Nuclear Physics Institute of the CAS
Department of radiopharmaceuticals

Ondřej Lebeda

Novel cyclotron radionuclides and radiopharmaceuticals

73rd Board Meeting of the EPS Nuclear Physics Division, 13th June 2017

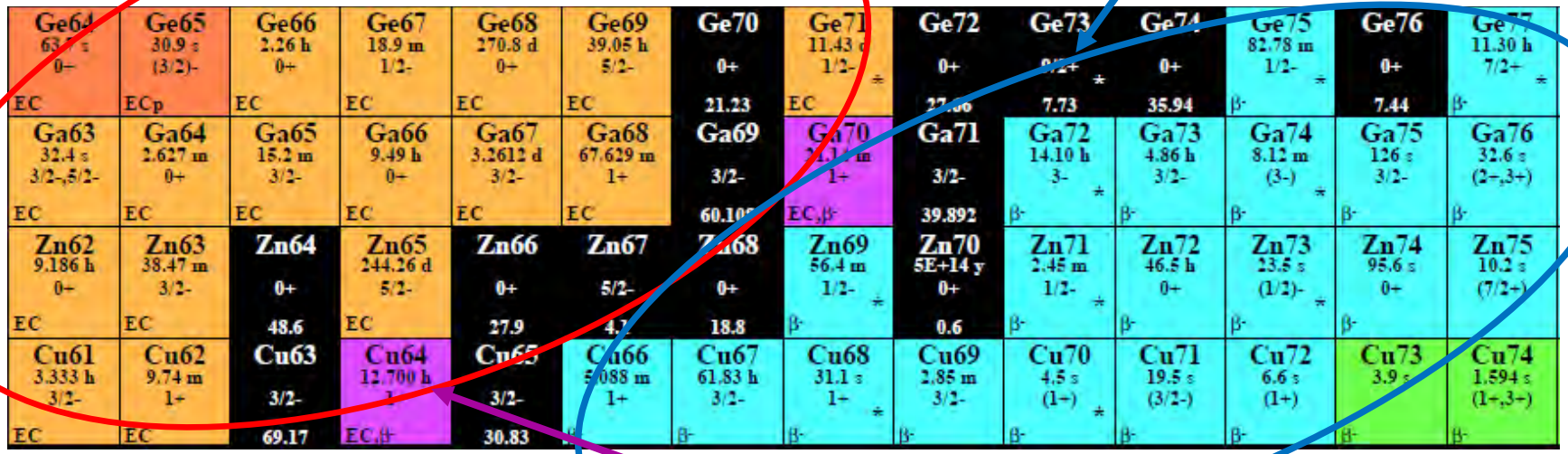
EUROPEAN UNION
European Structural and Investment Funds
Operational Programme Research,
Development and Education

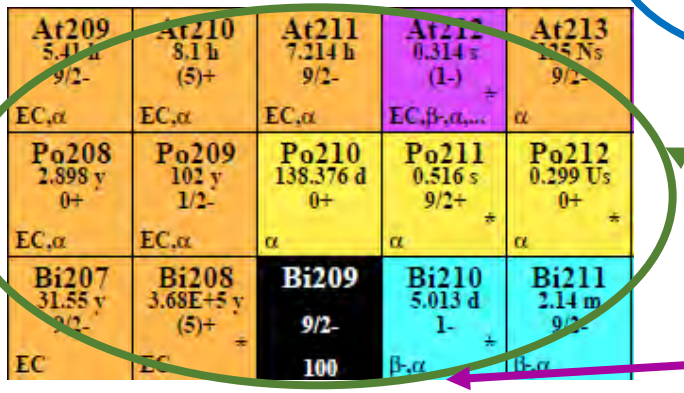
MINISTRY OF EDUCATION,
YOUTH AND SPORTS

Medical radionuclides

Neutron deficient nuclei: EC + β^+

Proton deficient nuclei: β^-



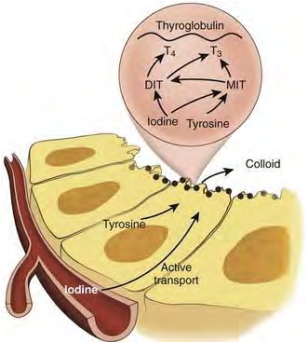


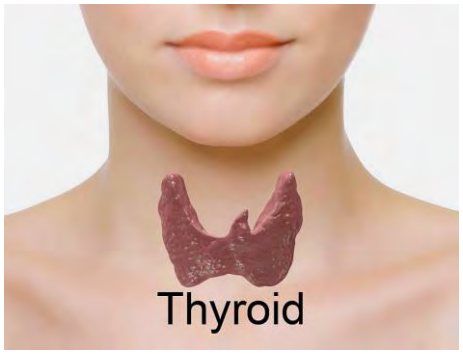
Heavy nuclei:
α, EC+β^+, β^-, SF

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

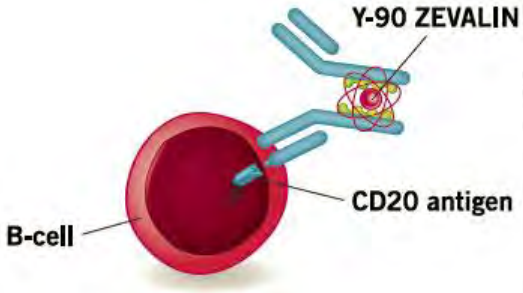
Examples of radiopharmaceuticals targeting

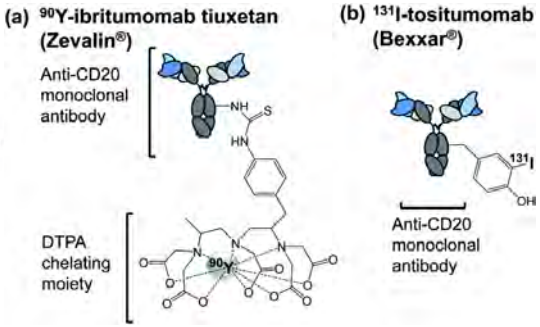
Active transport into specific organ/tissue
E.g. iodine isotopes → thyroid
It is an optimal case, because iodine isn‘t metabolized in any other way in organism. Highly specific and selective uptake.





