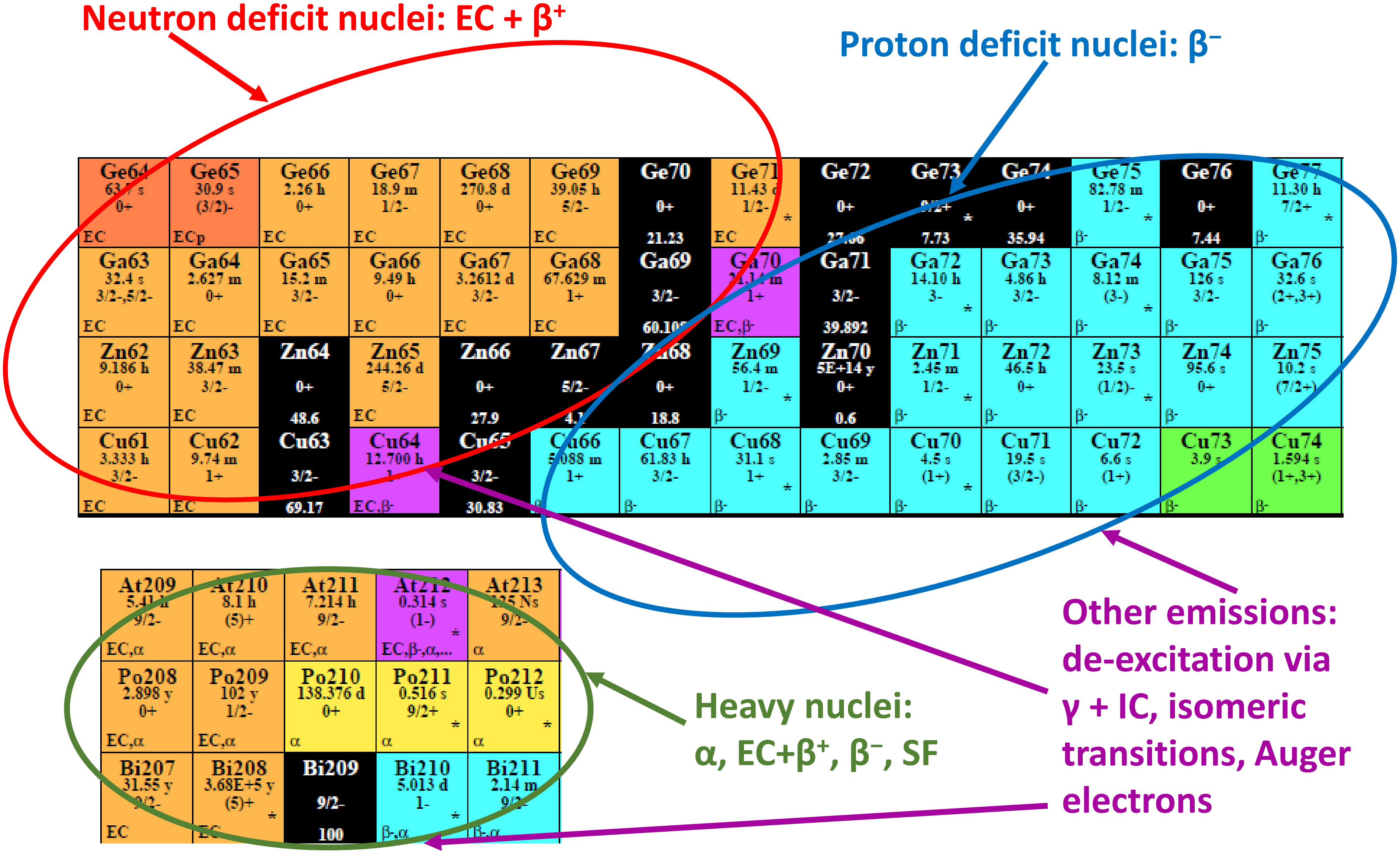
Compounds with β^- and α emitters

Accompanying γ-rays are desirable in order to follow biodistribution of the radionuclide

Targeted therapy of malignant diseases and therapy of chronic joint inflammation (radiosynovectomy)



