Forum for Nuclear Cooperation in Asia (FNCA)

Creation of Harmonious Diversity

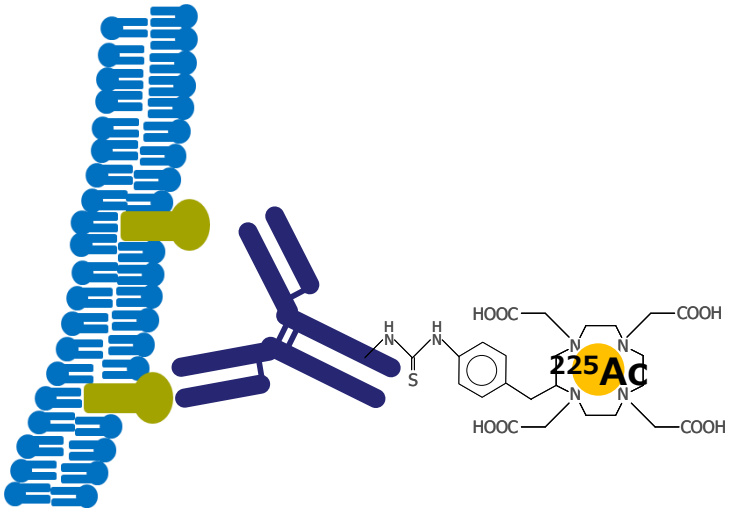
QST

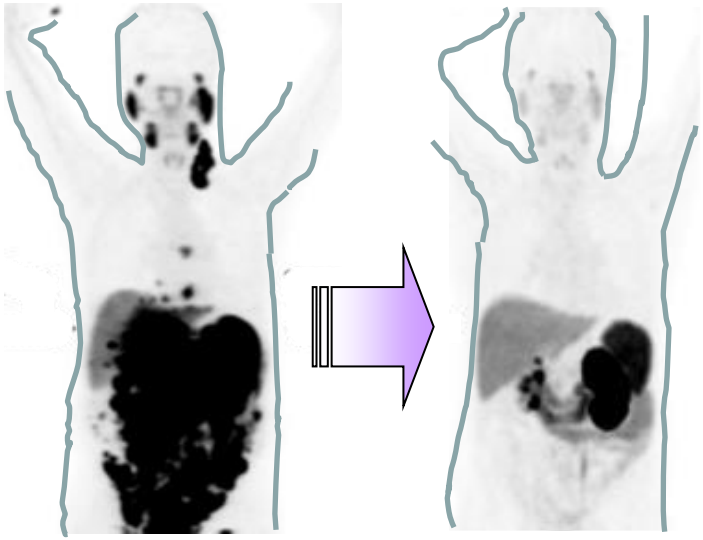
2024 Study Panel supported by Atomic Energy Commission of Japan

アジア原子力協力フォーラム

2024. 03. 11　三田共用会議所　大会議室

“Japan’s Action Plan for Production and Utilization of Medical Isotopes”





量子科学技術研究開発機構 QST

量子医科学研究所

分子イメージング診断治療研究部

東　達也

Tatsuya HIGASHI

Director

Dept. of Molecular Imaging and Theranostics

Institute for Quantum Medical Science (iQMS)

National Institutes for Quantum Science and Technology (QST), Chiba, Japan

Disclosure of Conflict of Interest
Tatsuya HIGASHI

Matters requiring disclosure of COI
with regard to our presentation are as follows;

Research funding : AMED JP17pc0101014

Nihon Medi-Physics Co.,Ltd.
(2018.04 ~ 2021.03)

Targeted Radiopharmaceuticals or
Targeted Radionuclide Therapy → **TRT**

Targeted Radionuclide Therapy（TRT）in Japan (2022~23)

Creation of Harmonious Diversity
QST

- **Health care insurance covered TRTs in Japan**

beta-emitters

- ① I-131 NaI: Graves disease
- ①’ I-131 NaI: Differentiated Thyroid Cancer (DTC)
- ~~② Sr-89 SrCl2: Metastatic Bone Tumors~~
- ~~③ Y-90 Zevalin: CD20+ low grade B-cell Lymphoma~~

Supply stopped

- ⑤ I-131 MIBG: pheochromocytoma & paraganglioma
  → Approved in 2021
- ⑥ Lu-177 DOTATATE: Neuroendocrine tumors
  → Approved in 2021
- ⑦ Lu-177 PSMA-617: Metastatic mCRPC : Under Clinical Trial
- ⑧~ Cu-64 ATSM and other beta emitters : Under Clinical Trial

alpha-emitter

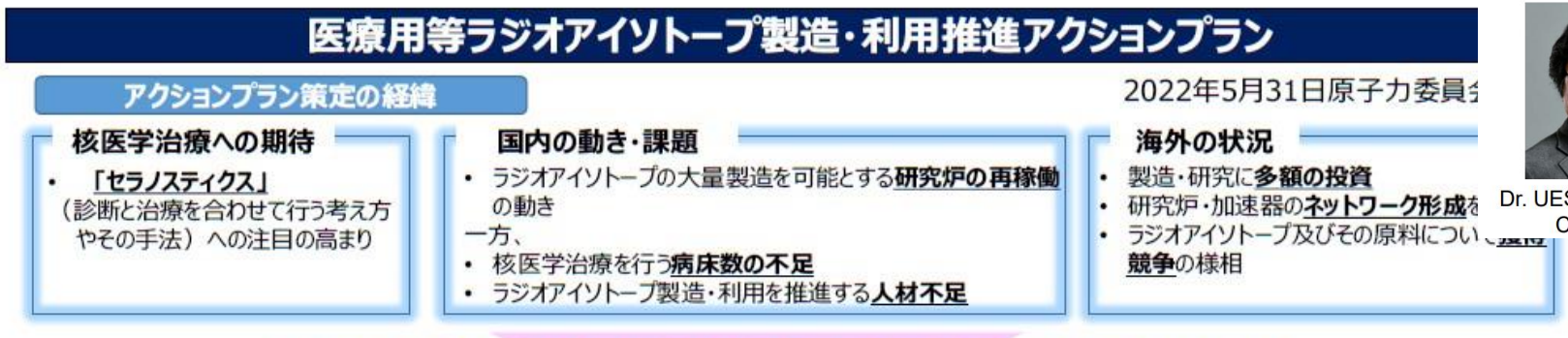
- ④ Ra-223 RaCl2: Metastatic Bone Tumors of mCRPC (from 2016)
- ⑧~ Several New Alpha Emitters: : Under Clinical Trial

Problems in Japan:
・Severe shortage of TRT inpatient room
・Most of Radionuclides & TRT agents imported ⇒Domestic Production needed

"Special Subcommittee for securing Medical Radioisotope Production and Utilization“ & Action Plan in 2022

Japan Atomic Energy Commission (JAEC)

Dr. UESAKA, Mitsuru
Chairman



National Action Plan in 2022 aiming to have successes within 10 years

- ① Promotion of initiatives for domestic production and stable supply of important isotopes
- ② Development of systems and structures for promoting the use of isotopes in medical settings
- ③ Promotion of research and development that contributes to domestic production of isotopes & radiopharmaceuticals
- ④ Strengthening research infrastructure, human resource development, and networks for isotope production and utilization

Ministries and agencies cooperation to promote TRT: A breakthrough in Japan

http://www.aec.go.jp/jicst/NC/senmon/radioisotope/index.htm

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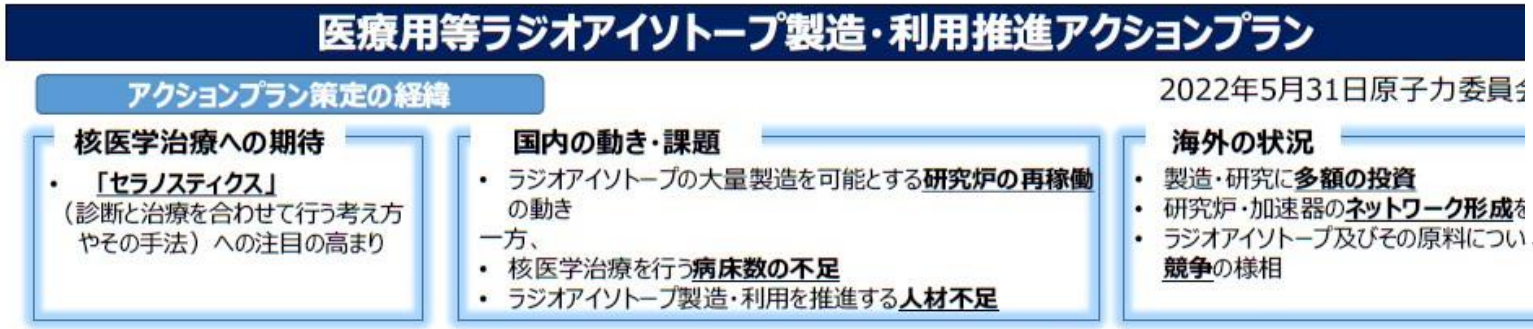


National Action Plan in 2022 aiming to have successes within 10 years

- ① **Promotion of initiatives for domestic production and stable supply of important isotopes: At-211 & Ac-225**
- ② Development of systems and structures for promoting the use of isotopes in medical settings
- ③ Promotion of research and development that contributes to domestic production of isotopes & radiopharmaceuticals
- ④ Strengthening research infrastructure, human resource development, and networks for isotope production and utilization