Receptor affinity based transport
Příklad: labelled MAb → tumour tissue
Ibritumomab tiuxetan labelled with ^{90}Y for therapy (Zevalin) or with ^{111}In for diagnostics of non-Hodg-kinova lymfomu (MAb targets transformed B-cells expriming antigen CD20).
Similarly [^{18}F]fluorethylspiperone → dopamine receptors etc.



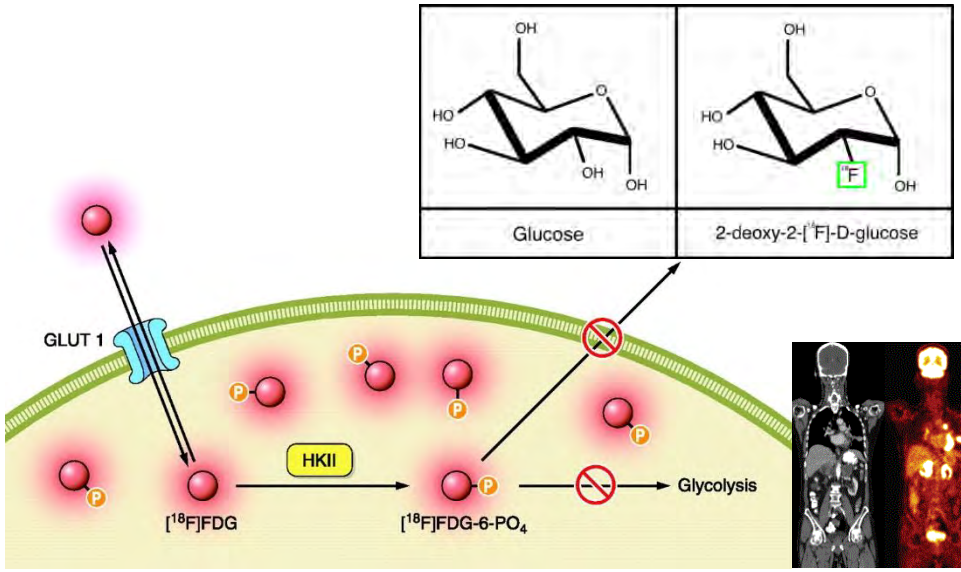


Examples of radiopharmaceuticals targeting

Substances with key role in the energy consumption

[^{18}F]FDG → tissues with an increased glucosis need

Highly sensitive, although non-specific radiopharmaceutical; imaging of cancer, brain centres activity, myocard etc.

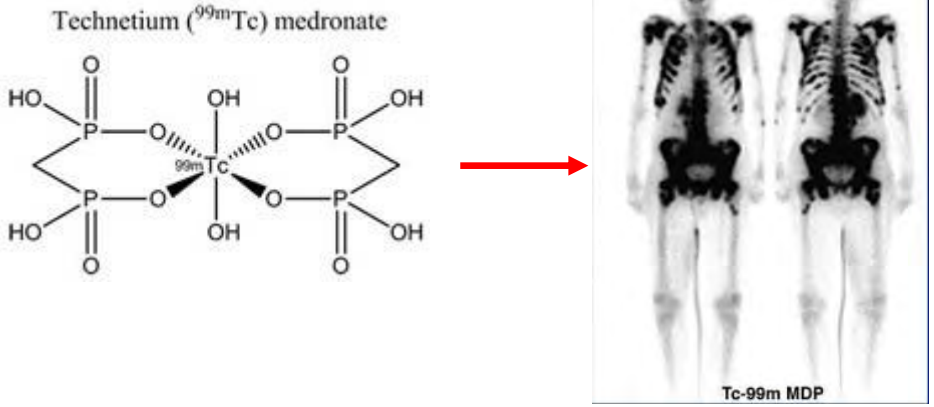


Exchange for a similar substance, Exchange of groups

$^{89}Sr^{2+}$, $^{223}Ra^{2+}$, $^{18}F^{-}$, ^{99m}Tc-medronate → bone tissue,

$^{201}Tl^{+}$ → heart tissue (similarity with potassium),

TcO_4^{-} → thyroid (similarity with iodide)

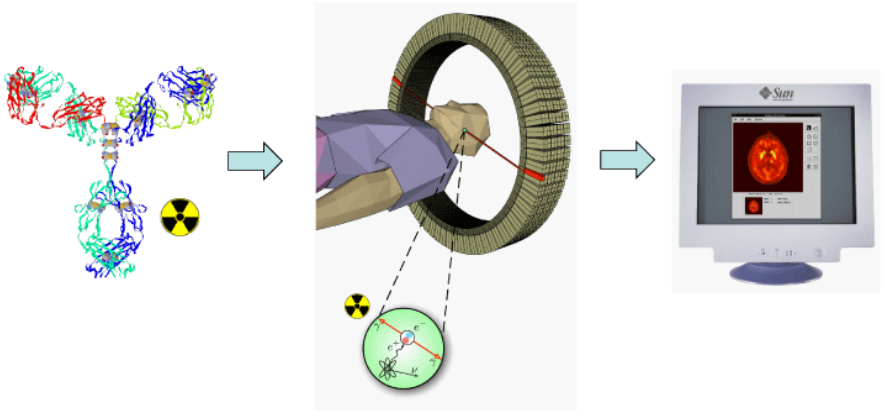


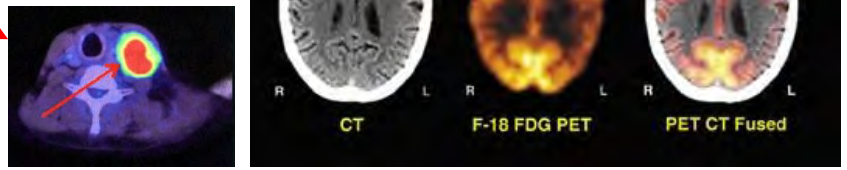
Molecular imaging – functional diagnostics