Medical radionuclides



Neutron deficit nuclei: EC + β^+

Proton deficit nuclei: β^-

Ge64 63.7 s 0+ EC	Ge65 30.9 s (3/2)- ECp	Ge66 2.26 h 0+ EC	Ge67 18.9 m 1/2- EC	Ge68 270.8 d 0+ EC	Ge69 39.05 h 5/2- EC	Ge70 0+ 21.23	Ge71 11.43 d 1/2- * EC	Ge72 0+ 27.66	Ge73 9/2+ * 7.73	Ge74 0+ 35.94	Ge75 82.78 m 1/2- * β-	Ge76 0+ 7.44	Ge77 11.30 h 7/2+ * β-
Ga63 32.4 s 3/2-,5/2- EC	Ga64 2.627 m 0+ EC	Ga65 15.2 m 3/2- EC	Ga66 9.49 h 0+ EC	Ga67 3.2612 d 3/2- EC	Ga68 67.629 m 1+ EC	Ga69 3/2- 60.108	Ga70 21.14 m 1+ EC,β-	Ga71 3/2- 39.892	Ga72 14.10 h 3- * β-	Ga73 4.86 h 3/2- β-	Ga74 8.12 m (3-) * β-	Ga75 126 s 3/2- β-	Ga76 32.6 s (2+,3+) β-
Zn62 9.186 h 0+ EC	Zn63 38.47 m 3/2- EC	Zn64 0+ 48.6	Zn65 244.26 d 5/2- EC	Zn66 0+ 27.9	Zn67 5/2- 4.1	Zn68 0+ 18.8	Zn69 56.4 m 1/2- * β-	Zn70 5E+14 y 0+ 0.6	Zn71 2.45 m 1/2- * β-	Zn72 46.5 h 0+ β-	Zn73 23.5 s (1/2)- * β-	Zn74 95.6 s 0+ β-	Zn75 10.2 s (7/2+)
Cu61 3.333 h 3/2- EC	Cu62 9.74 m 1+ EC	Cu63 3/2- 69.17	Cu64 12.700 h 1+ EC,β-	Cu65 3/2- 30.83	Cu66 5.088 m 1+ β-	Cu67 61.83 h 3/2- β-	Cu68 31.1 s 1+ * β-	Cu69 2.85 m 3/2- β-	Cu70 4.5 s (1+) * β-	Cu71 19.5 s (3/2-) β-	Cu72 6.6 s (1+) β-	Cu73 3.9 s β-	Cu74 1.594 s (1+,3+) β-

At209 5.41 h 9/2- EC,α	At210 8.1 h (5)+ EC,α	At211 7.214 h 9/2- EC,α	At212 0.314 s (1-) * EC,β-,α,...	At213 125 Ns 9/2- α
Po208 2.898 y 0+ EC,α	Po209 102 y 1/2- EC,α	Po210 138.376 d 0+ α	Po211 0.516 s 9/2+ * α	Po212 0.299 Us 0+ * α
Bi207 31.55 y 9/2- EC	Bi208 3.68E+5 y (5)+ * EC	Bi209 9/2- 100	Bi210 5.013 d 1- * β-,α	Bi211 2.14 m 9/2- β-,α

Heavy nuclei:
α, EC+β^+, β^-, SF

Other emissions:
de-excitation via
γ + IC, isomeric
transitions, Auger
electrons

Review of selected challenges

- Production of some theranostic radionuclides (therapeutic radionuclides that emit radiation suitable for imaging) – ^{47}Sc, ^{67}Cu
- Production of long-lived parent radionuclides for generators of the short-lived positron emitters – ^{44}Ti/^{44}Sc, ^{68}Ge/^{68}Ga

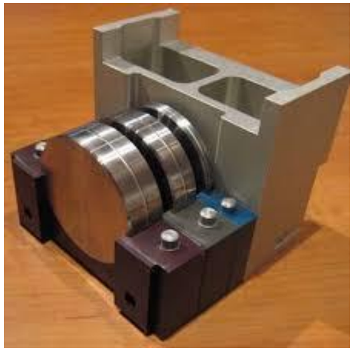
^{47}Sc

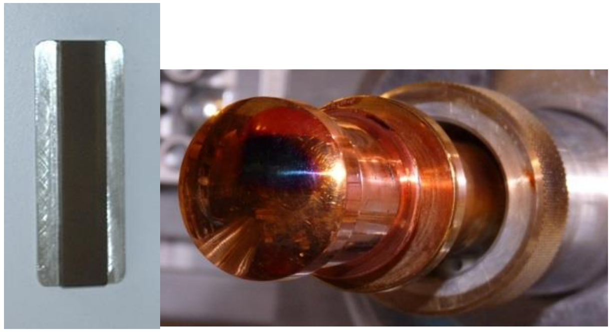
- Production of novel alpha emitters for targeted therapy of cancer – ^{225}Ac

