Production and applications of radioisotopes at RIKEN RI Beam Factory

- Chemistry of new elements through diagnosis and therapy of cancer -

Hiromitsu HABA*

Nishina Center for Accelerator-Based Science, RIKEN, Wako, Saitama 351-0198, Japan *Email: haba@riken.jp

We are developing production technologies of radioisotopes (RIs) for application studies at RIKEN RI Beam Factory (RIBF). More than 100 RIs produced at the AVF cyclotron, RIKEN Linear Accelerator, and RIKEN Ring Cyclotron have been used in research fields of physics, chemistry, biology, engineering, medicine, pharmaceutical and environmental sciences. In this paper, RIs for superheavy element chemistry and targeted alpha therapy at RIBF are emphasized. Purified RIs such as ⁶⁵Zn, ⁶⁷Cu, and ¹⁰⁹Cd are delivered to universities and research institutes through Japan Radioisotope Association. Short-lived RIs such as ⁸⁸Zr, ¹⁷⁵Hf, and ²¹¹At are also distributed to researchers through the platform for short-lived RI distribution, supported by JSPS KAKENHI.

1. Introduction

Due to its high sensitivity, the radioactive tracer technique has been successfully applied for investigations of the behavior of elements in the fields of physics, chemistry, biology, engineering, medicine, pharmaceutical and environmental sciences. At RIKEN RI Beam Factory (RIBF), we have been developing production technologies of radioisotopes (RIs) for application studies using the AVF cyclotron (AVF), RIKEN Linear Accelerator (RILAC), and RIKEN Ring Cyclotron (RRC). In this paper, the production and applications of RIs at RIBF are reported with focus on RIs for superheavy element chemistry and targeted alpha therapy. Distributions of RIs through Japan Radioisotope Association and Supply Platform of Short-lived Radioisotopes for Fundamental Research are introduced.

2. Production of RIs at RIBF

First of all, reliable excitation functions are necessary to effectively and quantitatively produce RIs of interest and to reduce contamination of undesired by-products. We have been systematically investigating the excitation functions especially for the d- and α -induced reactions on various targets at AVF in collaboration with Sunway University, Malaysia, International Atomic Energy Agency, Austria, Hokkaido University, and Institute for Nuclear Research (ATOMKI), Hungary. The excitation functions are compared in detail with the previous ones as well as the theoretical model calculations such as the TALYS code taken from the TENDL online database [1]. Then, we develop RI production apparatuses on the beam lines of AVF, RRC, and RILAC. We also develop chemical separation procedures to obtain

RIs with high radionuclidic purity, specific radioactivity, and chemical purity. Finally, radioactivity and chemical purity of RIs are specified by γ -ray/ α -particle spectrometry and Inductively Coupled Plasma Mass Spectrometry (ICP-MS), respectively.

RIKEN RIs developed for application studies since 2002 are summarized in Table 1. With light- to heavy-ion beams from the AVF cyclotron, we produce more than 100 RIs from ⁷Be (atomic number Z = 4) to ²⁶²Db (Z = 105) [2,3]. RIs for superheavy element chemistry such as ^{265a,b}Sg (Z = 106) and ²⁶⁶Bh (Z = 107) are produced using a gas-jet transport system coupled to the GAs-filled Recoil Ion Separator (GARIS) at RILAC [4]. On the other hand, RIs of a large number of elements, called multitracer, are simultaneously produced from metallic targets such as ^{nat}Ag and ¹⁹⁷Au irradiated with a 135 MeV/u ¹⁴N beam from RRC [5].

3. Application studies with RIKEN RIs

The RIKEN RIs have been used in the application studies in collaboration with many researchers in the world as annually reported in RIKEN Accelerator Progress Reports [6] (See the section "Nuclear chemistry and Radiochemistry".) and the references therein. In this paper, we focus on RIs used in chemistry of superheavy elements and targeted alpha therapy.