Compounds or constructs containing γ (SPECT) or β^+ (PET) emitters

ca 90 % of all radionuclide applications in nuclear medicine

Combined with CT, MR (anatomy)





Classical SPECT radionuclides

RN	$T_{½}$	decay mode	γ-lines (keV)	production route
^{67}Ga	3.2612 d	EC (100 %)	93.31 (39.2 %) 184.58 (21.2 %) 300.22 (16.8 %)	^{67}Zn(p,n) ^{68}Zn(p,2n)
^{81m}Kr	13.1 s	IT (99.998%)	190.46 (68 %)	^{81}Rb/^{81m}Kr
^{99m}Tc	6.01 h	IT (99.9963 %)	140.51 (88.5 %)	^{235}U(n,f)^{99}Mo
^{111}In	2.8047 d	EC (100 %)	171.28 (90 %) 245.40 (94 %)	^{111}Cd(p,n) ^{112}Cd(p,2n)
^{123}I	13.27 h	EC (100 %)	158.97 (83 %)	^{123,124}Te(p,n) ^{127}I(p,5n)^{123}Xe→ ^{124}Xe(p,2n)^{123}Cs→
^{201}Tl	72.912 h	EC (100 %)	135.34 (2.57 %) 167.43 (10 %)	^{203}Tl(p,3n)^{201}Pb→

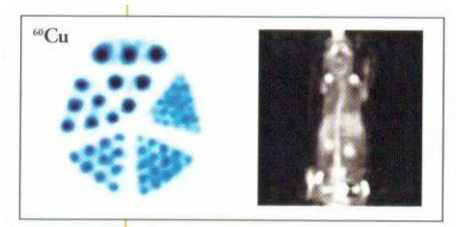
Established positron emitters

RN	$T_{½}$	decay mode	γ-lines (keV)	production via
^{11}C	20.39 min	β^+ (99.8 %)	—	$^{14}N(p,\alpha)$
^{13}N	9.965 min	β^+ (100 %)	—	$^{16}O(p,\alpha)$
^{15}O	122.23 s	β^+ (99.9 %)	—	$^{14}N(d,n)$ $^{15}N(p,n)$
^{18}F	109.77 min	β^+ (97 %)	—	$^{18}O(p,n)$ $^{20}Ne(d,\alpha)$
^{62}Cu	9.74 min	β^+ (97 %)	776.52 (13 %)	$^{63}Cu(p,2n)^{62}Zn$ $^{62}Zn(9.186\ h)\rightarrow{}^{62}Cu$
^{68}Ga	67.629 min	β^+ (89.1 %)	1077.35 (3.0 %)	$^{69}Ga(p,2n)^{68}Ge$ $^{68}Ge(270.8\ d)\rightarrow{}^{68}Ga$
^{82}Rb	1.273 min	β^+ (96 %)	776.52 (13.4 %)	$^{85}Rb(p,4n)^{82}Sr$ $^{82}Sr(25.55\ d)\rightarrow{}^{82}Rb$

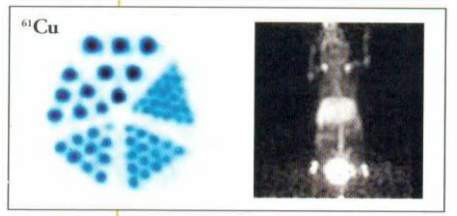
Some of the novel positron emitters

RN	$T_{½}$	decay mode	$E_{\beta+max}$ (MeV)	production via
^{52}Mn	5.6 d	β^+ (29 %)	0.57	^{52}Cr(p,n)
^{52}Fe	8.27 h	β^+ (56 %)	0.80	^{55}Mn(p,4n); ^{52}Cr(^{3}He,3n)
^{61}Cu	3.333 h	β^+ (61 %)	1.20	^{61}Ni(p,n)
^{64}Cu	12.70 h	β^+ (17.4 %)	0.66	^{64}Ni(p,n)
^{66}Ga	9.49 h	β^+ (57 %)	4.15	^{66}Zn(p,n)
^{73}Se	7.1 h	β^+ (66 %)	1.68	^{75}As(p,3n)
^{75}Br	96.7 min	β^+ (71 %)	1.74	^{76}Se(p,2n); ^{75}As(^{3}He,3n)
^{76}Br	16.2 h	β^+ (54 %)	3.98	^{76}Se(p,n); ^{75}As(^{3}He,2n)
^{89}Zr	78.41 h	β^+ (22.7 %)	1.21	^{89}Y(p,n)
^{121}I	2.12 h	β^+ (13 %)	1.20	^{122}Te(p,2n)
^{124}I	4.176 d	β^+ (22 %)	2.13	^{124}Te(p,n); ^{124}Te(d,2n); ^{125}Te(p,2n)

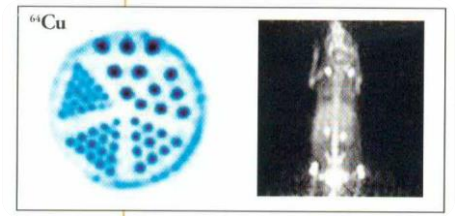
Comparison of some novel positron emitters with use of the Derenzo phantoms



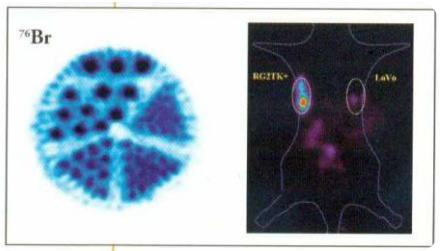
^{60}Cu, 23.70 min, β^+ 93 %
$E_{\beta mean}$ = 970 keV
E_γ = 826.4 keV (21.7 %)
1332.5 keV (88 %)
1791.6 keV (45.4 %)