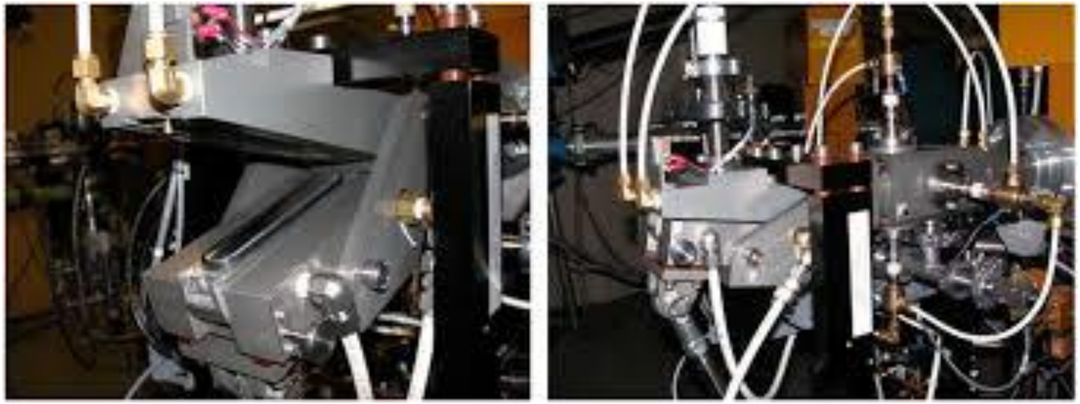
Some of the selected challenges

RN	$T_{½}$	decay mode	γ-lines (keV)	production via
^{44}Ti	59.1 a	EC (100 %)	78.3234 (94.4 %)	^{45}Sc(p,2n)
^{47}Sc	3.3492 d	β^- (100 %)	159.38 (68.3 %)	^{48}Ti(p,2p) ^{50}Ti(p,α)
^{67}Cu	61.83 h	β^- (100 %)	93.31 (16.10 %) 184.58 (48.7 %)	^{64}Ni(α,p) ^{68}Zn(p,2p) ^{70}Zn(p,α)
^{68}Ga	67.629 min	β^+ (89.1 %)	1077.35 (3.0 %)	^{69}Ga(p,2n)^{68}Ge ^{68}Ge(270.8 d)→^{68}Ga
^{211}At	7.214 h	α (41.80 %)	Po X-rays	^{209}Bi(α,2n)
^{225}Ac	10.0 d	α cascade	440.45 (25.9 %)	^{229}Th decay ^{226}Ra(p,2n)^{225}Ac

External targets – perpendicular, slanted, rotating







All the external solid targets may easily combine water-cooling from the backside and helium-cooling of the target surface exposed to the incident beam. Slanting the target distributes the heat power over the larger area and reduces its thickness.

A detailed analysis of the most challenging task

Production of ^{225}Ac via ^{226}Ra(p,2n) reaction

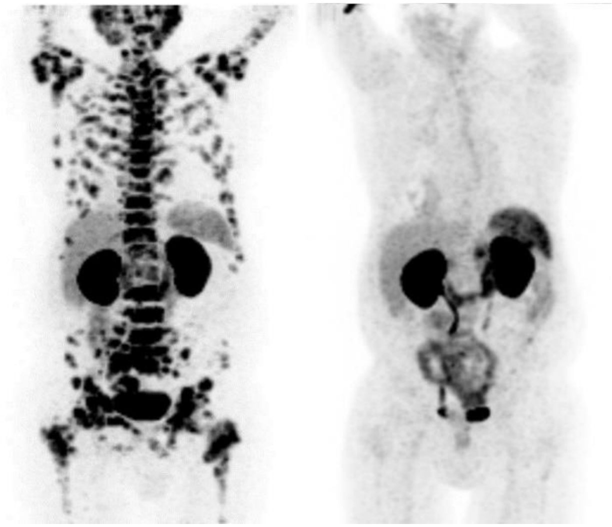
Motivation: Prostate cancer therapy

Prostate carcinoma is the second most frequent cause of death in men suffering from cancer in Europe and its incidence increases.

GOOD DIAGNOSTICS

[^{68}Ga]PSMA or [^{18}F]PSMA – molecules that provide the best imaging option of metastatic disease stages and therapy response.

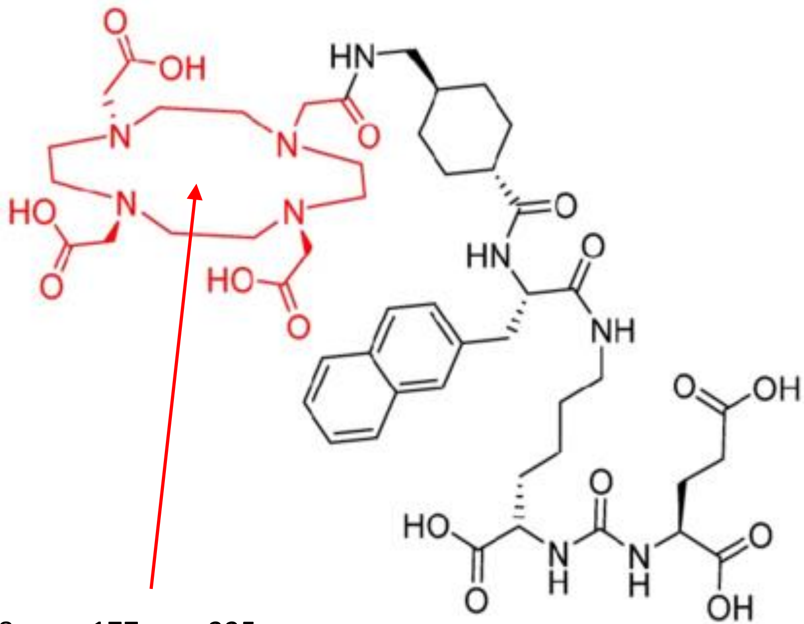
Patient before and after therapy
[^{225}Ac]PSMA – DKfZ Heidelberg