Ministries and agencies cooperation to promote TRT: A breakthrough in Japan

○ 科学技術・イノベーション政策、健康・医療政策、がん対策の観点からも重要であるため、関係する政府戦略の方向性とも軌を一にして取り組む

http://www.aec.go.jp/jicst/NC/senmon/radioisotope/index.htm

R&D achievement of QST in ^{211}At production method

Creation of Harmonious Diversity
QST

Vertical irradiation system

- **Bending Magnet : horizontal beam line → vertical beam**
- **Solution for low melting point's targets (Ga, Bi, etc)**
- **Solution for non-self-supported targets (powder, granule, shots and others)**

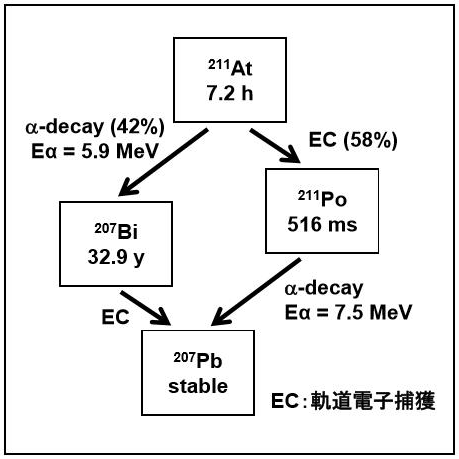
Glove box for safety At-211 handling

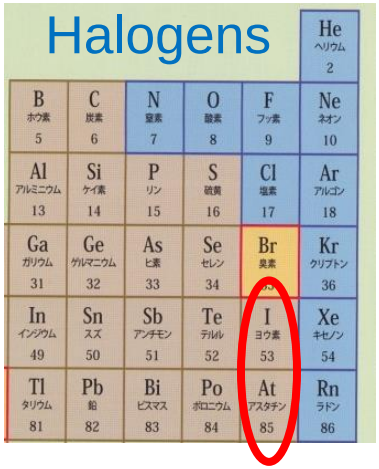
QST : Established stable manufacturing methods of ^{211}At) in 2014, suppling to other facilities nation-wide.
Technology Transfer to FMU in 2018.

Nagatsu K., Hasegawa S., et al. Appl. Radiat. Isot. (2014)

^{211}At astatine: Japan leading the way in manufacturing research

- 100% α-emitter without gamma ray: Half life : 7.2 hours
- Mean energy : 6.79 MeV
- Ray range : 55-70μm
- ^{211}Po X-ray: imaging is available
- For production: **middle > cyclotron**
- **Bi-209 (alpha,2n) At-211**





Problems:

- **At-211 can be produced only by middle or large sized cyclotron: QST, RIKEN, Osaka U., Fukushima MU in Japan.**
- **At-211 cannot be produced by reactors.**
- **The half-life of At-211 is only 7 hours: this is a big problem for supply network for clinical use of radiopharmaceuticals.**

For nation-wide supply of At-211 : An innovation is needed.

A new small sized cyclotron (can be installed in usual hospitals) is under R&D in Osaka U and others. Further R&D is needed.

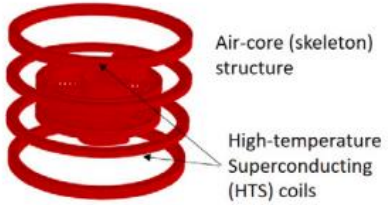
ELSEVIER

Results in Physics
Volume 33, February 2022, 105090

Beam dynamics and characterization of a new high-intensity compact air-core high temperature superconducting skeleton cyclotron (HTS-SC)

H.W. Koay, M. Fukuda, H. Kanda, T. Yorita

HTS-SC



Field shaping	Linear (Easy-operation)
Saturation	No
Weight	< 5 ton (light)
Magnet size	Compact (R < 60 cm)
Rooms for Subcomponents	Spacious and flexible
Power consumption	Lower (cheaper)
Stability and reproducibility	High

QiSS (Quantum Innovation for Safe and Smart Society) Research Project / Osaka U.

Creation of Harmonious Diversity QST

AIM: to realize nationwide clinical supply of At-211(T1/2=7.2hr)

QiSS consortium

QiSS adopted in 2017.9.20 with
Total Research Expenditure: 6 million dollars

Leading Secretariat: Osaka University

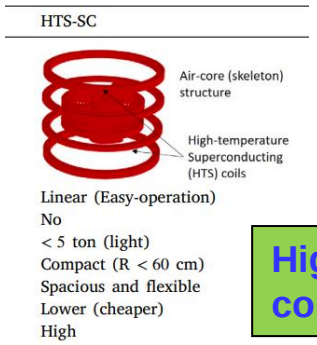
Participating institutions:
RIKEN
Nagoya University
Kyushu University
Tohoku University
Tohoku University
Kyoto Institute of Technology
QST
JAEA
J-PARC
Nagoya University
Nagoya University
Institute of Physical Structural Science

Participating Companies:
TOYOTA
Nihon Medi Physics
Telix Pharm Japan
Fuji RI Pharma
Sumitomo Heavy Industries
Atox
Metal Engineering
Chubu Electronic Power
Fuji Electronics
Socio Next
Kyoto Medical Technology
Shimafuji Electronics
Nihon Systemware, etc

In addition, QiSS Supporting Two nation-wide At-211 supply system:

① **Short-life Radionuclide Supply Platform** : for basic research (2016~)

② **RI Collaborative Academic Inter-Disciplinary Platform** : for clinical research & trial (2023~)



High-intensity compact accelerator

Research Plan Chronology (planned in 2018)

年度	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
	第3期中長期目標期間					第4期中長期目標期間					
At-211 radiopharmaceuticals	Non-clinical POC				First in Human		Corporate III clinical trial		PMDA approval		
High-intensity compact accelerator			Design development		Creation of actual machine		Full-scale supply of At-211				

Ac-225 : Useful but having big problems in production and supply

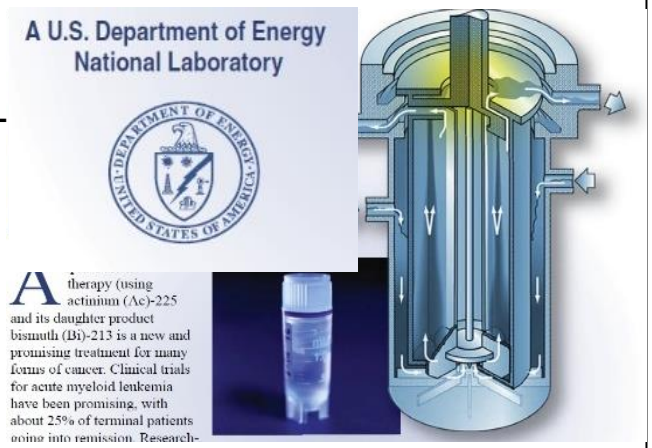
^{225}Ac is produced by ^{229}Th generator at present

- ^{229}Th comes from atomic fuels (available only in USA, Russis, and EU, the export / import strictly limited)

- ^{229}Th generator can produce very small amount of Ac-225

(^{229}Th comes from nuclear fuel: ^{233}U)

Th-229 generator
- 225Ra Yield = >99%
- 225Ac Yield = 99.2 + 0.5%
- 229Th Recovery = >99%
- 225Ac purity
  < 0.0001% 229Th
  < 0.0001% 225Ra



- At present :

Total production : 50,000MBq/ year →

225Ac-PSMA-617: 10,000/year・only 2,500 patients can be treated

Every year, 140,000 patients die from prostate cancer in the World

- US: Oak Ridge NL → US 16 > mCi/week
- Russia: Joint Stock Company, Obninsk → EU and US 50mCi/m

Ac-225
Short supply

Total production in the World : about 50,000MBq/y

Feasible Candidates for Ac-225 synthesis Methods

	Th-229/Ac-225 generator **At present**	Th-232 Nuclear Spallation	Ra-226 Neutron Capture	Ra-226 Photo Nuclear Reaction	Ra-226 Nuclear Transmutation
	^{233}U $_{(160k\ a)}$ → ^{229}Th $_{(7.3k\ a)}$ → ^{225}Ra $_{(15\ d)}$ → ^{225}Ac	$^{232}Th(p,x)^{225}Ra$ → ^{225}Ac **cyclotron**	$^{226}Ra(3n,2\beta)^{229}Th$ → ^{225}Ra → ^{225}Ac $^{228}Ra(n,\gamma)^{229}Ra$ → ^{229}Th* **reactor**	$^{226}Ra(\gamma,n)^{225}Ra$ → ^{225}Ac **Linear accelerator**	$^{226}Ra(p,2n)^{225}Ac$ **cyclotron**
Machine	Th-229 Solution Natural Process	Large Scale Accelerator (100 MeV+)	Nuclear Reactor	Linear Accelerator, etc	**Small Scale Accelerator (<25 MeV)**
Institution	ORNL JRC IPPE	Tri-Lab, NorthStar **TRIUMF** INR	ORNL OBRINSK* CNL	ANL, NIOWAVE TRIUMF	JRC, ZAG, DKFZ SCK-CEN CNEA$_{/IAEA}$ NPI KIRAMS **QST** **Hitachi,Tohoku U., Tokyo U.**
Pros	**Only One Current Method**	Easy in Handling of Th-232, 110 nCi/g-Th			**Convenient with small scale, relative high yield**
Cons	**Short Supply**	Ac-227 Impurities: may be problematic in GMP as Medical Use	Challenging production path： **Short Supply**	**Very Low Yield** 10g of Ra-226 is necessary： **Short Supply**	50mg of Ra-226 is necessary： **Short Supply**
Reactor Regulation Law	**Problematic in the presence of Th Impurities**	**Problematic in the presence of Th Impurities**	**Problematic in the presence of Th Impurities**	**No Problem**	**No Problem**