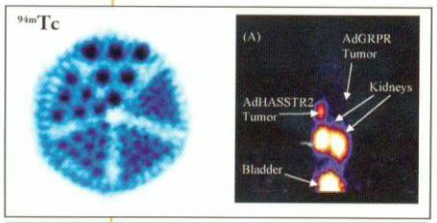
^{61}Cu, 3.333 h, β^+ 61 %
$E_{\beta mean}$ = 500 keV
E_γ = 282.96 keV (12.2 %)
656.01 keV (10.8 %)
1185.23 keV (3.7 %)



^{64}Cu, 12.701 h, β^+ 17.6 %
$E_{\beta mean}$ = 278 keV
E_γ = 1345.77 keV (0.48 %)



^{76}Br, 16.2 h, β^+ 55 %, $E_{\beta mean}$ = 1 180 keV
E_γ = 559.09 keV (74.0 %), 657.02 keV (15.9 %)
1216.8 keV (8.8 %), 1853.67 keV (14.7 %)



^{94m}Tc, 52.0 min, β^+ 70.2 %, $E_{\beta mean}$ = 1 072 keV
E_γ = 871.05 keV (94.2 %), 1522.1 keV (4.5 %)
1868.68 keV (5.7 %)

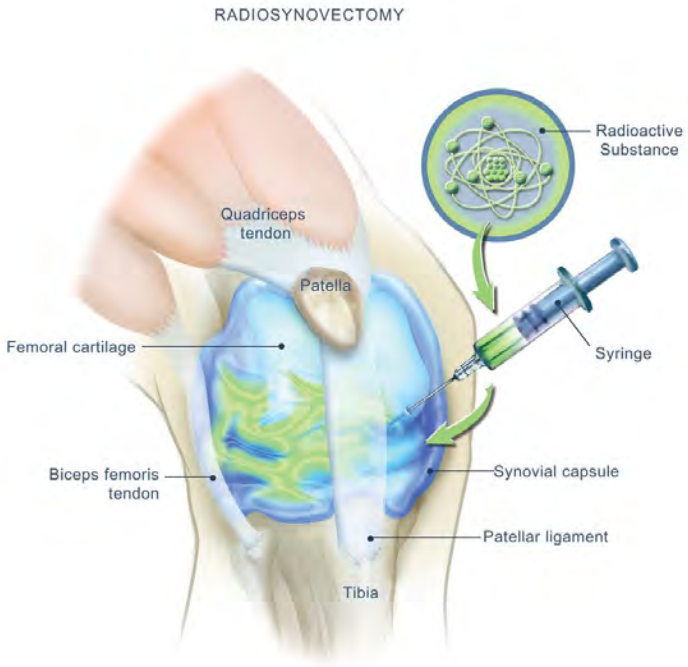
Therapeutic use of radionuclides

α-particle inducing DNA „double strand breaks“

Constructs containing β^- (energy controls the range) and α emitters

γ-rays are desirable for distribution imaging

Targeted cancer therapy and chronic joint inflammation therapy (radiosynovectomy)



Some novel β^- and α therapeutic emitters

RN	$T_{½}$	decay mode	γ-lines (keV)	production via
^{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)
^{186}Re	3.7183 d	β^- (92.5 %)	137.16 (9.47 %)	^{186}W(p,n) ^{186}W(d,2n)
^{211}At	7.214 h	α (41.80 %)	Po X-rays	^{209}Bi(α,2n)
^{213}Bi	45.59 min	α (2.20 %) ^{213}Po (100 %)	440.45 (25.9 %)	^{226}Ra(p,2n)^{225}Ac ^{225}Ac(10.0 d)→^{213}Bi
^{223}Ra	11.43 d	α (100 %)	154.21 (5.70 %) 269.46 (13.9 %)	^{226}Ra(α,3n)^{227}Th ^{227}Th(18.7 d)→^{223}Ra

Kinetics of the radionuclide production

$$A_{EOB}(\mathrm{MBq}) = \frac{\varrho f N_A I}{Aze\ 10^{12}}\left(1 - e^{\lambda t_b}\right) \int_{E_{out}}^{E_{in}} \frac{\sigma_{(E)}}{\left(-\frac{dE}{dx}\right)} dE = Y_{sat} I\left(1 - e^{\lambda t_b}\right)$$