EFFICIENT THERAPY

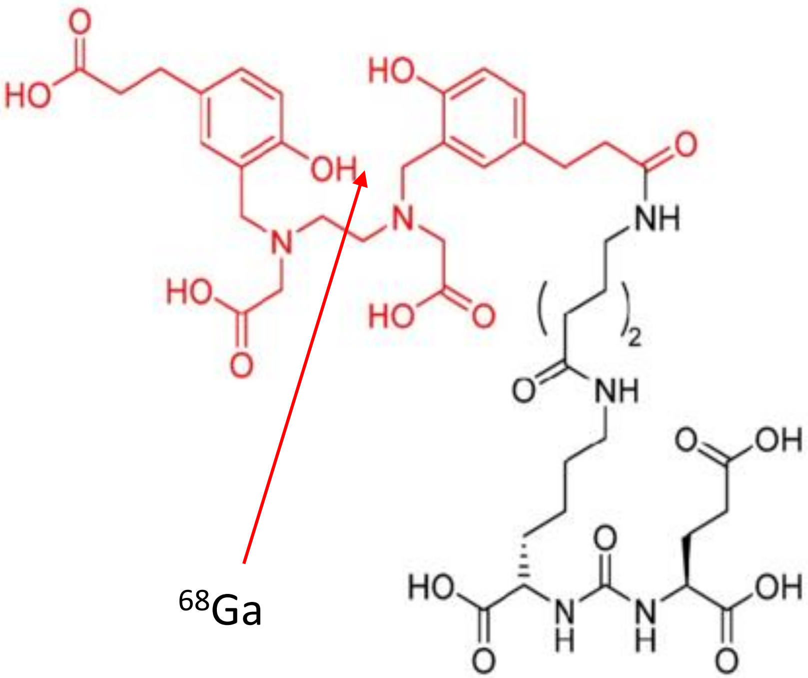
[^{225}Ac]PSMA – molecule that seems to be promising for some patients in terminal stadium of the disease

A single molecule for imaging & therapy



^{68}Ga, ^{177}Lu, ^{225}Ac

(a)



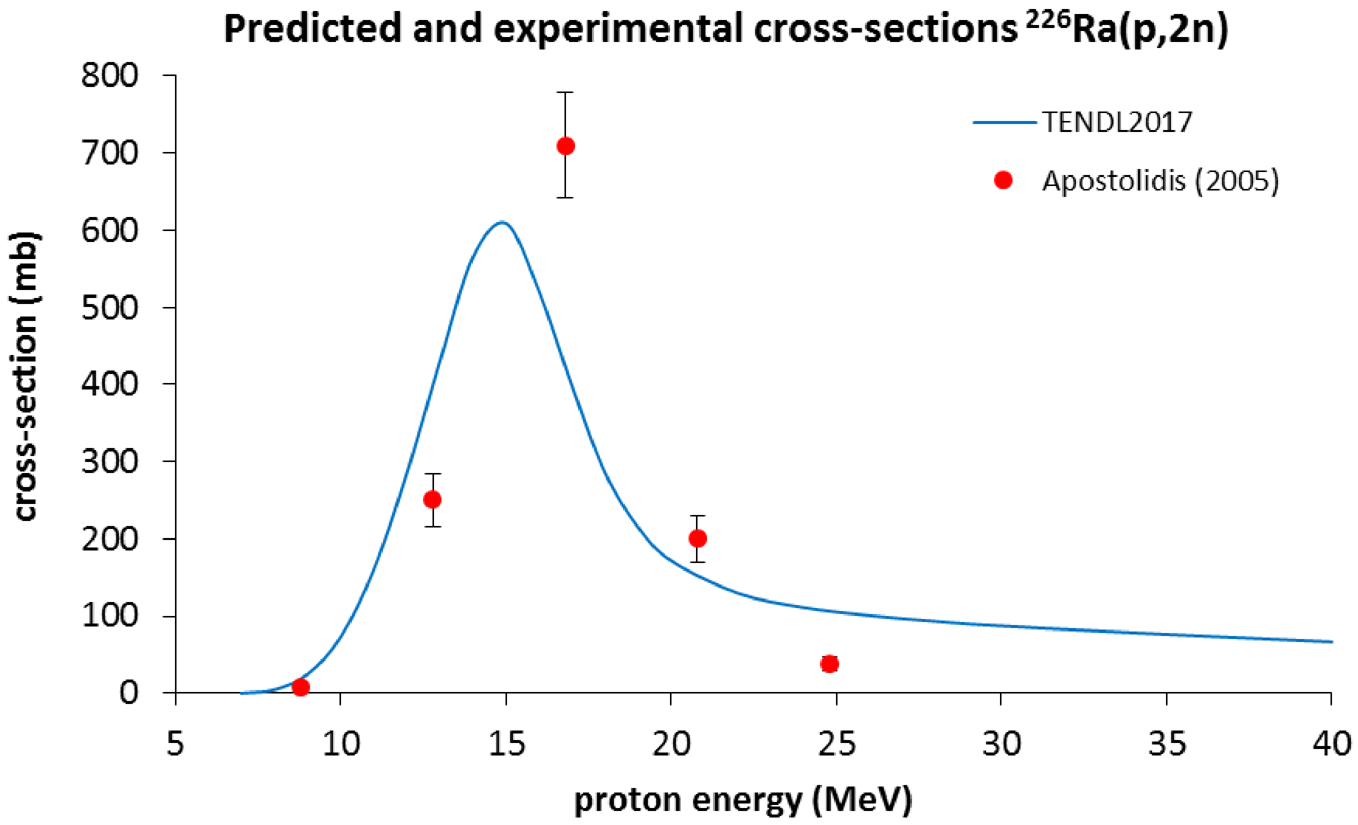
^{68}Ga

(b)