TAT Project at QST : ^{225}Ac Production

Creation of Harmonious Diversity QST

Ra-226: $T_{1/2}$ = 1600 years
Ac-225: $T_{1/2}$ = 10 days

・Ac-225: high yield production in one batch has not established worldwide

・**QST focused on the use of ^{226}Ra needles for brachytherapy stored as medical waste**

AMED: government funding study project "**CiCLE**" started in 2018, by **Nihon Medi-Physics (NMP)**

CiCLE
Cyclic Innovation for Clinical Empowerment

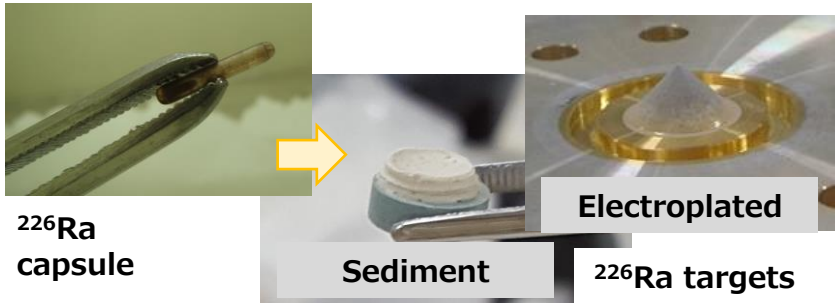
Transmutation path

^{226}Ra(p, 2n)^{225}Ac

+ chemical separation + cooling

"CRADLE Building" in Chiba
Est'd in Sep. 2019
Investment: 3.3Bi JPY
= about 30M USD

・QST: A trial of Ac-225 cyclotron production succeeded in 2017



^{226}Ra capsule

^{226}Ra targets

European Journal of Nuclear Medicine and Molecular Imaging (2021) 49:279–289
https://doi.org/10.1007/s00259-021-05460-7

ORIGINAL ARTICLE

Nagatsu, Suzuki, et al. Eur J Nucl Med Mol Imaging 2021

Cyclotron production of ^{225}Ac from an electroplated ^{226}Ra target

Kotaro Nagatsu[1] · Hisashi Suzuki[1] · Masami Fukada[1] · Taku Ito[1,2] · Jun Ichinose[1,2] · Yoshio Honda[1,2] · Katsuyuki Minegishi[1] · Tatsuya Higashi[3] · Ming-Rong Zhang[1]

NMP succeeded in cyclotron production of the world's first GBq amount of ^{225}Ac by the transmutation in April 2022

^{225}Ac Production R&D/ Import/ Distribution status in Japan

Higashi, Nagatsu, et al. Processes 2022

The situation of Ac-225 production is always in flux

Supplier

NIDC

NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

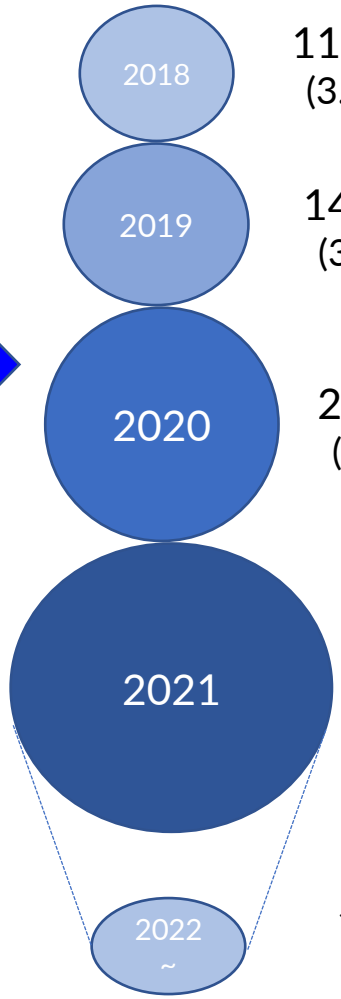
GMP

GLOBAL MORPHO PHARMA
GMP FOR LIFE

IPPE

Kitaoka A. Supply and demand status of medical isotopes (2021) in Japanese (modified). Available at http://www.aec.go.jp/jicst/NC/iinkai/teirei/siryo2021/siryo18/index.htm

Import trend



Research Institutes

Supplier

TRIUMF

TRIUMF

Cross appointment

Import/Distribute

RCNP

pqba
Multidisciplinary PhD Program for Pioneering Quantum Beam Application
先導的量子ビーム応用卓越大学院プログラム

JRIA

QASS
Quantum beam Applications for Safe and Smart society

Osaka Univ.
Japan Radioisotope Association

Production R&D・sell (plan)

TOHOKU UNIVERSITY

Charged particles

Electrons

Electrons

Reactor

NMP・QST／Univ Tokyo・QST・ELPH-Tohoku Univ／
HITACHI・KURNS-Kyoto Univ・ELPH-Tohoku Univ／Tokyo City Univ

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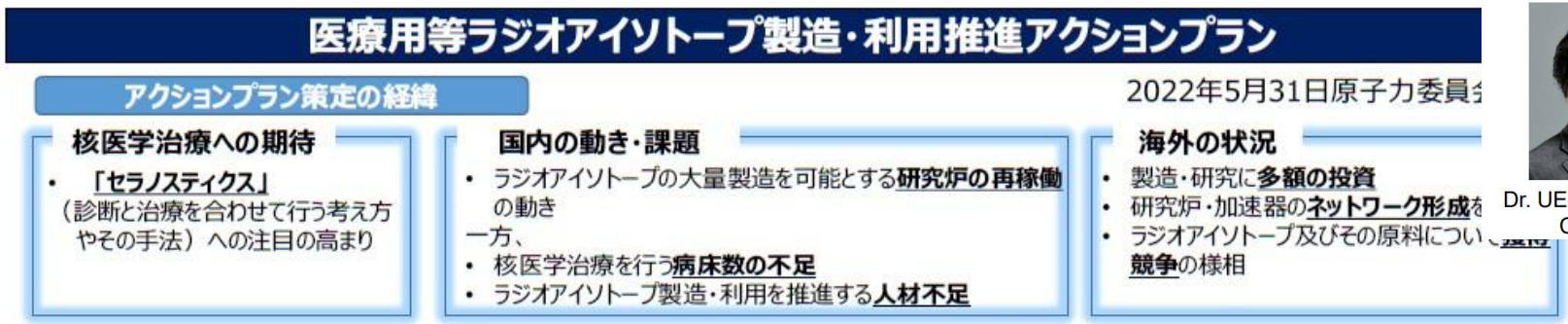

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http://www.aec.go.jp/jicst/NC/senmon/radioisotope/index.htm

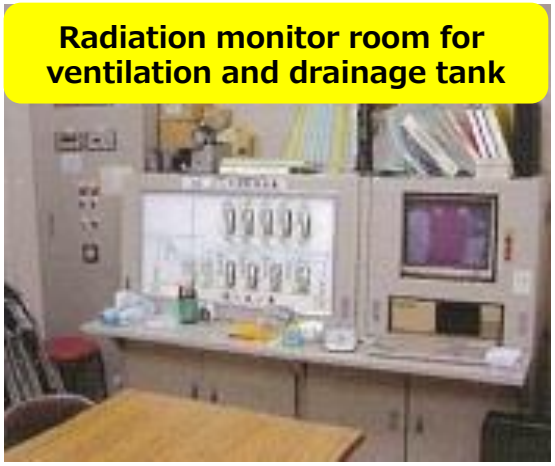
Great concern in Japan: Regulation of radionuclides

Creation of Harmonious Diversity QST

- The use of radionuclides is regulated by Radionuclide Control Act. Clinical use of radiolabeled pharmaceuticals is regulated by Medical Care Act.
- (1) **Administration** of radiolabeled pharmaceuticals is permitted only in designated-controlled-areas (with special radiation protection system) by these laws.
- (2) **Administration** of radiolabeled pharmaceuticals **with higher amount** requires an **inpatient room in designated –controlled-areas** (with special radiation protection system)
- (3) **The total amounts** of radionuclides and radiolabeled pharmaceuticals available in a designated-controlled-area per day, year, etc, are strictly regulated by these laws.