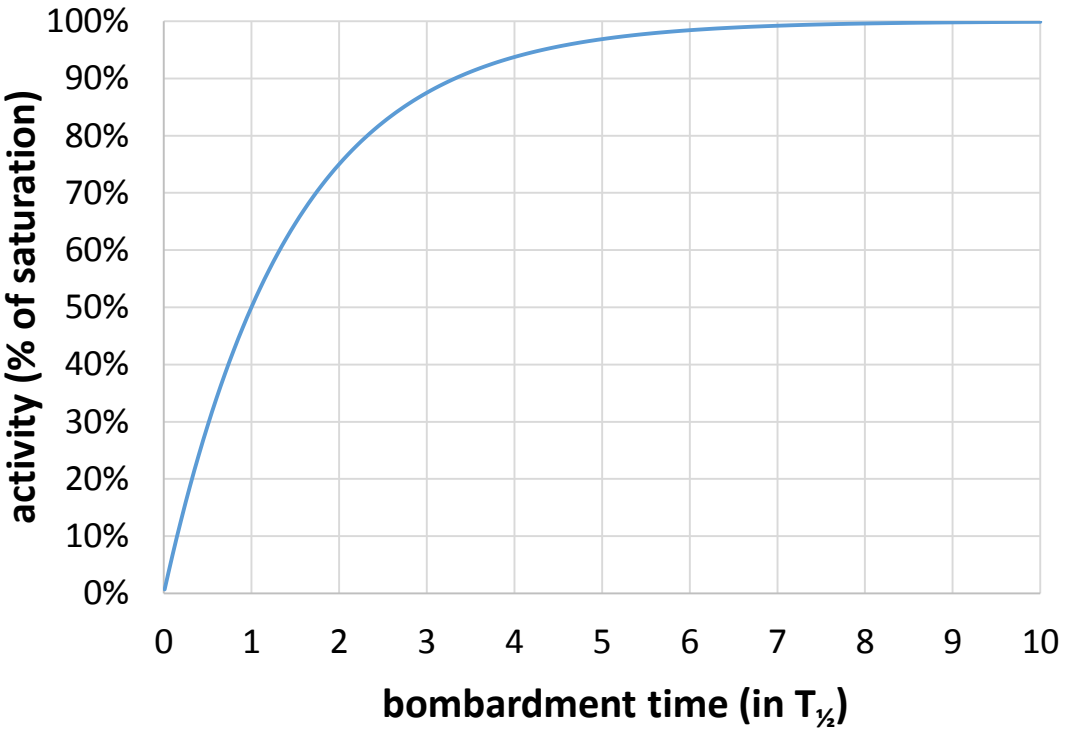
A_{EOB} is the radionuclide's activity at the end of bombardment (MBq)
ρ is the target material density (g/cm^3)
f is abundance of the target nuclei in the target material
N_A is Avogadro's number (6.022137×10^{23} mol^{-1})
I is beam current (μA)
A is atomic weight of the target material (g/mol)
z is the bombarding particle charge (for protons z = 1)
e is elementary charge (1.602177×10^{-19} C)
λ is decay constant of the radionuclide (h^{-1})
t_b is irradiation (bombardment) time (h)
$\sigma_{(E)}$ is cross-section as a function of energy, i.e. excitation function (cm^2)
(−d*E*/d*x*) is stopping power of the bombarding particle in the target (MeV/cm)
E_{in} and E_{out} are the bombarding particle energies at the target entrance and exit
Y_{sat} is the saturation thick target yield (MBq/μA)

Parameters to optimize the available activity

As obvious from the equation, for a given radionuclide and given production route there are four parameters available to increase the activity obtained at EOB:

$$A_{EOB}(\mathrm{MBq}) = Y_{sat} I \left(1 - e^{\lambda t_b}\right)$$

- enrichment of target isotope and use of pure element instead of its compounds (*f*)
- entrance energy E_{in} and beam energy loss in the target ($E_{in} - E_{out}$)
- time of bombardment (t_b)
- beam current (*I*)



Challenges in increasing the available activity

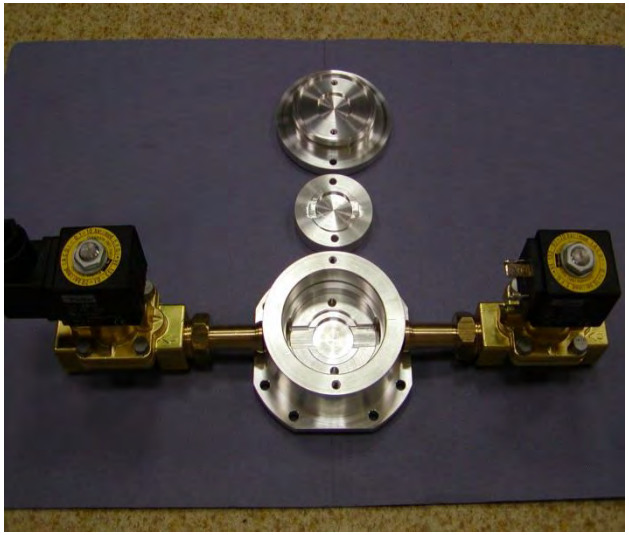
- bombardment time (t_b) – economical constraint, for the shorter-lived medical radionuclides it hasn‘t usually sense to irradiate for more than a half-life of the produced radionuclide
- beam current (I) – two technical constraints: maximum beam current available from a given cyclotron; maximum current applicable on a target without damage (efficient cooling, thermal conductivity); proton beam energy loss of 1 MeV at 1 μA beam current delivers 1 W heat input in a target
- entrance energy E_{in} and beam energy loss in the target ($E_{in} – E_{out}$) – it may be increased until radionuclidic purity is at acceptable level and until the target cooling prevents target damage
- enrichment of target isotope and use of pure element instead of its compounds (f) – it requires efficient recycling of the target matrix; the use of the pure element may be excluded due to unfavorable physical properties (poor thermal conductivity and low melting point, e.g. Te→TeO_2 in production of ^{124}I)

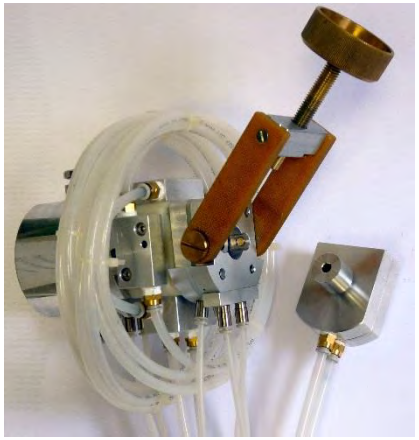
Other requirements to be met

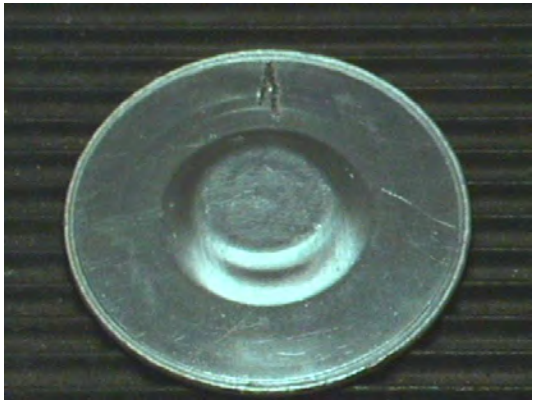
- Chemical purity & enrichment level of the target matrix define specific activity and chemical purity of the product – inappropriate choice may complicate the separation process and in particular affects labelling yield and specific activity of the labelled compound (majority of the labellings have character of complexation or rather chelating of a radiometal)
- Proper choice of the target support – so-called backing – regarding thermal conductivity, chemical purity and appropriate behaviour during the separation process. E.g. dissolving the backing together with the target layer puts higher requirement on the backing parameters
- Efficient recycling of the enriched target – in contrast to gas targets the losses during recycling solid targets are not negligible (in some exceptional cases, target may be re-used several times before re-processing, like $^{124}TeO_2$ or thick metal targets).