a) PSMA-617

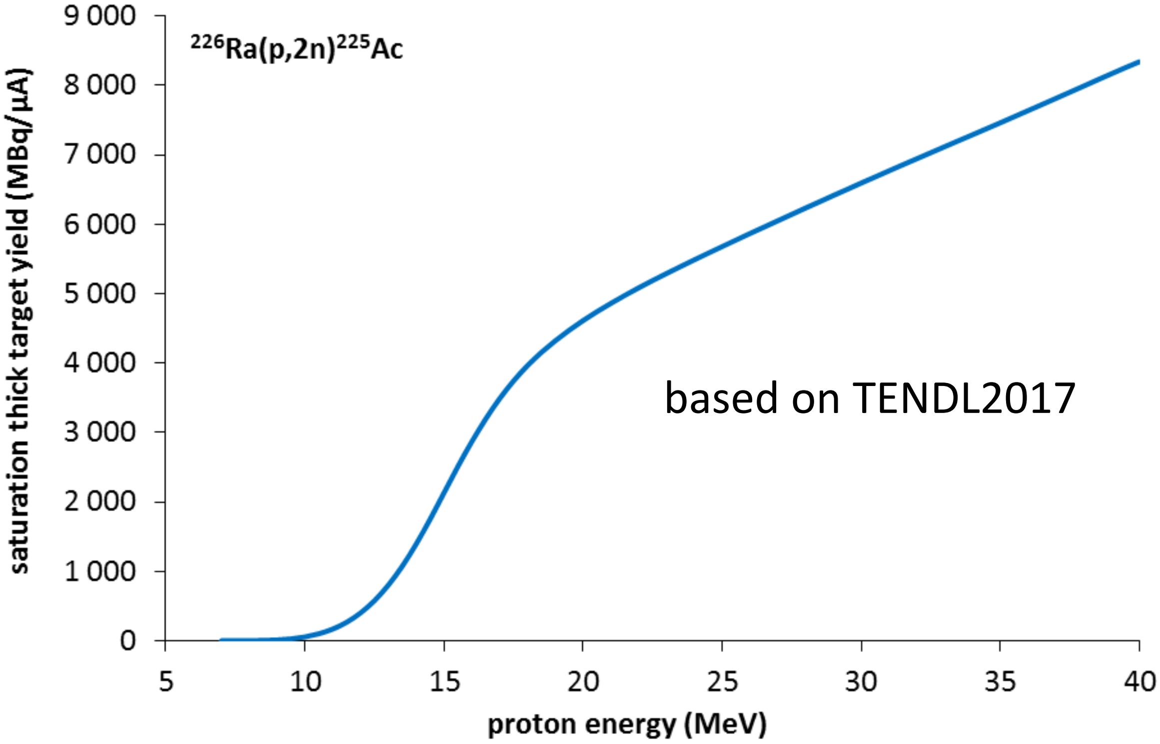
b) PSMS-11

Excitation function



Obviously, experimental data are scarce, slightly shifted towards higher energies and in a fair agreement with the prediction of the TALYS nuclear reaction model code. A new, detailed measurement is highly desirable.