Designated TRT inpatient room in controlled area

Radiation monitor room for ventilation and drainage tank

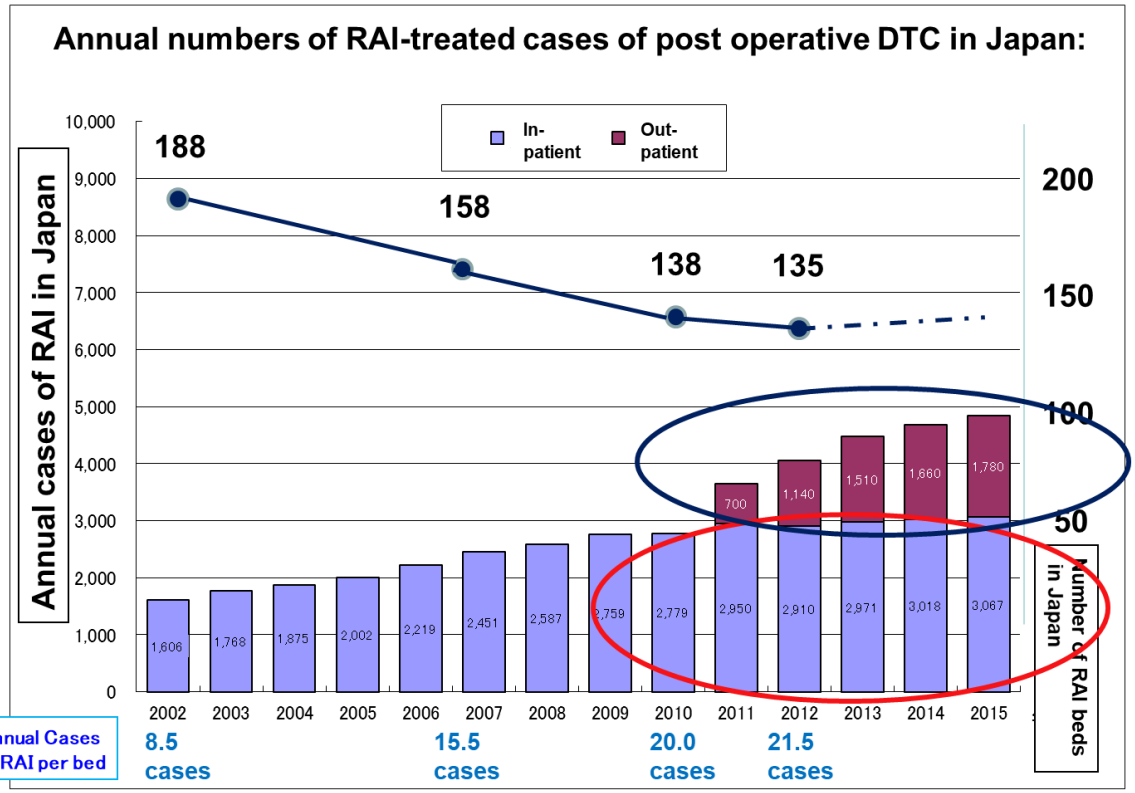


Strict regulation results in severe shortage of

①TRT inpatient rooms & ②designated-controlled -areas in Japan.

TRT: I-131 RAI Therapy for DTC in Japan

Creation of Harmonious Diversity
QST



Higashi T. Kaku Igaku 53:27-43, 2016

I-131 RAI therapy has been struggling against the shortage of radionuclide inpatient room

Out-patient "ablation" using 1.1GBq is increasing steadily from 2010

RAI inpatient rooms in Japan: in full blast for RAI therapy using more than 3.7GBq for more than 20 years

表24. 放射性ヨウ素内用療法の分類

呼称	アブレーション Remnant ablation	補助療法 Adjuvant therapy	治療 Cancer treatment
対象と意図	残存腫瘍がないと考えられる患者における正常濾胞細胞除去	画像診断で確認できないが，顕微鏡的な残存腫瘍が存在すると考えられる患者における癌細胞の破壊	肉眼的残存腫瘍や遠隔転移が存在する患者における癌細胞の破壊
目的	経過観察の単純化	再発予防，遅延	顕在する癌の治療
投与量	1.1 GBq (30 mCi)	3.7–5.6 GBq (100–150 mCi)	3.7–7.4 GBq (100–200 mCi)

Need to increase the dose

Conventionally performed "Ablation" was actually Adjuvant therapy

Japanese Clinical Guideline for Thyroid Cancers 2018 (←2010 First Edition) :

Concept change of I-131 RAI therapy results in severe shortage of radionuclide inpatient room

New Regulation of radionuclides in 2022:
"Hospital rooms with special measures (HSM)"

Creation of Harmonious Diversity
QST

- **Administration** and clinical use of some radiolabeled pharmaceuticals **with higher amount** is strictly regulated and **only permitted in an inpatient room in a designated controlled area** by **Medical Care Act**.
  → Strict regulation results in severe shortage of TRT inpatient rooms in Japan.
- From 2022, due to a revision of Medical Care Act, only in case of Lu-177, which does not evaporate and does not need special ventilation system and drainage tank for radionuclides, **TRT using Lu-177 radiopharmaceuticals** is allowed to be performed in a simplified TRT inpatient room, **"Hospital rooms with special measures (HSP)"**.

病室内（全景）

Only minimum radiation protection procedure is required

Radiation monitor room for ventilation and drainage tank

No need to have special ventilation system, drainage tank & monitoring system

A solution of
①TRT inpatient rooms in Japan!

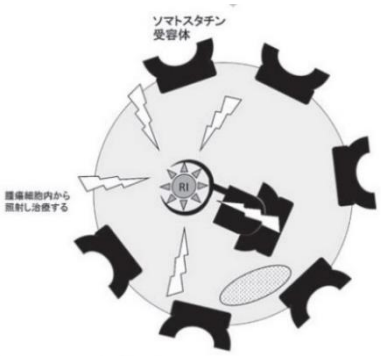
This simplified TRT room: **HSP** is
- **much cheaper in maintenance and**
- **easier to construct or prepare**

as compared to a traditional TRT inpatient room.

The impact of "Hospital rooms with special measures (HSM)"

Creation of Harmonious Diversity
QST

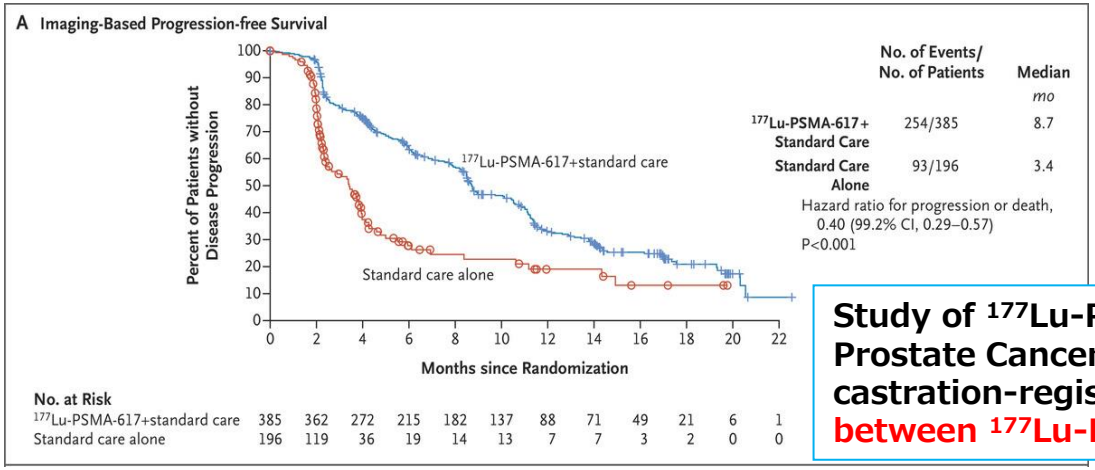
In 2021, Japanese PMDA approved PRRT by ^{177}Lu-DOTATATE "Lutathera ®"

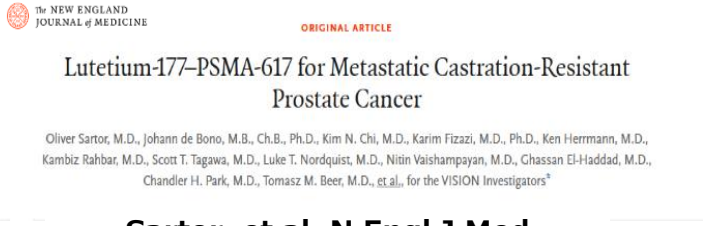


① National Insurance fee of HSM: set high
② HSM: already installed in > 70 hospitals
③ Hospitalized care of Neuro Endocrine Tumor (NET) patients is only **needed for 1~2 days** in an inpatient TRT room

Big solution to the problem of ①TRT inpatient rooms in Japan.

In 2022, FDA approved mCRPC-PSMA therapy by ^{177}Lu-PSMA-617 "Pluvicto ®"




The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer
Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*

Sartor, et al. N Engl J Med 2021;385(12):1091-1103.

Study of ^{177}Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (VISION) Phase III finished. Metastatic castration-registant prostate cancer 831 cases. Comparison between ^{177}Lu-PSMA-617+SC v.s. Standard Care

Not approved in Japan, but a clinical trial has already started in Japan

At present, it is concerned that hospitalized care of patients will be **needed for 2~5 days** in an inpatient TRT room because of strict regulation in Japan.