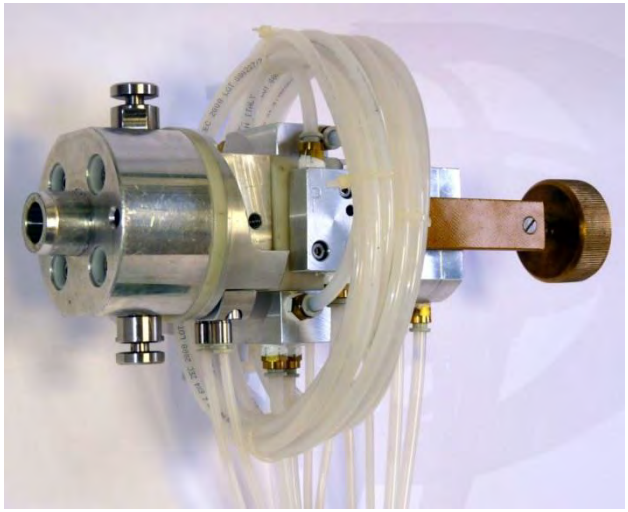
External targets – perpendicular

External targets are the most common and actually the only available on the modern, compact cyclotrons. They can be either perpendicular,



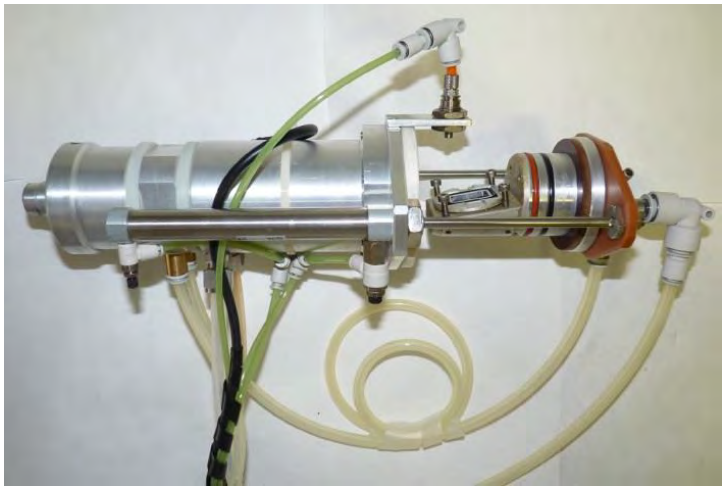






or

External targets – slanted (tangential)



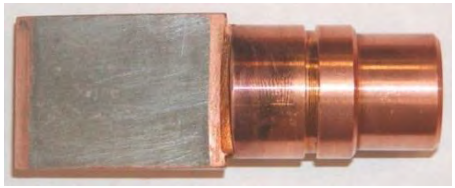
All the external solid targets may easily combine water-cooling from the backside and helium-cooling of the target surface exposed to the incident beam. Slanting the target distributes the heat power over the larger area and reduces its thickness. It is important for e.g. low thermal conductivity materials.

Internal targets

They allow for efficient use of the accelerated beam, in particular of the alpha particles that cannot be easily extracted from a cyclotron; limited to machines providing such a solution, usually 30–40 MeV cyclotrons. Only water cooling from the back-side is applicable.

Such targets may be stationary (double-slanted targets) – extremely low angles may be achieved, demanding positioning – or revolving:

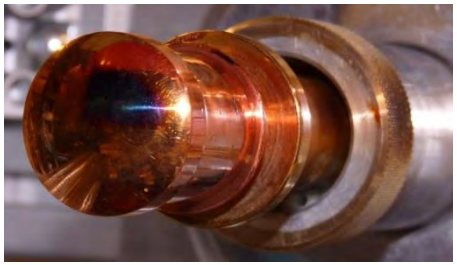
1°–1.5°



- ^{67}Ga
- ^{201}Tl
- ^{111}In

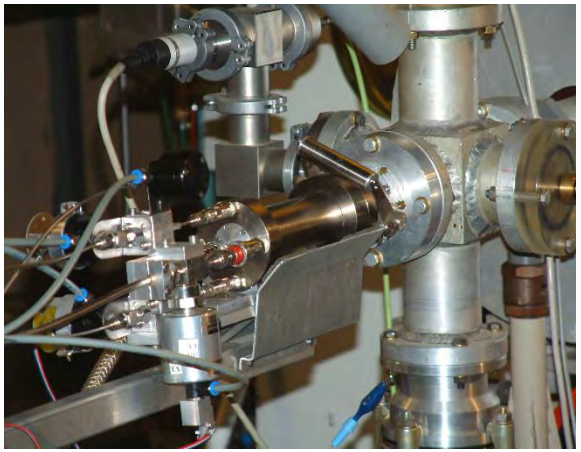
- ^{211}At
- ^{64}Cu

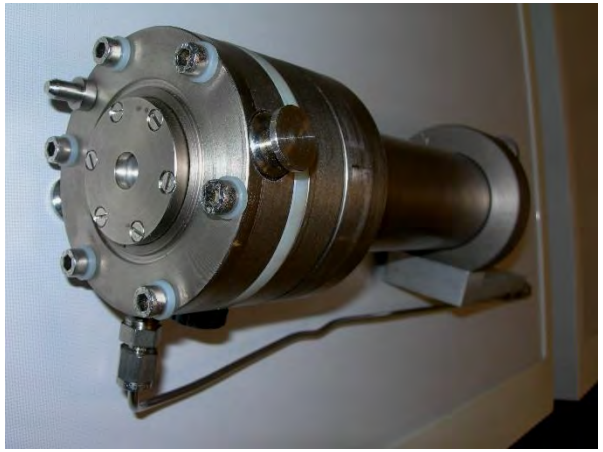
revolving



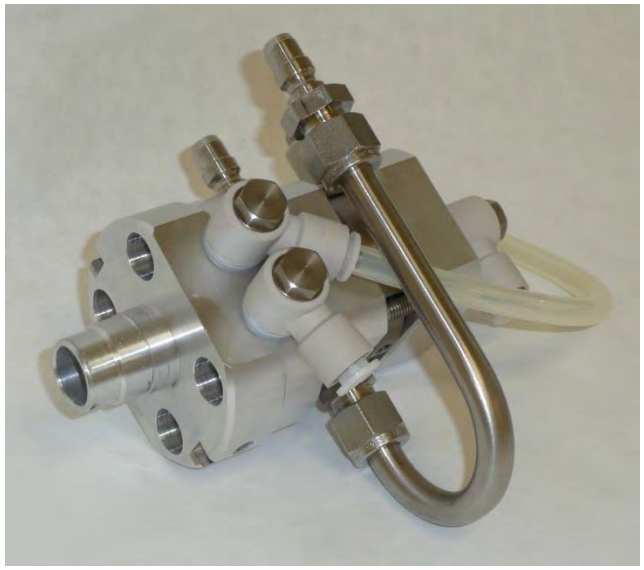
- ^{211}At, ^{68}Ga etc.
- Cu isotopes

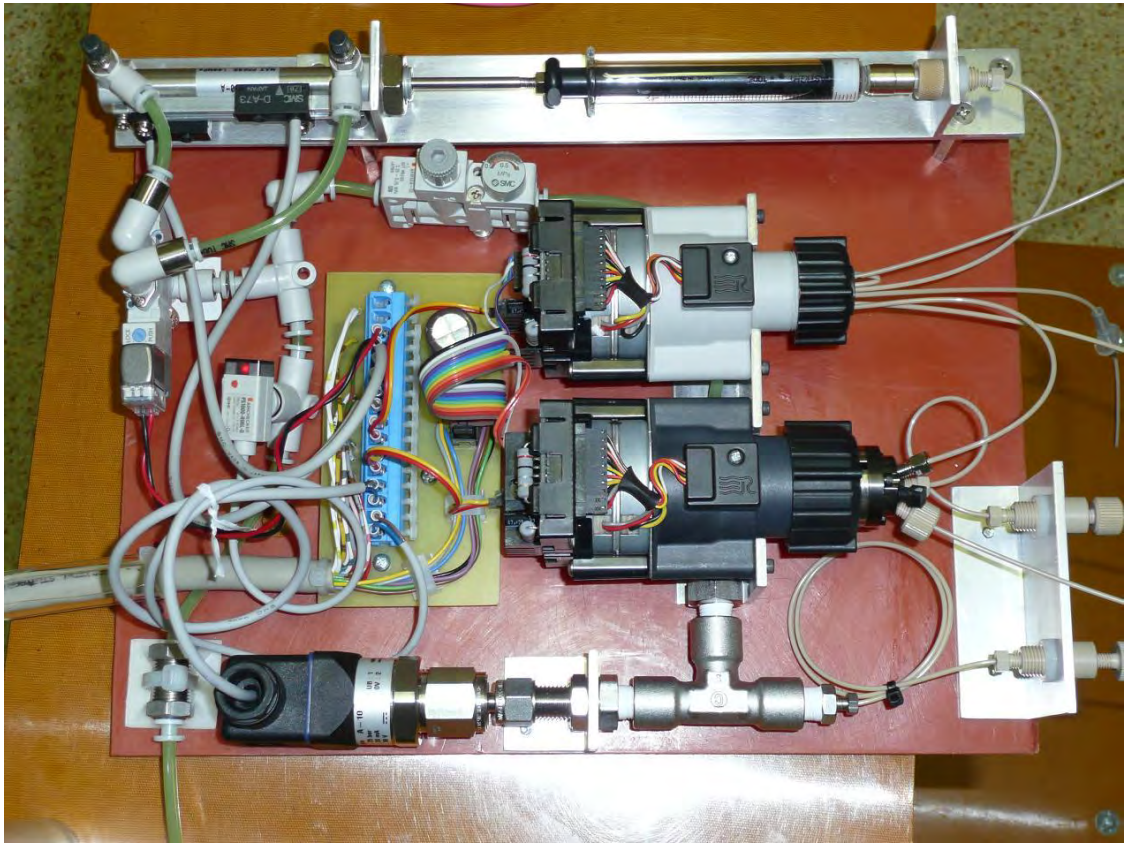
Gas targets for production of ^{81,83}Rb and ^{123}I





Universal liquid target for production of ^{18}F and non-conventional PET radionuclides

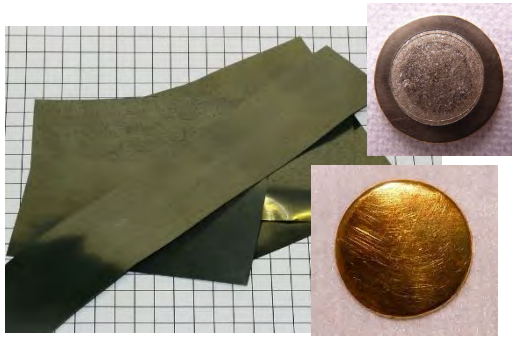




Target manufacturing methods

Electrolytical deposition, e.g. ^{64}Ni

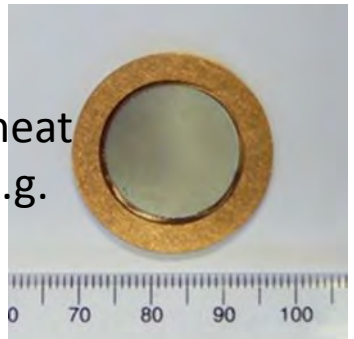
Cold pressing for powders, e.g. ^{100}Mo