Yield

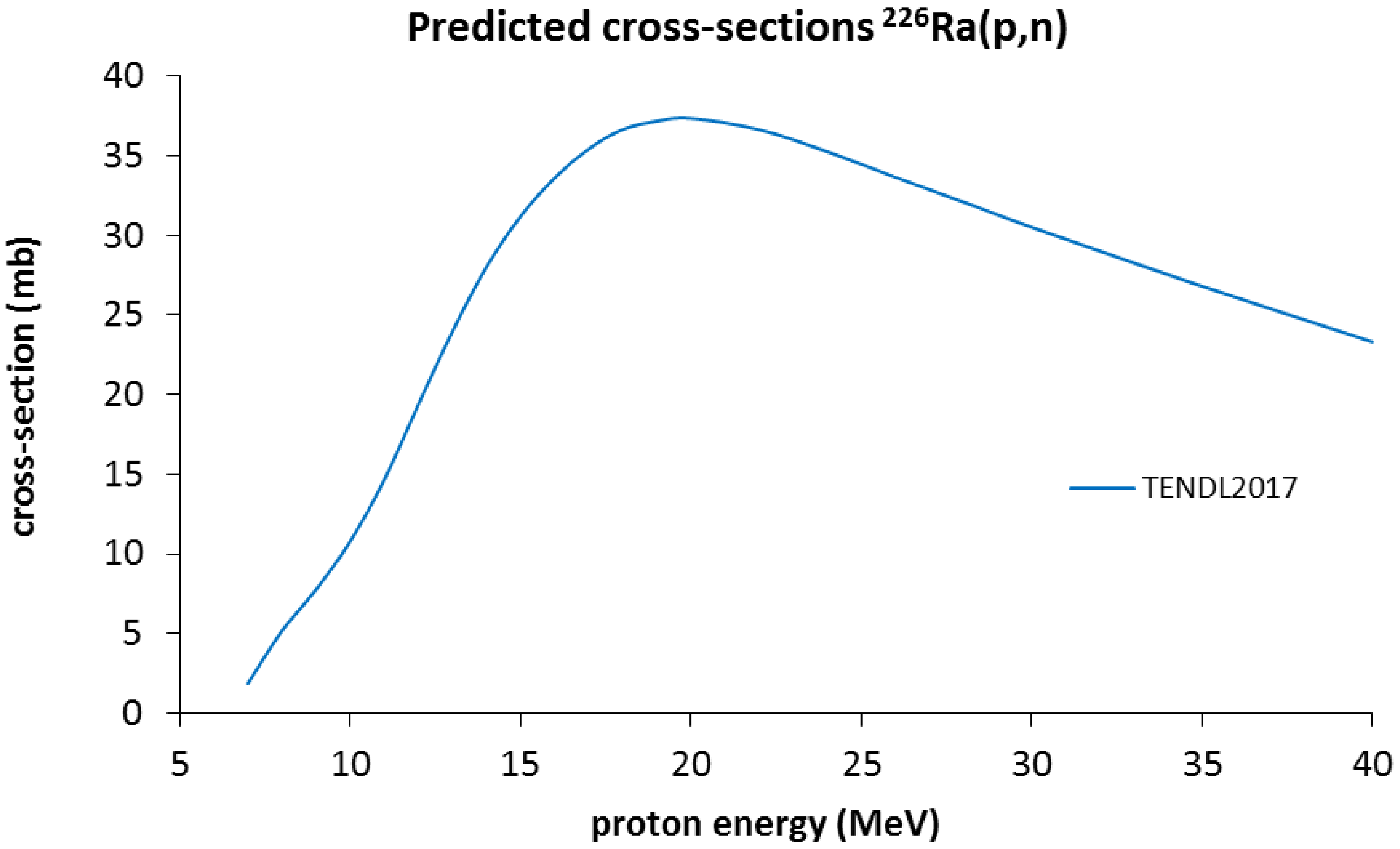


based on TENDL2017

The ^{225}Ac EOB activity for 1 d irradiation with 50 µA beam

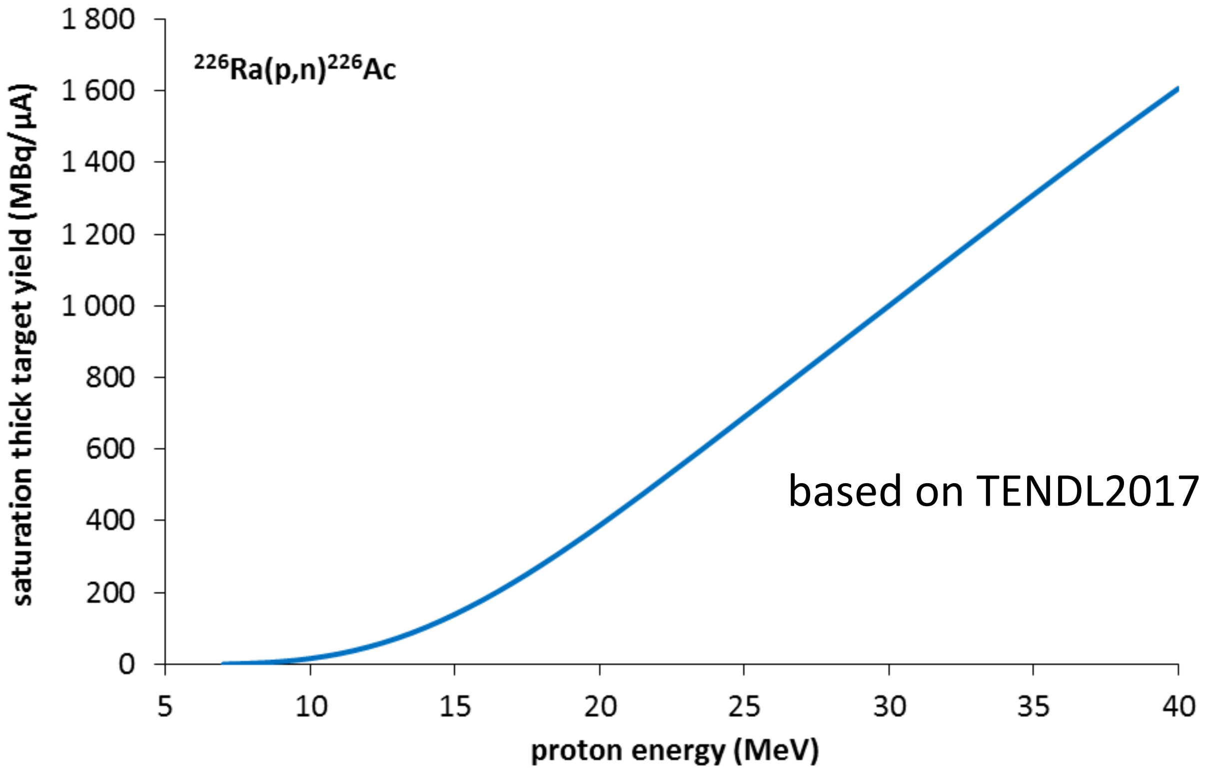
E_{in} (MeV)	E_{out} (MeV)	Y_{sat} (MBq/µA)	A_{EOB} (GBq)
20.0	10.0	4 558	15.4
17.0	12.0	3 088	10.4
16.0	14.0	1 475	4.98
15.5	14.5	759.6	2.56

Isotopic impurity – ^{226}Ac ($T_{½}$ = 29.4 h, β^-+EC resulting in ^{226}Th decay chain)


Predicted cross-sections ^{226}Ra(p,n)

No experimental data are available, we may work only with the predictions.