3.1. Superheavy element chemistry

Chemical characterization of newly-discovered superheavy elements (SHEs, atomic numbers $Z \ge 104$) is an extremely interesting and challenging subject in modern nuclear and radiochemistry [7]. To start up the SHE chemistry at RIBF, we installed a gas-jet transport system to the focal plane of GARIS [4]. This system is a promising approach for exploring new frontiers in the SHE chemistry: the background radiations from unwanted products are strongly suppressed, the intense primary heavy-ion beam is absent in the gas-jet chamber, and hence the high gas-jet extraction yield is attained. Furthermore, the beam-free condition makes it possible to investigate new chemical systems. Long-lived SHE RIs of 261a,b Rf (Z = 104), 262 Db, 265a,b Sg, and 266 Bh were produced in the 248 Cm(18 O,5n) 261a,b Rf, 248 Cm(19 F,5n) 262 Db, 248 Cm(22 Ne,5n) 265a,b Sg, and 248 Cm(23 Na,5n) 266 Bh reactions, respectively, and their decay properties were investigated in detail using a rotating wheel apparatus for α and SF spectrometry [8–11]. The decay properties determined for 261a,b Rf, 262 Db, 265a,b Sg, and 262 Bh reactions, respectively, and their decay properties determined for 261a,b Rf, 262 Db, 265a,b Sg, and 262 Db, 265a,b Sg, and 266 Bh reactions, respectively.

Using the GARIS gas-jet system, the first chemical synthesis and gas-chromatogrphic analysis of Sg(CO)₆ were successfully conducted under an international collaboration lead by GSI Helmholtzzentrum für Schwerionenforschung GmbH, Helmholtz Institute Mainz, and University of Mainz, Germany [12]. A detailed experiment to investigate the stability of the metal carbon bond in Sg(CO)₆ is in progress with a thermal decomposition setup developed by Paul Scherrer Institute, Switzerland [13]. Also, syntheses and properties of Tc, Ru, Rh, and Re carbonyls are under study at Institute of Modern Physics (IMP), China and RIBF for future studies on Bh, Hs (Z = 108), and Mt (Z = 109) carbonyls [14–16]. To realize aqueous chemistry studies of Sg and Bh, we have been developing a continuous and rapid solvent extraction apparatus which consists of a continuous dissolution apparatus Membrane DeGasser (MDG), a Flow Solvent Extractor (FSE), and a liquid scintillation detector for α /SF-spectrometry [17].

A conventional target/gas-jet system for the production of SHE RIs is also available at AVF [18]. The automated batch-type solid-liquid extraction apparatus for repetitive experiments of transactinides

