Review on *in vivo* radionuclide generators for diagnostic and therapy

B. B. Cho, K. H. Choi *
Korea Atomic Energy Research Institute, P. O. Box 105, Yusung, Daejeon 305-600, Korea
Corresponding author: khchoi@kaeri.re.kr

1. Introduction

Conventional methods of radiotherapy have often been limited by physical drawbacks, use nuclides with high decay energies and short half-lives, and radionuclide loss resulting in dose to non-target tissue while circulating in the blood. [1-2] To overcome these limitations, a novel approach for radiotherapy is use of parent isotopes with low energy-emitting and longer-lives of therapeutic isotopes.

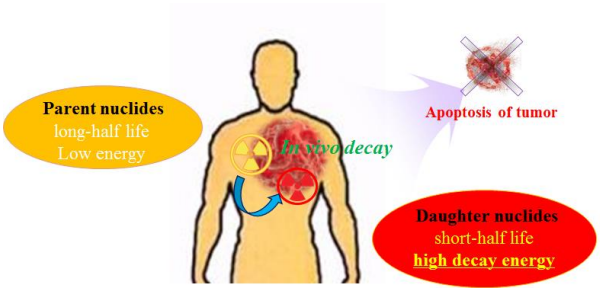

Figure 1. Concept of *in vivo* generator

An "*in vivo* generator" is a concept that the long-lived and low energy-emitting parent radionuclides are delivered to a target tissue followed by their *in vivo* decay into short-lived daughter radionuclides with high decay energetic beta particles to achieve high-dose targeted radiotherapy.

The term '*in vivo* generator' was first reported in a conference abstract (1989), discussing the use of targeted monoclonal antibodies with long-lived parent radionuclides, by Mausner et al. [3]

The most important consideration by introducing *in vivo* generator concept is the chemical consequence of the parent decay. [4] The elemental changes between parent and daughter isotopes following *in vivo* decay could be exploited for novel diagnostic and therapeutic methods. [2] Also, In case of using lanthanide as parent and daughter isotopes, the lifetime of daughter nuclides in target site could be increased without escape to other site due to their similar chemical properties between parent and daughter isotopes.

In this presentation, we will cover and discuss on many of the *in vivo* radionuclide generators that have been used clinically and pre-clinically for imaging and therapy. [4]

Table 1. Radionuclides for *in vivo* generator

	Parent	Decay	$t_{1/2}$	Daughter	Decay	$t_{1/2}$	Use
Diagnostics	^{81}Rb	EC	4.6 h	^{81m}Kr	IT	13s	SPECT
	^{52}Fe	EC/β^+	8.3 h	^{52m}Mn	β^+	21 min	PET
	^{62}Zn	EC/β^+	8.2 h	^{62}Cu	β^+	9.7 min	PET
Therapy	^{103}Pb	EC	16 d	^{103m}Rh	EC	46 min	Auger
	^{112}Pd	β^-	21.04 h	^{112}Ag	β^-	3.14 h	β
	^{166}Dy	β^-	81.5 h	^{166}Ho	β^-	26.6 h	β
	^{213}Bi	α	45.6 min	^{209}Pb	β^-	3.3 h	α
	^{212}Pb	β^-	10.64 h	^{212}Bi	α	1.01 h	α

2. *In vivo* generators for diagnostic

There are some examples that an *in vivo* generator system is applied in a wide range of medicinal applications. [4]

2.1. ^{81}Rb/^{81m}Kr

^{81}Rb/^{81m}Kr pair is one of first purposeful uses of in vivo generation system, which is effective imaging agent for tissue blood flow. The parent ^{81}Rb ($t_{1/2}$=4.3 h) accumulates in cells due to acting like potassium ion, but ^{81m}Kr ($t_{1/2}$ = 13 s), the inert metastable daughter of ^{81}Rb, leaves the cells via diffusion. Using of this characteristic, the ^{81}Rb/^{81m} Kr ratio could allow for measuring the quantitative indices of blood perfusion.

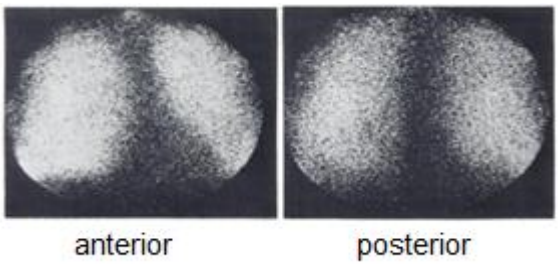

Figure 2. Scintigraphic images of lungs after singles breath inhalation of ^{81m}Kr.