Yield of ^{226}Ac

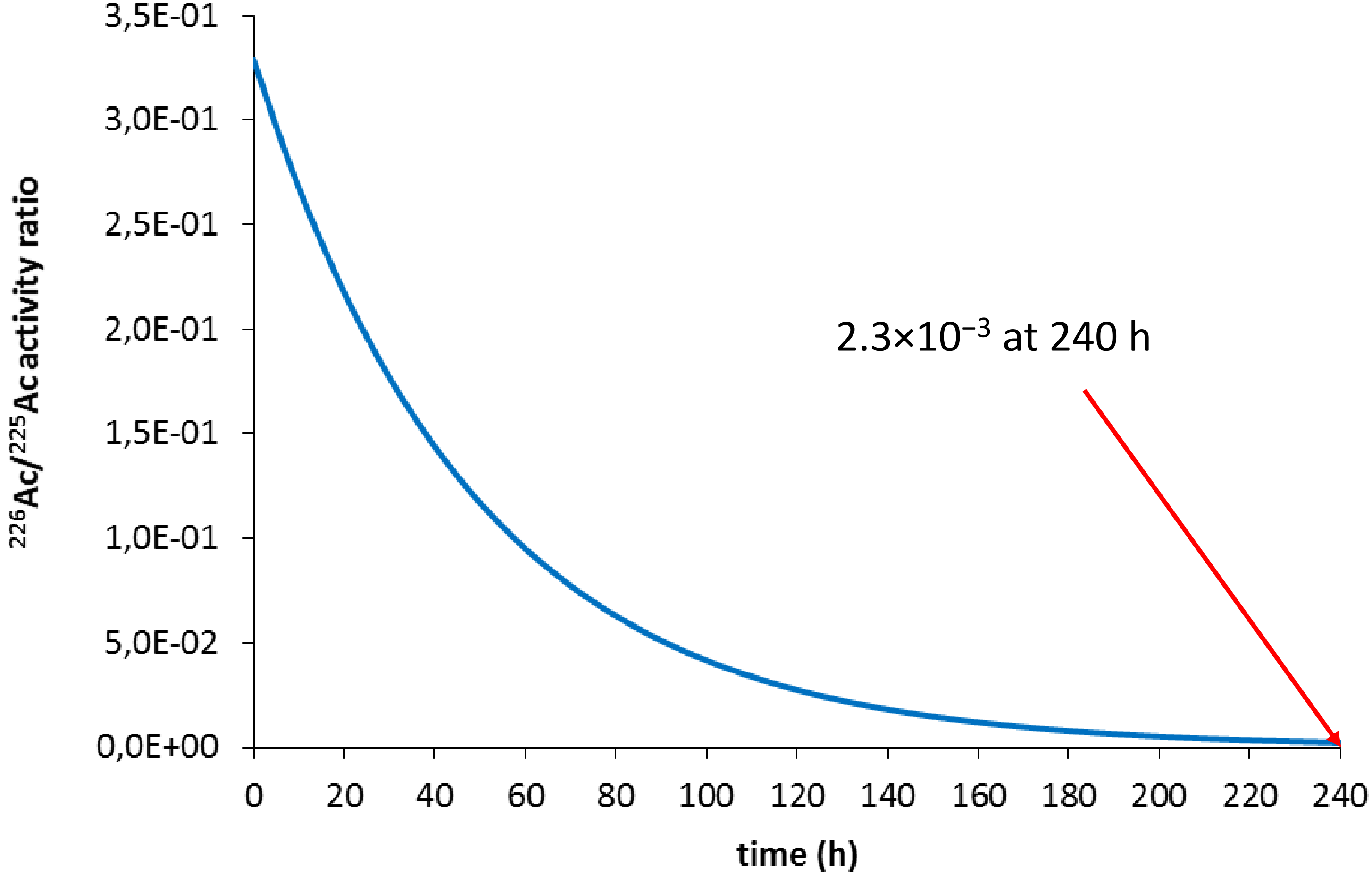


based on TENDL2017

The ^{226}Ac EOB activity for 1 d irradiation with 50 µA beam

E_{in} (MeV)	E_{out} (MeV)	Y_{sat} (MBq/µA)	A_{EOB} (GBq)
20.0	10.0	371.5	8.03
17.0	12.0	179.3	3.88
16.0	14.0	77.8	1.68
15.5	16.5	39.0	0.843