Nuclides	Ζ	T 1/2	Accelerator	Reactions	Nuclides	Ζ	T 1/2	Accelerator	Reactions
⁷ Be	4	53.29 d	AVF	^{nat} Li(p,xn)	¹³⁹ Ce	58	137.640 d	AVE	^{nat} La(p,xn)
²⁴ Na	11	14.9590 h	AVF	natMg(d,x)		38	157.040 d	AVF	natLa(d,xn)
²⁸ Mg	12	20.91 h	AVF	27 Al(α ,3p)	¹⁴¹ Ce	58	32.501 d	AVF	$^{nat}Ba(\alpha,x)$
^{42,43} K	19	12.360 h, 22.3 h	AVF	nat,43,44 Ca(d,x)	^{141m} Nd [*]	60	62.0 s	AVF	¹⁴¹ Pr(d,2n)
				^{nat} Ti(d,x)	¹⁴³ Pm	61	265 d	AVF	¹⁴¹ Pr(α,x)
^{44m,g} Sc	21	58.6 h, 3.927 h	AVF —	^{nat,44} Ca(d,x)	¹⁴³ Sm*	62	66 s	AVF	144Sm(d,p2n
⁴⁴ Ti	22	40	AVF	⁴⁵ Sc(d,3n)	^{143,144} Eu*	63			¹⁴⁴ Sm(d,xn)
48V		49 y			146Gd		2.63 min, 10.2 s	AVF	Sm(d,xn)
48,51 Cr	23	15.9735 d	AVF	nat nat	162,163 Yb*	64	48.27 d	AVF	¹⁴⁴ Sm(α,2n)
	24	21.56 h, 27.702 d	AVF	nat Ti(a,xn)		70	18.87 min, 11.05 min	AVF	natGd(¹² C,xn
⁴⁸ Cr	24	21.56 h	AVF	46Ti(α,2n)	^{163,164} W*	74	2.75 s, 6.0 s	RILAC	144Sm(²⁴ Mg,x
^{52g,54} Mn	25	5.591 d, 312.3 d	AVF	^{nat} Cr(p,xn)	¹⁶⁹ Hf [*]	72	3.24 min	AVF/RILAC	natGd(¹⁸ O,xn
^{56,57,58} Co	27	77.27 d, 271.79 d, 70.82 d	AVF	^{nat} Fe(d,xn)	¹⁷⁰ Ta*	73	6.76 min	AVF/RILAC	^{nat} Gd(¹⁹ F,xn
⁶¹ Cu	29	3.333 h	AVF	^{nat} Zn(d,x)	¹⁷⁰ Re*	75	9.2 s	RILAC	¹⁵² Gd(²³ Na,5)
⁶⁵ Zn	30	244.26 d	AVF -	^{nat} Cu(p,xn)	¹⁷³ Hf*	72	23.6 h	AVF	$^{nat}Yb(\alpha,xn)$
	30	244.20 u	AVI	^{nat} Cu(d,xn)	¹⁷³ W*	74	7.6 min	AVF/RILAC	^{nat} Gd(²² Ne,xr
^{66,67} Ga	31	9.49 h, 3.2612 d	AVF	natZn(d,xn)	¹⁷⁴ Re*	75	2.40 min	RILAC	natGd(23Na,xr
				70 Zn(p, α)	175				^{nat} Lu(p,xn)
⁶⁷ Cu	29	61.83 h	AVF —	⁷⁰ Zn(d,αn)	¹⁷⁵ Hf	72	70 d	AVF	natLu(d,xn)
^{69m} Zn	30	13.76 h	AVF	nat Zn(d,x)					nat Hf(p,xn)
⁷⁴ As	33	17.77 d	AVF	2n(d,x) natGa(α,x)	^{177,178a,179} Ta	73	56.56 h, 2.36 h, 1.82 y	AVF	natHf(d,xn)
AS .	55	17.77 U	1141	$Ga(\alpha, \mathbf{x})$ ⁷⁵ As(p,n)	177W*	74	135 min	AVF	
⁷⁵ Se	34	110 770 4	A 1/17	As(p,n)	178ªTa*				nat Hf(α,xn)
	34	119.779 d	AVF	⁷⁵ As(d,2n)	^{179a} Ta ^{179m} W [*]	73	2.36 h	AVF	^{nat} Hf(d,xn)
				^{mat} Ge(α ,xn)		74	6.40 min	AVF	nat Ta(d,xn)
⁸⁵ Sr	38	64.84 d	AVF	^{nat} Rb(p,xn)	¹⁸⁰ Re [*]	75	2.44 min	AVF	^{nat} Ta(α,xn)
				^{nat} Rb(d,xn)	¹⁸¹ W	74	121.2 d	AVF	^{nat} Ta(p,xn)
^{85g} Zr [*]	40	7.86 min	AVF/RILAC	^{nat} Ge(¹⁸ O,xn)					^{nat} Ta(d,xn)
⁸⁸ Y	39	106.65 d	AVF	^{nat} Sr(p,xn)	¹⁸¹ Re*	75	19.9 h	AVF	^{nat} W(d,xn)
				^{nat} Sr(d,xn)	¹⁸² Ta	73	114.43 d	AVF	$^{nat}Hf(\alpha,x)$
				^{nat} Rb(a,xn)	^{182a,183,184m,184g} Re	75	12.7 h, 70.0 d, 169 d, 38.0 d	AVF	natW(d,xn)
^{88,89} Zr	40	83.4 d, 78.41 h	AVF	⁸⁹ Y(p,xn)	¹⁸³ Re	75	70.0 d	AVF	^{nat} Ta(α,xn)