→ **Various deregulation efforts are still underway to resolve issues.**

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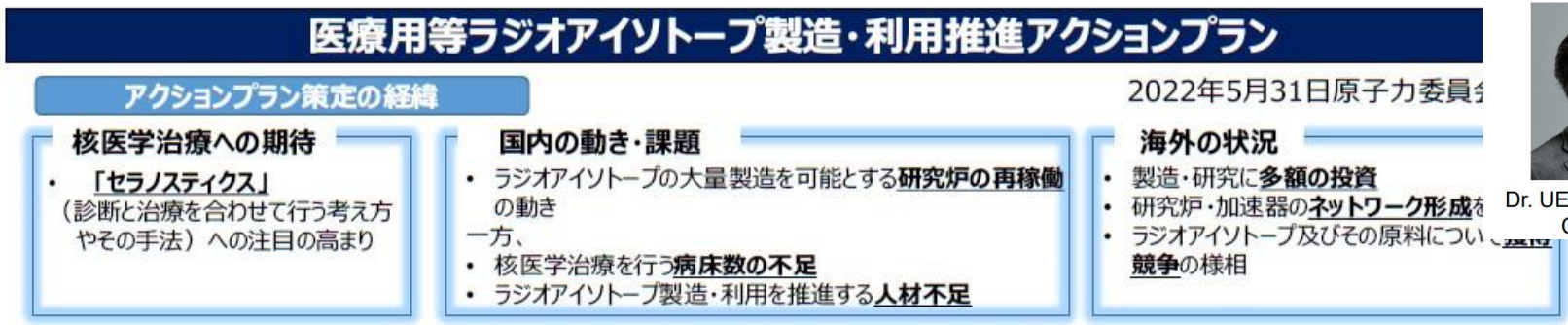

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- ④ Strengthening research infrastructure, human resource development, and networks for isotope production and utilization

Ministries and agencies cooperation to promote TRT: A breakthrough in Japan

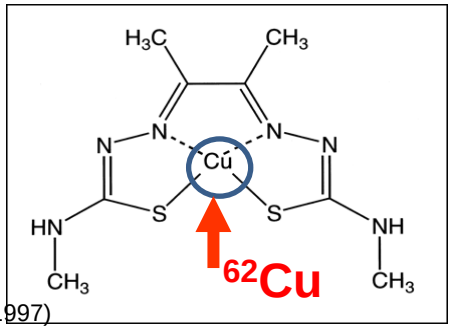
○ 科学技術・イノベーション政策、健康・医療政策、がん対策の観点からも重要であるため、関係する政府戦略の方向性とも軌を一にして取り組む

http://www.aec.go.jp/jicst/NC/senmon/radioisotope/index.htm

^{64}Cu-ATSM:
A very-first Japan-made TRT radiopharmaceutical

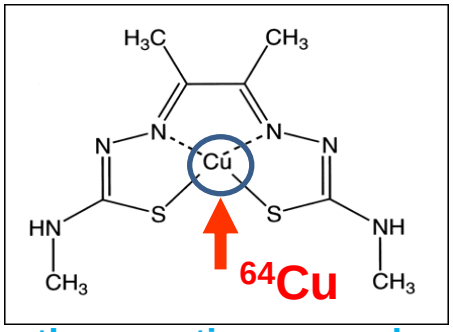
Cu-ATSM was at first developed as a cancer-imaging agent as ^{62}Cu-ATSM

Cancer Imaging with ^{62}Cu-ATSM



(Fujibayashi Y et al. J Nucl Med. 1997)

Cancer Treatment with ^{64}Cu-ATSM



^{64}Cu-ATSM was developed in a **theranostic approach**

^{64}Cu
STAR-64

Phase I Clinical Study of TRT agent

→ **A First Time in Japan to have a Clinical Study of Japan-made TRT agent**

QST Press Release 2018/7/17

^{64}Cu-ATSM

^{64}Cu β$^+$ (0.66 MeV, 19 %), β$^-$ (0.58 MeV, 40 %), EC (44 %).
$T_{1/2}$ = 12.7 hr

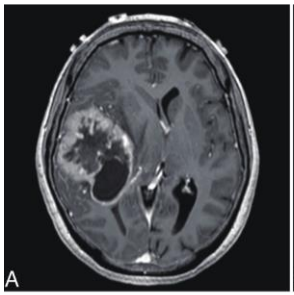
TRT and PET imaging for Hypoxic Cancer;

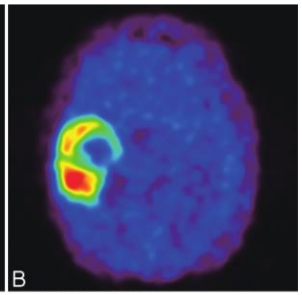
QST Chiba: GMP manufacturing

Collaboration

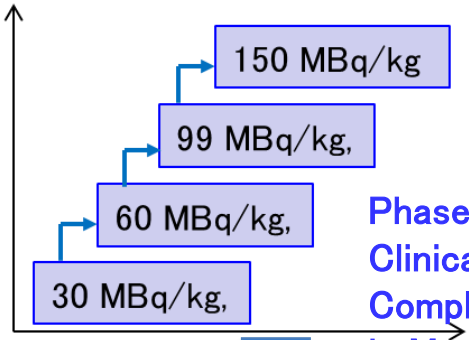
Supply

National Cancer Center & Kanagawa Cancer Center : Clinical Study





Target: GBM and other brain tumors



Phase I Clinical Study Completed in March, 2023

Phase II Clinical Study

A start-up company "LinkMed"

^{211}At-NaAt: [^{211}At] sodium astatine ^{211}At-MABG: Meta-[^{211}At]astatobenzylguanidine

Creation of Harmonious Diversity
QST

^{211}At-NaAt:
D. Thyroid Cancer

Osaka Univ. substituted Iodine to At , and produced ^{211}At NaAt for the treatment of refractory DTC

大阪大学 OSAKA UNIVERSITY

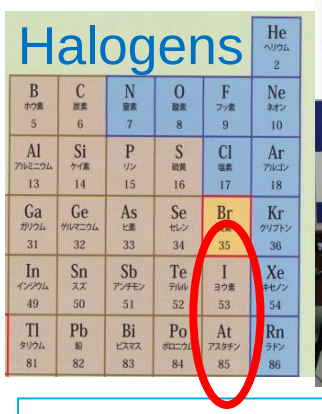
QiSS 安心・安全・スマートな長寿社会実現のための高度な量子アプリケーション技術の創出 Quantum Innovation for Safe and Smart Society

OPERA

Nation-wide At-211 network

In 2021, **Osaka U. Drug discovery venture "Alpha Fusion Inc."** was settled.

Alpha Fusion Inc.



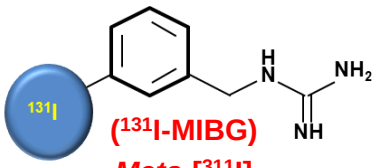
Clinical study of ^{211}At-NaAt has started from 2021 at Osaka Univ. for the first time in the world

^{211}At-MABG:
Pheochromocytoma

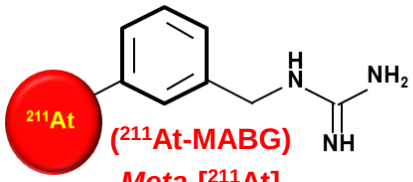
福島県立医科大学 FUKUSHIMA MEDICAL UNIVERSITY
ふくしま国際医療科学センター 先端臨床研究センター

QST substituted Iodine to At , and produced ^{211}At, an alpha emitter, and finally synthesized MABG which has a similar structure to MIBG

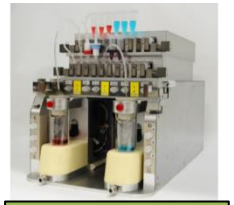
Zalutsky 1996
Ishioka 2016



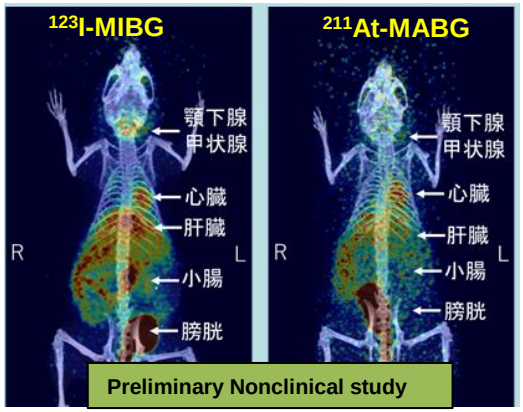
(^{131}I-MIBG)
Meta-[^{311}I]
iodobenzylguanidine



(^{211}At-MABG)
Meta-[^{211}At]
astatobenzylguanidine



Synthesizer Unit



Preliminary Nonclinical study

Clinical study of MABG has started from 2022 at FMU for the first time in the world

QST Press Release *2016/6/06*

TAT Project at QST : Anti-PDPN antibody

Anti-podoplanin (NZ-16) antibody for malignant mesothelioma

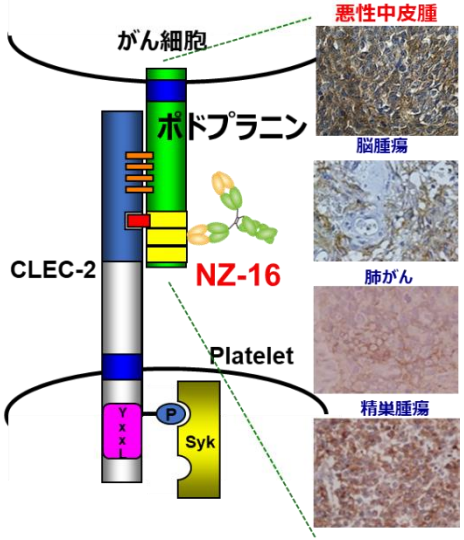
Mesothelioma: Refractory malignant tumor in pleura. Main cause of the diseases is **asbestos exposure.**
Morbidity more than 10,000 person/year (900 in Japan)
Increase in patients is expected world wide