The ^{226}Ac/^{225}Ac activity ratio in time

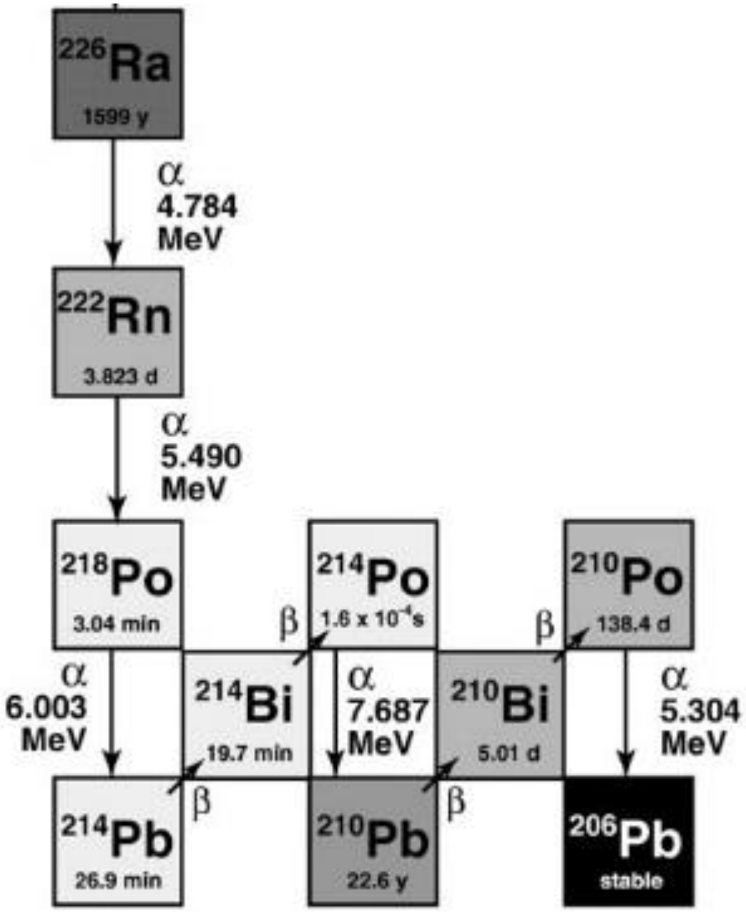


The data were calculated for the 1 d irradiation and the beam energy loss 15.5→14.5 MeV

Targetry, QC, recycling

- Radium metal is rather reactive and unstable on the air. Its production routes are demanding. Radium chemistry was studied until 1940, since that time almost no further knowledge was gained.
- The target material of choice is probably radium chloride, $RaCl_2$. This will result in certain decrease of the yield, however not dramatic. Moreover, this may decrease the maximum applicable beam current on such a target due to lower thermal conductivity. Actually, thermal conductivity of the metal itself is anyhow low, only 18.6 $W\ m^{-1}\ K^{-1}$.
- Applying the target layer is to be solved. Uniformity of the target layer should be checked by e.g. autoradiography.
- Vacuum-tight encapsulation is inevitable. It should provide good heat exchange between the encapsulation material and the target itself.
- Cooling: 4π water cooling, He/water cooling?
- Recycling the Ra metal seems to be easily feasible.
- The process should be fully automated.

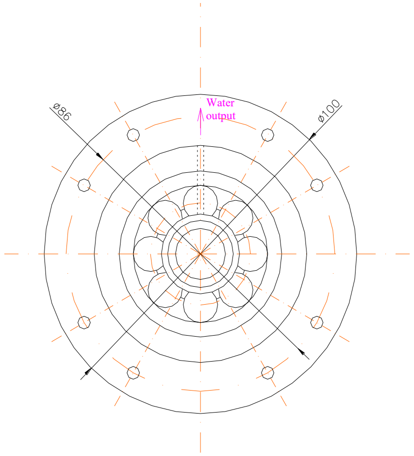
The biggest challenge – ^{222}Rn and long-lived active deposit management

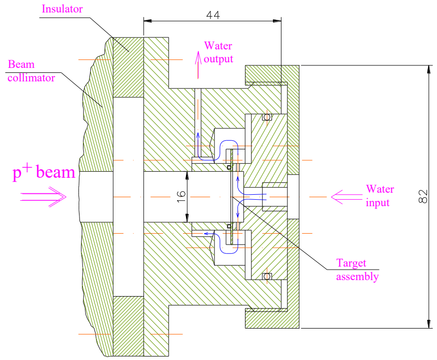


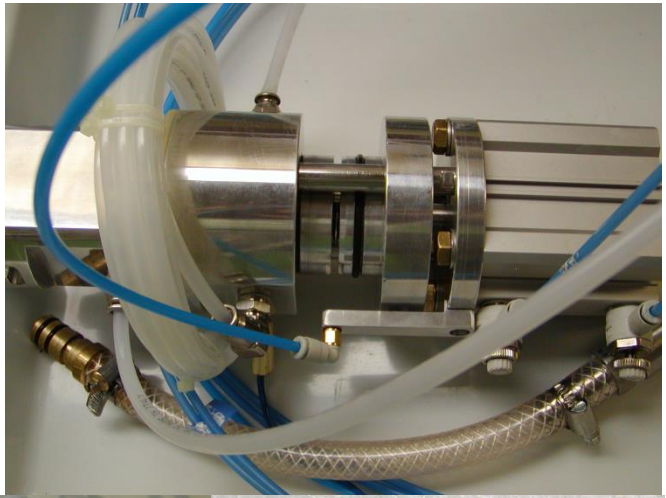
The target layer should be minimized not only due to the target material radioactivity, but mainly due to the continuous emanation of relatively long-lived radon isotope ^{222}Rn ($T_{½}$ = 3.8235 d, t_b = −61.7 °C, t_m = −71 °C). Its decay chain unfortunately produces long-lived active deposit started from ^{210}Pb ($T_{½}$ = 22.6 a).

The pressure due to ^{222}Rn in equilibrium with ^{226}Ra is negligible, as well as the amount of the helium due to the emitted α particles – it won‘t increase the target inner pressure. Major issue is the Rn release, whenever the Ra is exposed to open atmosphere.

A possible solution: 4π water-cooled target







An encapsulated target should:

- ☐ be vacuum tight
- ☐ be welded under vacuum
- ☐ provide good contact between the target material and the foils

The target layer required to degrade 15.5 MeV beam to 14.5 MeV is 0.138 mm for Ra metal. It corresponds to ca 38 mg of ^{226}Ra for 8 mm diameter target. Due to the radiation safety, limiting the irradiated ^{226}Ra amount to 50 mg is reasonable.

TR-24 cyclotron