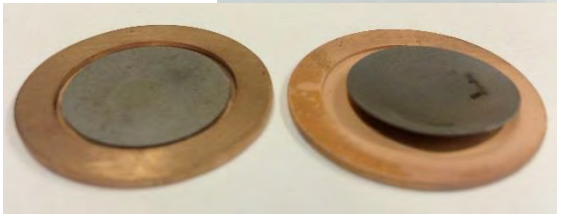
Evaporation, e.g. ^{209}Bi

Using the foils as delivered, e.g. Y, Cr, Ni, Au etc.

Pressing, sintering, heat pressing, e.g. ^{100}Mo



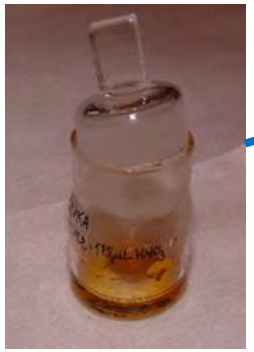
Melting, e.g. $^{124}TeO_2$ with Al_2O_3

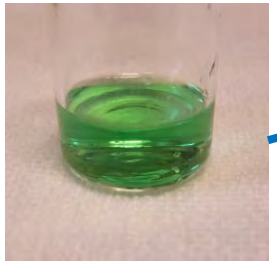


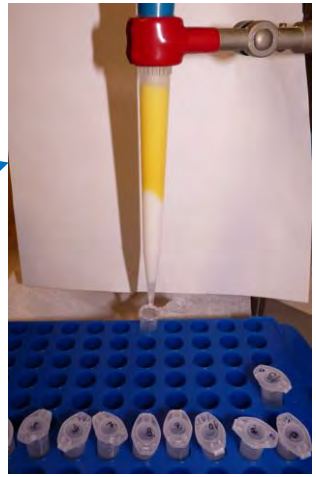
Target processing methods

Dry distillation – limited to radiohalogens like ^{211}At, ^{124}I, ^{76}Br

Efficient, sensitive to setting the parameters of the process.







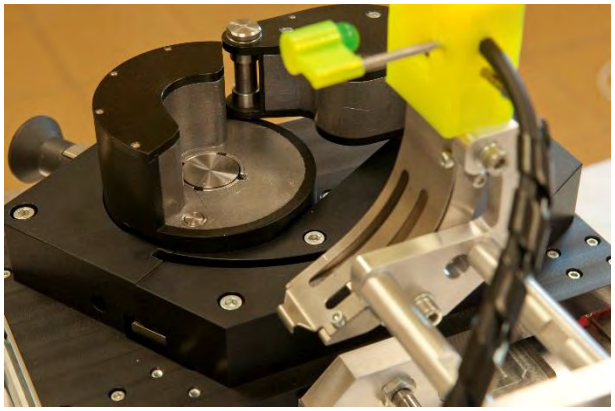
Wet chemistry – applicable to practically all radiometals; dissolving of the target is followed by a suitable separation method like solid phase extraction, liquid-liquid extraction, ion-exchange chromatography (standard or complex-based)

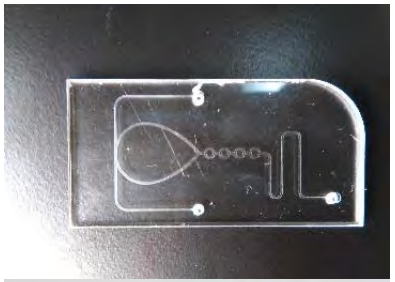
Recycling of the enriched material – example ^{100}Mo

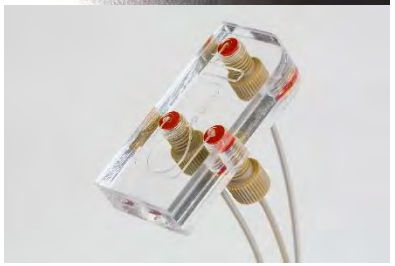
Highly enriched target matrix appears in the form of the ammonium molybdate solution after the processing. It is then lyophilized and thermally decomposed in steps to MoO_3 and finally to metal Mo. This process have efficiency of 85–87 % (Gagnon et al., 2012, Bénard et al., 2014).

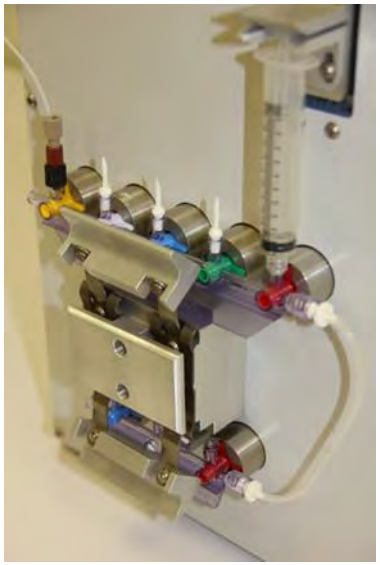
Increasing the recycling efficiency is highly desirable. Large-scale re-processing improves recovery. It is a good example of both commercial and collaboration topic similarly to target manufacturing.

The contemporary challenge – automation, rapid separation methods









Hot cells for production of radiopharmaceuticals

Laminar flow box for aseptic operations

Acknowledgements

I am much grateful to my colleagues from the Department of Radiopharmaceuticals and Department of Accelerators, and also my colleagues from all over the world who work in the field.