Developed by Prof. Yukinari KATO

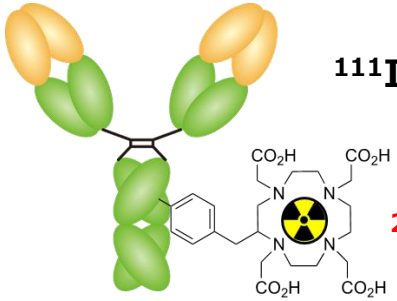
TOHOKU UNIVERSITY

AMED preB 2021. Adopted

AMED Advanced Anti-cancer Research 2022. Adopted



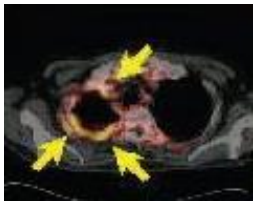
NZ-16 with DOTA : 3 types of RI



^{111}In (imaging)

^{90}Y (β-TRT)

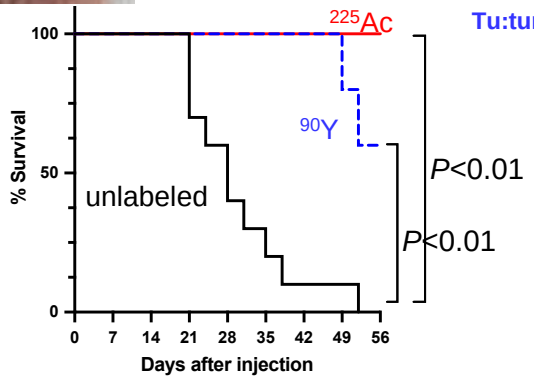
^{225}Ac (α-TRT)



https://www.qst.go.jp/site/press/20210923.html

Unlabeled (0MBq)	^{90}Y-labeled (3.7MBq)	^{225}Ac-labeled (18.5kBq)

Tu:tumor



Non-clinical safety and toxicological studies are going on.
Clinical trials in Chiba Rosai Hospital, etc. (expected to start from2025)

→ ***To obtain approval and commercialization for the first Japan-made ^{225}Ac-agent***

TAT Project at NMP : Achievement of CiCLE project

Creation of Harmonious Diversity

Anti-MUC5AC antibody (NMK89) for pancreatic cancer: Theranostics Approach

QST: Transmutation path

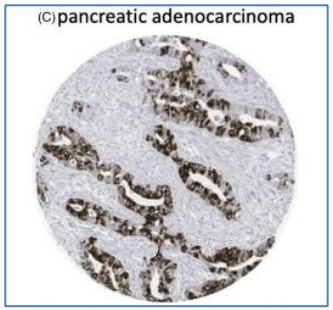
$^{226}Ra(p, 2n)^{225}Ac$

+ chemical separation + cooling

AMED: government funding study project "Medical Research and Development Innovation Infrastructure Creation Project (**CiCLE**)" started in 2018, by **Nihon Medi-Physics (NMP)**

CiCLE
Cyclic Innovation for Clinical Empowerment

Pancreatic Cancer:
One of the most refractory ca. in the world.
Morbidity about 40,000 person/year in Japan with 5YS rate of 8.5%.
Increase in patients is expected world wide



MUC5AC expression

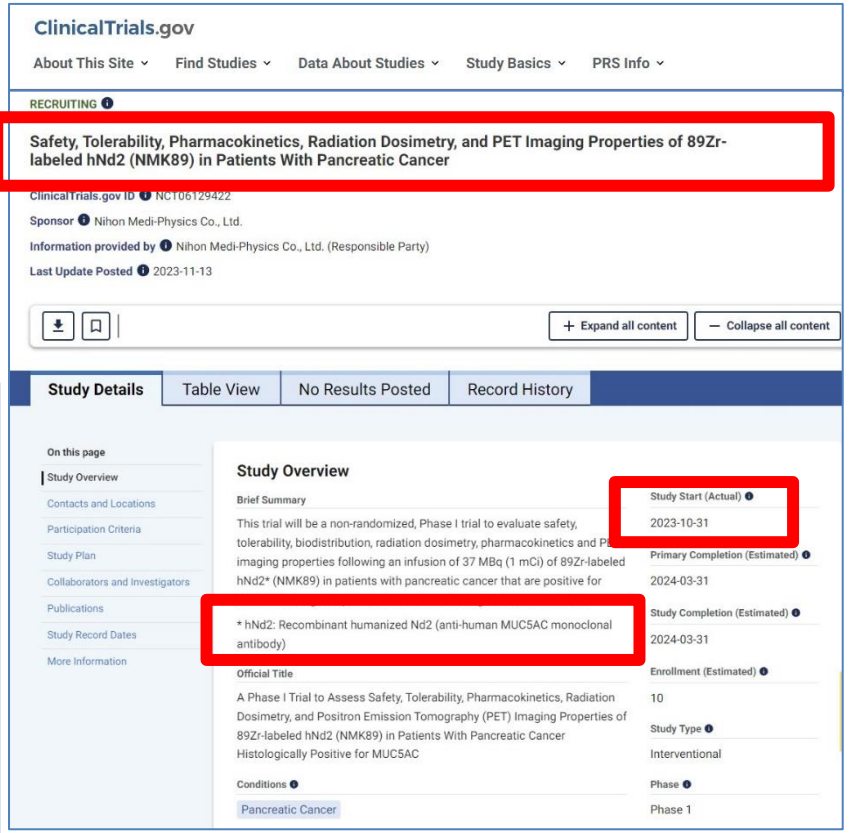


Table 1. (continued)

	Tumor entity	*n* on TMA	MUC5AC immunostaining: *n* analyzable	Negative (%)	Weak (%)	Moderate (%)	Strong (%)	Positive (%)
Tumors of the digestive system	Adenomatous polyp, low-grade dysplasia	50	22	36.4	18.2	13.6	31.8	63.6
	Adenomatous polyp, high-grade dysplasia	50	30	40.0	16.7	10.0	33.3	60.0
	Adenocarcinoma of the colon	50	36	83.3	0.0	8.3	8.3	16.7
	Adenocarcinoma of the small intestine	10	6	66.7	0.0	0.0	33.3	33.3
	Gastric adenocarcinoma, diffuse type	146	113	55.8	8.0	8.8	27.4	44.2
	Gastric adenocarcinoma, intestinal type	144	115	60.9	16.5	5.2	17.4	39.1
	Gastric adenocarcinoma, mixed type	62	54	64.8	9.3	5.6	20.4	35.2
	Adenocarcinoma of the esophagus	50	39	28.2	23.1	17.9	30.8	71.8
	Squamous cell carcinoma of the esophagus	49	31	96.8	0.0	0.0	3.2	3.2
	Squamous cell carcinoma of the anal canal	50	26	92.3	0.0	0.0	7.7	7.7
	Cholangiocarcinoma	120	100	79.0	1.0	7.0	13.0	21.0
	Hepatocellular carcinoma	50	48	100.0	0.0	0.0	0.0	0.0
	Ductal adenocarcinoma of the	50	33	36.4	24.2	6.1	33.3	63.6
	Pancreatic/Ampullary adenocarcinoma	30	17	58.8	11.8	5.9	23.5	41.2
	GIST	50	34	100.0	0.0	0.0	0.0	0.0

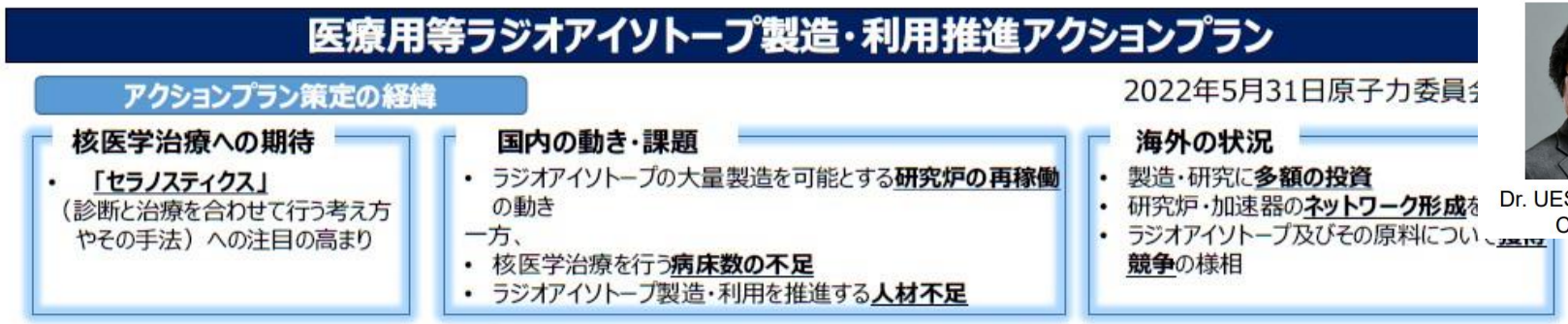
Rico, et al. Technol Cancer Res Treatment 2021

NMP succeeded in starting their CiCLE-related First-in-Human trial in Oct. 2023 using Zr-89 MUC5AC antibody. 22

"Special Subcommittee for securing Medical Radioisotope Production and Utilization“ & Action Plan in 2022

Japan Atomic Energy Commission (JAEC)

Dr. UESAKA, Mitsuru
Chairman



National Action Plan in 2022 aiming to have successes within 10 years

- ① Promotion of initiatives for domestic production and stable supply of important isotopes
- ② Development of systems and structures for promoting the use of isotopes in medical settings
- ③ Promotion of research and development that contributes to domestic production of isotopes & radiopharmaceuticals
- **④ Strengthening research infrastructure, human resource development, and networks for isotope production and utilization**