				⁸⁹ Y(d,xn)	¹⁸⁵ Os	76	93.6 d	AVF	^{nat} Re(p,xn)
^{89m} Zr*	40	4.18 min	AVF	⁸⁹ Y(p,n)	¹⁸⁶ Re	75	90.64 h	AVF	¹⁸⁶ W(d,2n)
				⁸⁹ Y(d,2n)					^{nat} Os(a,xn)
				^{nat} Sr(a,xn)	^{188,189,191} Pt	78	10.2 d, 10.87 h, 2.802 d	AVF	nat Ir(d,xn)
^{88m,88g} Nb [*]	41	7.9.14.5		^{nat} Ge(¹⁹ F,xn)	²⁰³ Pb	82	51 072 h	AVF	²⁰³ Tl(p,n)
ND	41	7.8, 14.5 min	AVF/RILAC		Pb	82	51.873 h	AVF	
^{90m,90g} Nb [*]	41	18.81 s, 14.60 h	AVF	^{nat} Zr(p,xn)	²⁰⁶ Bi	83	6.243 d	AVF	^{nat} Pb(p,xn)
00 *				natZr(d,xn)	205 #				^{nat} Pb(d,xn)
⁹⁰ Mo*	42	5.67 h	AVF/RILAC	^{nat} Ge(²² Ne,xn)	²⁰⁶ Fr*	87	15.9 s	RILAC	169Tm(40Ar,31
^{92m,95} Nb	41	10.15 d, 34.975 d	AVF —	^{nat} Zr(p,xn)	²⁰⁹ Fr*	87	50.0 s	RILAC	¹⁹⁷ Au(¹⁸ O,6n
				^{nat} Zr(d,xn)	²¹¹ At	85	7.214 h	AVF	²⁰⁹ Bi(α,2n)
^{92,94} Tc*	43	4.23 min, 293 min	AVF	^{nat} Mo(d,xn)	²¹² Fr*	87	20.0 min	AVF	206,207,208,natPb(11
				93Nb(p,n)	²¹⁴ Ac*	89	8.2 s	RILAC	197Au(22Ne,51
^{93m} Mo*	42	6.85 h	AVF	⁹³ Nb(d,2n)	²²⁵ Ac	89	10.0 d	RRC	232Th(14N,xny
				$^{nat}Zr(\alpha,xn)$	229Pa	91	1.50 d	AVF	²³² Th(p,4n)
^{93g,94} Tc [*]	43	2.75 h, 293 min	AVF	$^{93}Nb(\alpha,xn)$	²³⁶ Np	93	1.54×10 ⁵ y	AVF	²³² Th(⁷ Li,3n
95,96 Tc	43	20.0 h, 4.28 d	AVF	^{mt} Mo(d,xn)	245 Fm*	100	4.2 s	RILAC	²⁰⁸ Pb(⁴⁰ Ar,3r
10		20.0 II, 7.20 U	1141	⁹⁵ Mo(p,n)		100	7.2 0	AVF/RILAC	²³⁸ U(²² Ne,5n
^{95m} Tc	43	61 d	AVF		²⁵⁵ No [*]	102	3.1 min		248 12
				^{nat} Mo(d,xn)		102		AVF	²⁴⁸ Cm(¹² C,5n
				⁹³ Nb(α,2n)	255Lr*	103	22 s	RILAC	²⁰⁹ Bi(⁴⁸ Ca,2r
⁹⁹ Mo	42	65.94 h	AVF	$^{nat}Zr(\alpha,xn)$	²⁵⁷ Lr*	103	0.646 s	AVF	²⁴⁸ Cm(¹⁴ N,5r
99Rh	45	16.1 d	AVF	99Ru(p,n)	²⁵⁹ Lr*	103	6.3 s	AVF	²⁴⁸ Cm(¹⁵ N,4r
109mPd*	46	4.696 min	AVF	^{nat} Pd(d,x)	^{261a,b} Rf [*]	104	68, 1.9 s	AVF/RILAC	²⁴⁸ Cm(¹⁸ O,5r
104mgAg*	47	33.5 min, 69.2 min	AVF	^{nat} Pd(d,xn)	²⁶² Db*	105	34 s	AVF/RILAC	248Cm(19F,5r
¹¹¹ Ag	47	7.45 d	AVF	natPd(d,xn)	^{265a,b} Sg [*]	106	8.5, 14.4 s	RILAC	²⁴⁸ Cm(²² Ne,5
				^{nat} Ag(p,xn)	²⁶⁶ Bh*	107	10.0 s	RILAC	²⁴⁸ Cm(²³ Na,5
¹⁰⁹ Cd	48	462.6 d	AVF —	^{nat} Ag(d,xn)	Multitracer	<22		RRC	natTi(¹⁴ N,xnyp
¹²⁴ Sb	51	60.20 d	AVF	^{nat} Sn(d,x)	Multitracer	<29		RRC	natCu(¹⁴ N,xny
	51	00.20 u	1141		Multitracer				
^{121m} Te	52	154 d	AVF	$^{nat}Sn(\alpha,xn)$		<47		RRC	^{nat} Ag(¹⁴ N,xny
				^{nat} Sb(d,xn)	Multitracer	<72		RRC	nat14
¹²⁴ I	53	4.1760 d	AVF	¹²⁴ Te(d,2n)	Multitracer	<73		RRC	^{nat} Ta(¹⁴ N,xny
135mBa	56	28.7 h	AVF -	$^{133}Cs(\alpha,x)$	Multitracer	<79		RRC	¹⁹⁷ Au(¹⁴ N,xny
^{135m} B ^a		-0.7 11		nat		<83		RRC	²⁰⁹ Bi(¹⁴ N,xnyj
^{135m} Ba				^{nat} La(d,x)	Multitracer	~05		KKC	²³² Th(¹⁴ N,xnyj