2.2 ^{52}Fe/^{52m}Mn

^{52}Fe ($t_{1/2}$=8.27h)/^{52m}Mn ($t_{1/2}$=21min) pair could result in positron emission tomography images to determine the iron kinetics of the blood-brain barrier in a quantitative and qualitative way. Iron transport in the body is very important as improper iron transfer is linked to a number of disease

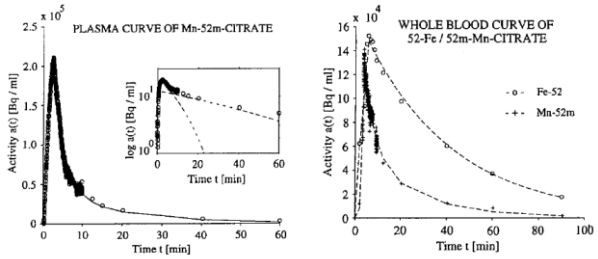

Figure 3. A representative activity distribution of ^{52m}Mn-citrate in plasma and kenetic of ^{52}Fe/^{52m}Mn in whole blood.

2.3 ^{62}Zn/^{62}Cu

^{62}Zn ($t_{1/2}$=9.18h)/ ^{62}Cu ($t_{1/2}$=9.67min) also potentially provides biological information as a tracer for Zn. This isotopic pair can also be used as immune-PET or small molecule imaging. Especially, ^{62}Zn labeled medicine (laserphyrin) showed greater accumulation in tumor compared to other PET agents because it provides ^{62}Cu as daughter isotope following *in vivo* decay and it would affect to biological and imaging results with parent radionuclide.

3. *Therapeutic in vivo* generators

3.1. ^{212}Pb/^{212}Bi

^{212}Pb ($t_{1/2}$=10.64h)/ /^{212}Bi ($t_{1/2}$=60.56min) pair has been investigated for direct targeting and pre-targeted radiotherapy using a variety of mAb systems. The ^{212}Pb/^{212}Bi nuclides are incorporated into biological molecules using chelating ligands such as DOTA and TCMC. But, the ^{212}Bi in the ligand is unstable to release from tumor into non-targeted health tissue and it cause some side effects. Nevertheless, this system have been shown to be more effective when applied to internalizing specific mAbs as trastuzumab for HER2 compared to non-internalizing or nonspecific mAbs. Also, this system could higher absorb into tumor site than β-emitting ^{90}Y-derivatives due to the higher LET of α-particles from ^{212}Bi.

3.2. ^{166}Dy/^{166}Ho

Lanthanides containing Dy and Ho have similar physical and chemical characteristics. The ^{166}Dy/^{166}Ho *in vivo* generator system promise more efficient radiotherapy than other *in vivo* generator systems since the ^{166}Ho ($t_{1/2}$=26.8h)/, daughter isotope, will not escape from the target site after the *in vivo* decay of parent isotope,^{166}Dy ($t_{1/2}$=81.6h). ^{166}Dy/^{166}Ho labeled Ethylene-diamine-tetra-methylene-phosphonate (EDTMP) has been shown to accumulate in skeletal tissue and it could be applied for marrow ablation.

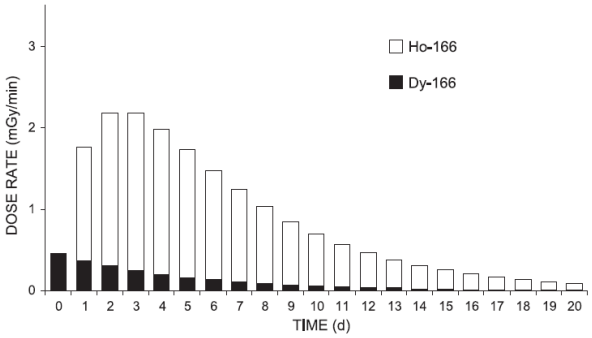

Figure 4. Average dose rate of [^{166}Dy]Dy/^{166}Ho-EDTMP to bone marrow in mice.

4. Conclusion

In conclusion, the advantage of *in vivo* generators is to enhance to diagnose and treatment condition with combine nuclear and chemical properties of the parent and daughter nuclides. The development of *in vivo* generators would expand the scope of radioisotopes use as diagnostic and therapeutic radiopharmaceuticals in nuclear medicine.

REFERENCES

[1] S.V. smith, N.D. Bartolo, S. Mirzadeh, R.M. Lambrecht, F.F.Knapp, and E.L. Hetherington, [^{166}Dy]Dysprosium/ [^{166}Ho]Holmiun In Vivo Generator, Appl. Radiat. Isot, 46, 8, 759-764, 1995

[2] B.B Cho, and K.H. Choi, Preparation of Chitosan microspheres containing ^{166}Dy/^{166}Ho in vivo generators and their theranostic potential, J Radioanal Nucl Chem, 317, 1123-1132, 2018

[3] L.F. Mausner, R.F. Straub, and S.C. Srivastava, The *in-vivo* generator for radio-immunotherapy, Symposium abstracts, 1989

[4] P.E. Edem, J. Fonslet, A. Kjaer, M. Herth, and G. Severin, In Vivo Radionuclide Generators for Diagnostics and Therapy, Bioinorg Chem Appl, 2016, 6148357, 2016