Ministries and agencies cooperation to promote TRT: A breakthrough in Japan

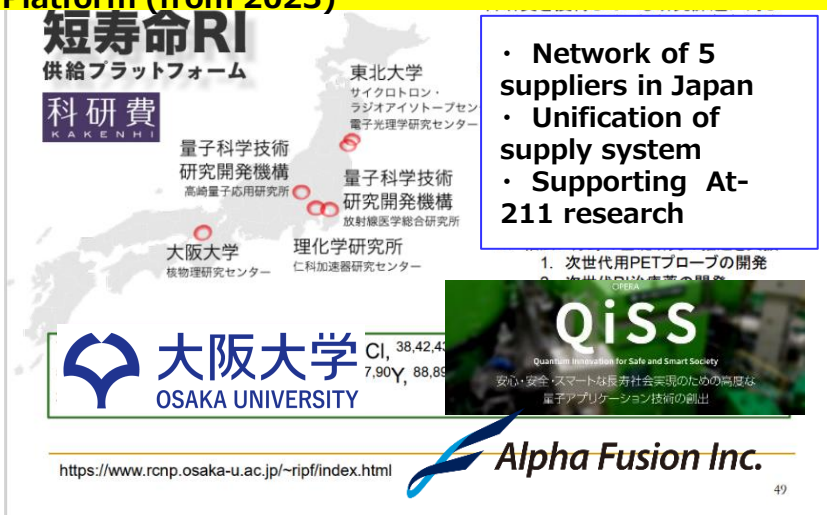
http://www.aec.go.jp/jicst/NC/senmon/radioisotope/index.htm

211At & 225Ac Production R&D/ Import/ Distribution status in Japan

Creation of Harmonious Diversity
QST

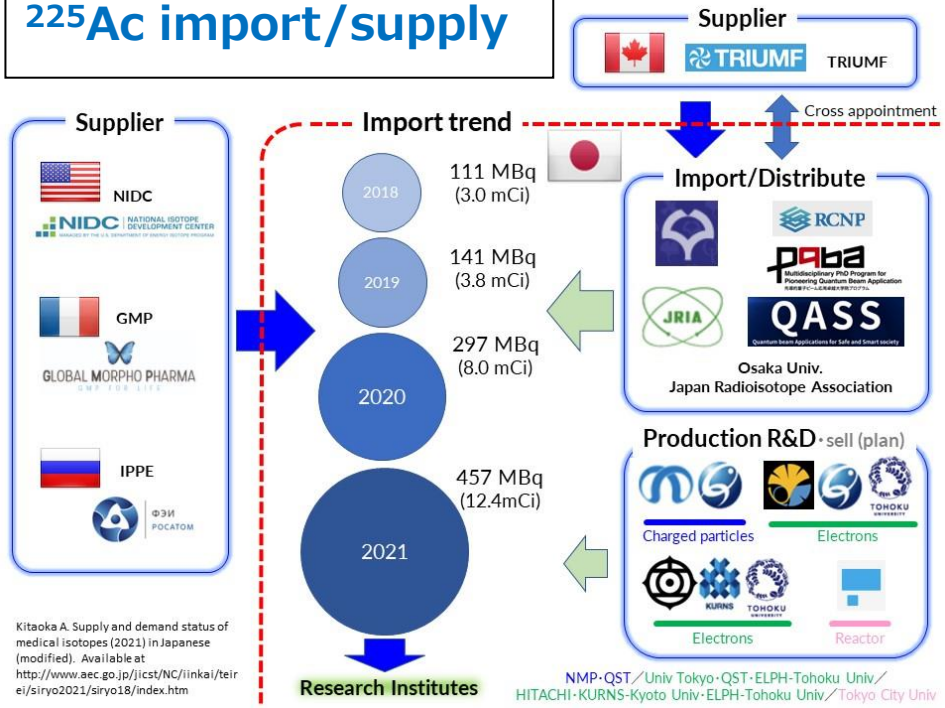
^{211}At supply

① Short-life Radionuclide Supply Platform (from 2016) & ② RI Collaborative Academic Inter-Disciplinary Platform (from 2023)



- Network of 5 suppliers in Japan
- Unification of supply system
- Supporting At-211 research

^{225}Ac import/supply



Kitaoka A. Supply and demand status of medical isotopes (2021) in Japanese (modified). Available at http://www.aec.go.jp/jicst/NC/iinkai/teirei/siryo2021/siryo18/index.htm

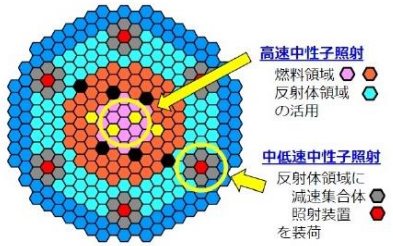
FMU own supply system

Fukushima MU

FUKUSHIMA MEDICAL UNIVERSITY 公立大学法人 福島県立医科大学

ふくしま国際医療科学センター
先端臨床研究センター

CiCLE
Cyclic Innovation for Clinical Empowerment



多様な中性子照射場

TRT in Japan: Potential use of reactors

FY2020 Research Fund: "Research and development towards establishing self-sufficient technology for medical RI using domestic nuclear infrastructure" Naoyuki Takagi
Japan Medical Isotope Co., Ltd., Kanazawa University, Mitsubishi Heavy Industries, Ltd., Japan Atomic Energy Agency

- ^{225}Ac production: R&D accelerated world-wide
- Production by reactor is being focused

JAEA: Fast breeder reactor·Joyo（Higher fast neutron flux, higher heat removal amount than light-water reactor）

Fast Breeder Reactor "Joyo"

^{225}Ac production method ①

^{226}Ra(n, 2n)^{225}Ac

^{226}Ra →中性子照射(n, 2n) → ^{225}Ac

^{225}Ac production method ②

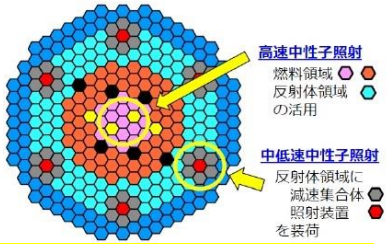
^{230}Th(n, 2n)^{229}Th → ^{225}Ra → ^{223}Ac → ^{229}Thを製造

→ ^{229}Thジェネレーター製造

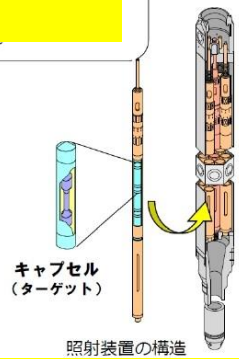
Characteristics of nuclide production at Joyo

Neutron irradiation over a wide range of energies

High neutron flux and large capacity neutron irradiation



Simulation of neutron irradiation



Capsule for irradiation

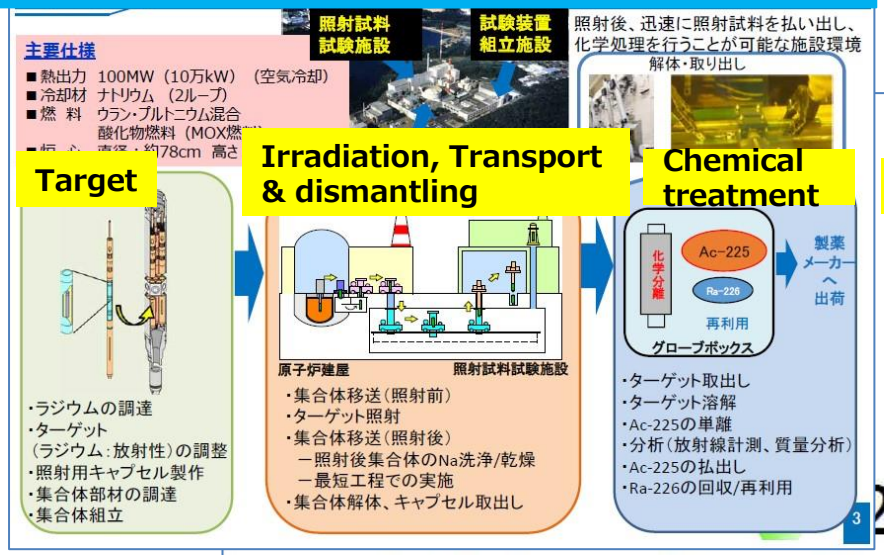
Problem :