Table 1. List of radioisotopes developed for application studies at RIBF since 2002.

* RIs produced with the gas-jet system.

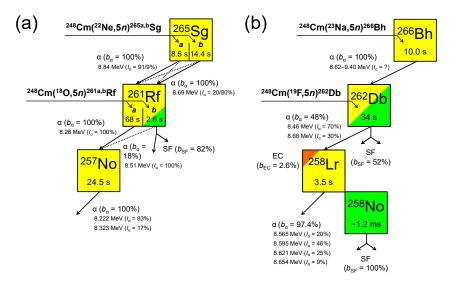


Figure 1. Decay pattern for the chains (a) ${}^{265a,b}Sg \rightarrow {}^{261a,b}Rf \rightarrow {}^{257}No \rightarrow and$ (b) ${}^{266}Bh \rightarrow {}^{262}Db \rightarrow {}^{258}Lr \rightarrow {}^{258}No \rightarrow [8-11].$

(AMBER) was developed by Osaka University, and distribution coefficients of Rf were determined in HCl [19]. Reversed-phase extraction behavior of Rf with thenoyltrifluoroacetone in HF/HNO₃ was investigated using Automated Rapid Chemistry Apparatus (ARCA) developed by Japan Atomic Energy Agency [20]. Recently, co-precipitation of Rf in basic solutions containing NH₃ or NaOH was investigated in collaboration with Osaka University using a semiautomatic suction filtration apparatus, CHIN [21].

3.2. Production of ²¹¹At for Targeted Alpha Therapy

In recent years, the needs for α -particle-emitting RIs for targeted alpha therapy (TAT) is rapidly increasing in the world. The α particles have a shorter range (40–100 µm) in living tissues than β particles (0.05–12 mm), and have a high linear energy transfer (~80 keV/µm), so they are highly cytotoxic. Thus, medicines labeled with α -particle-emitting RIs are considered to be effective in treating disseminated cancer, blood cancer, micrometastasis cancer, and microcancer remaining in a postoperative site. ²¹¹At decays to the stable nuclide ²⁰⁷Pb by emitting an α particle with the half-life of 7.214 h. ²¹¹At is produced in the ²⁰⁹Bi(α ,2n)²¹¹At reaction by irradiating a metallic ²⁰⁹Bi target with α particles accelerated by a cyclotron. The optimum incident beam energy for the production is ~28 MeV in order to minimalize the production of ²¹⁰At in the ²⁰⁹Bi(α ,3n)²¹⁰At reaction: ²¹⁰At decays to the long-lived and toxic ²¹⁰Po by an electron capture. Since the half-life of ²¹¹At is very short, it is difficult to import ²¹¹At from abroad and domestic production is essential. In order to realize the radionuclide therapy with ²¹¹At in Japan, it is necessary to establish a platform for the production and supply of ²¹¹At among domestic accelerator facilities that have large accelerators. Since 2015, we have been developing a production technology of ²¹¹At at AVF and distributing it to 16 research groups in Japan [22].