- **how to obtain Ra-226, Th-230**
- **Production system with GMP level**

https://www.tcu.ac.jp/news/all/20201126-33360/

National Action Plan: Follow-up in 2023 : JAEA

Production Flow of ^{225}Ac at Joyo

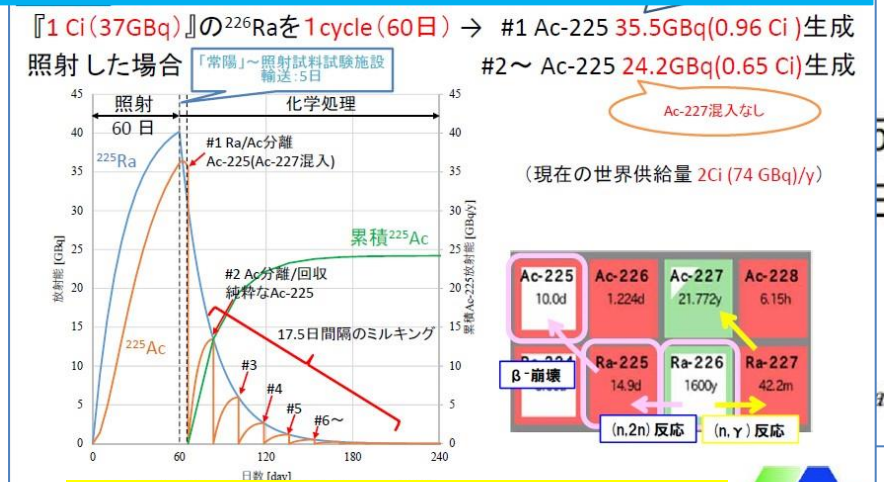


How to secure ^{226}Ra

調達先			実施状況	保有量
Domestic	機構内	大洗研	・機構内線源の把握 ・使用可否を確認中	30 mCi (1.11 GBq)
		その他		220 mCi (8.14 GBq)
	機構外		・外部機関の調査による国内線源の把握 ・譲り受け候補の絞り込み	177 mCi (6.55 GBq) 候補：57 mCi (2.11 GBq)
Global	海外	IAEA Global Radium-226 Management Initiative	・参加登録済 ・電子メールで確認済み ・2023/6/5～9 Technical Meeting(web)	全加入国：77 Ci（2.85 TBq） 返答あり：22 Ci（0.81TBq） 最大保有機関：6 Ci（0.22TBq）

Sector of Fast Reactor and Advanced Reactor Research and Development SeFARD 5

Predicted Production of ^{225}Ac at Joyo



Ra-226 : 37GBq → Ac-225 : 35.5GBq
At 60 days

SeFARD 12

R&D plan for ^{225}Ac production at Joyo

SeFARD 15

Implementation of test irradiation in 2025

Where to have TRT :Mobile Controlled Area for TRT (MCAT™)

Creation of Harmonious Diversity
QST

A solution of
①TRT inpatient rooms &
②designated-controlled-areas in Japan!

- **Expensive** budget is needed for initial construction & renewal of each **traditional TRT inpatient room (about 5million dollors. 5億円)**

- Alpha emitters do not need thick wall for radiation protection
- Trailer house type TRT room would be OK for Alpha emitter TRT

Mobile Controlled Area for TRT (MCAT™)

◆Patent pending : 2020-025584

MOBILITY
- ◆ Easiest installation and decommission
- ◆ Anytime, anywhere, as well as in emergency

COMPACT
- ◆ Only 3-cars parking space (footprint)
- ◆ Minimum, but full-satisfactory equipment/utilities

ACCESS-FRIENDLY
- ◆ Best way to perform emerging ^{225}Ac treatments
- ◆ Solution for shortage and disparities in cancer-care

TRAILER
- ◆ Approx. 10% installation cost than building
- ◆ Quiet and comfortable inside than imagine.

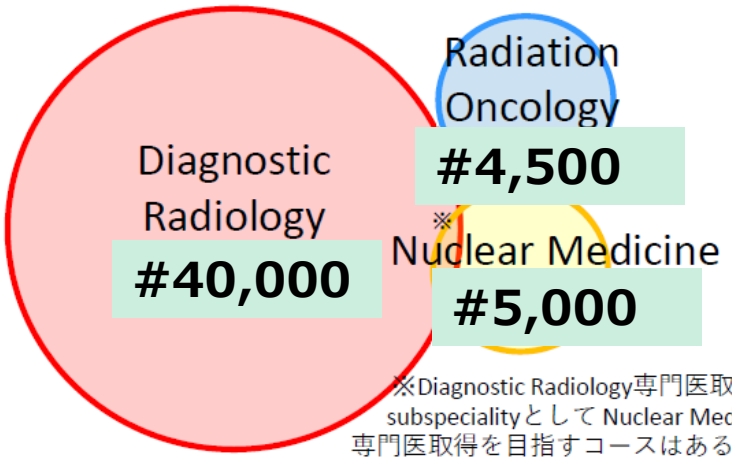
In 2022, Nuclear Regulation Authority approved MCAT™ in Radionuclide Control Act.

WHO will take care of TRT practices in Japan

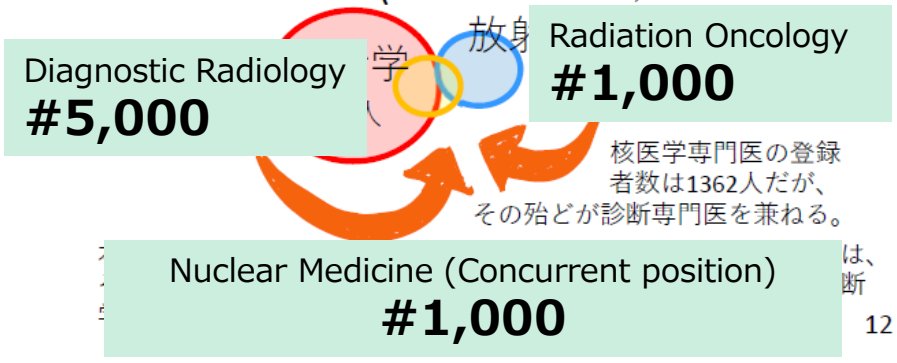
Creation of Harmonious Diversity
QST

The number of specialist:

USA (Population 300M)



Japan (Population 120M)



Population per specialist :

USA :

Diagnostic radiologist : 7,500

Radiation Oncologist : 66,667

Nuclear Medicine Physician (independent position) : 60,000

日本 :

Diagnostic radiologist : 26,000

Radiation Oncologist : 130,000

Nuclear Medicine Physician (concurrent position) : 95,450

Need for training education program for experts (doctor, medical radiology technician, medical physicist, nurse, etc)

Feb. 1. 2022: Atomic Energy Commission, Medical Radioisotope Production and Utilization Subcommittee: Prof. Yoko Takano's presentation: modified

Problems of the development of TRT/TAT in Japan

Creation of Harmonious Diversity
QST

- To secure raw materials, to develop **methods of synthesis**
- To **develop new TRT agents, start clinical trials**
- To establish companion diagnostics: theranostic twins
- To establish standards of clinical dosimetry for beta emitters
- To establish standards of dosimetry and release criteria for alpha emitters because of its multiple decay scheme

Innovation

- **Where: Shortage of location of therapy**, (1) radionuclide-controlled-area, (2) inpatient room in radionuclide-controlled-area, (3) total amount of radionuclide pharmaceuticals available in radionuclide-controlled-area.
- **How:** To make TRT/TAT agents in GMP level
- **How:** Japanese Guidelines for radioactive pharmaceuticals : enough for imaging agents, not enough for TRT agents
- **Who & How**: To cultivate Human Resource: **TRT experts in medicine, radiology, dosimetry, nursing, etc.**
- For citizen to accept this new radiation therapy
- Problems in logistics, regulations and radioactive wastes

Social Innovation

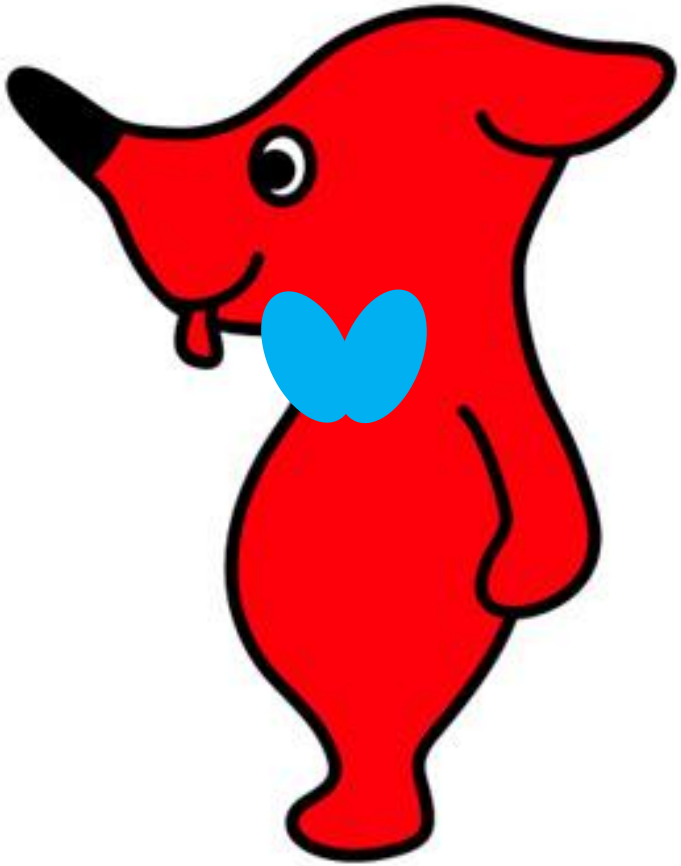
Closing remarks

"Japan's Action Plan for Production and Utilization of Medical Isotopes"

- TRT/TAT scientific fields is booming & medical markets are glowing with supports from Japan's Action Plan.
- Clinical trials of At-211 labelled agents including NaAt & MABG have already been in progress.
- Accelerator production of Ac-225 was already established in AMED/CiCLE research project and an Ac-225 labelled agent is in a non-clinical study.
- For TRT, Who, Where, How to perform: important aspects, especially Where: "Hospital rooms with special measures (HSP)" and "MCAT™" are attracting attentions.
- "All-Japan" cooperation including Atomic Energy Commission, QST, FMU, Osaka U, & others is need to strive to develop technological and social innovations for further promotion & spread of TRT/TAT.

Thank you for your attention.

Stay safe and healthy!



千葉県PRマスコット
キャラクター
チーバくん