Figure 2 shows a schematic and photos of the ²¹¹At production system developed at RIBF. The metallic ²⁰⁹Bi target is irradiated with α particles accelerated to 29.0 MeV by AVF. The beam energy is controlled with an accuracy of ±1% using a time-of-flight (TOF) beam energy measuring device. The metallic ²⁰⁹Bi target in 20 mg/cm² thickness is prepared by a vacuum evaporation method on an Al plate. Since the melting point of the Bi metal is low (271.5 °C), the target placed at an angle of 15° with respect

to the beam axis is effectively cooled by water (1.5 L/min) and He (30 L/min). In addition, the beam axis is rotated at 120 rpm by an electromagnet (beam wobbler) to reduce heat load on the target. The current setup can accept a beam intensity up to 40 μ A to produce 2 GBq of ²¹¹At in 1 h. After irradiation, as shown in Figure 2 (c), the Bi target is placed on a Cu boat in a quartz tube (i.d. 30 mm × L180 mm), and O₂ is passed through the tube (20 mL/min). The quart tube is heated up to 850 °C with an electric furnace. ²¹¹At sublimated from the ²⁰⁹Bi target is transported to a PFA tube (i.d. 1 mm×L1000 mm) bound in a spiral and cooled to –100 °C with a chiller. After collecting ²¹¹At, the inside of the PFA tube is washed with a few hundred μ L of pure water, methanol, chloroform, etc. to recover ²¹¹At. The chemical yield is >80%. The purified ²¹¹At is shipped to universities and research institutes in Japan to develop novel nuclear medicines for cancer therapy [23–25].

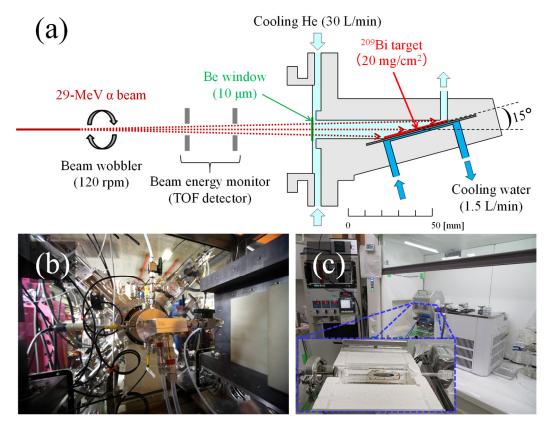


Figure 2. (a) Schematic of the target chamber for ²¹¹At production. (b) Photo of the target chamber. (c) Photo of a dry distillation apparatus for ²¹¹At separation.

²²⁵Ac is also one of the most promising α-particle-emitting RIs for TAT. However, a stable supply system of ²²⁵Ac has not yet been established in Japan even at the basic research scale (~100 MBq). Thus, we started to develop the production technologies of ²²⁵Ac in the ²³²Th(¹⁴N,xnyp)²²⁵Ac and ²²⁶Ra(p,2n)²²⁵Ac reactions using RRC and AVF, respectively.

4. Distributions of RIKEN RIs

Since 2007, the purified RIs of ⁶⁵Zn, ⁶⁷Cu, ⁸⁵Sr, ⁸⁸Y, and ¹⁰⁹Cd are delivered to Japan Radioisotope Association for fee-based distribution to more than 40 universities, research institutes, and companies in

Japan. More than 150 deliveries have been conducted until March, 2020. The RIKEN RIs such as ⁸⁸Zr, ⁹⁵Nb, ¹⁷⁵Hf, ¹⁷⁹Ta, and ²¹¹At are also available under the JSPS KAKENHI program "Supply Platform of Short-lived Radioisotopes for Fundamental Research" in collaboration with Research Center for Nuclear Physics, Osaka University, Cyclotron and Radioisotope Center and Research Center for Electron Photon Science, Tohoku University, National Institute of Radiological Sciences and Takasaki Advanced Radiation Research Institute, National Institutes for Quantum and Radiological Science and Technology [26]. Until March, 2020, RIBF accepted a total of 99 orders for 23 research projects.

5. Summary

Present status of the production and applications of RIs at RIBF is briefly reviewed. RIs for SHE chemistry and TAT are highlighted. Very recently, the RILAC facility was upgraded as SRILAC with a 28 GHz superconducting ECR ion source, a super-conducting quarter-wavelength resonator, and a new gas-filled recoil ion separator (GARIS III) being installed. The SRILAC facility is expected to open the next generation RI applications at RIBF with an order of magnitude larger production yields. Using Superconducting Ring Cyclotron and the fragment separator BigRIPS, RIBF can generate more than 3,000 RI beams with the world's highest intensity. In near future, the RI beams will be used for application studies by implanting them into various materials such as water and pharmaceuticals.

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著者名:羽場宏光