New Treatment Facility and Targeted Alpha-particle Therapy in FMU

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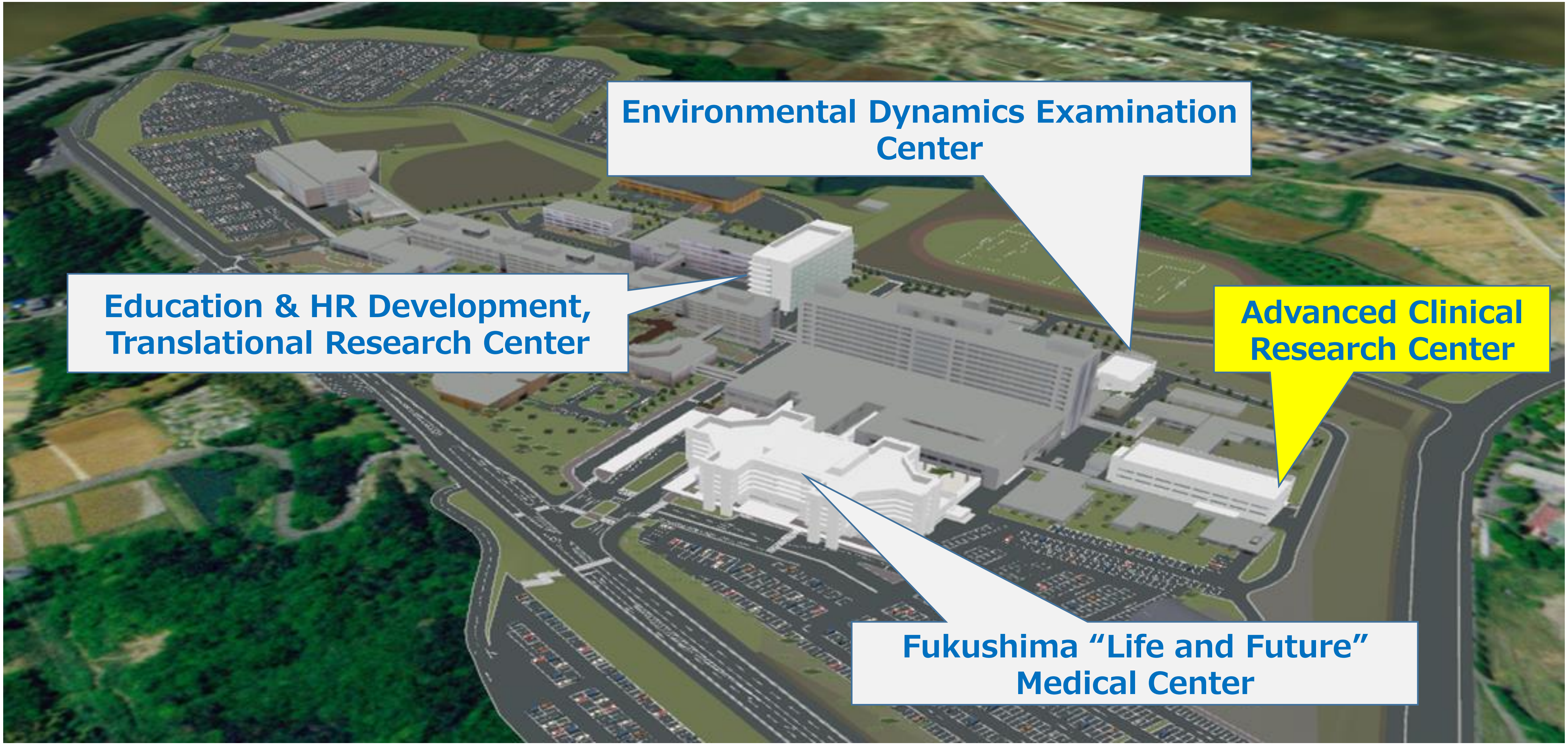
FMU-ICRP Workshop on Radiological Protection in Medicine
October 3, 2017, Fukushima Medical University

Fukushima Global Medical Science Center



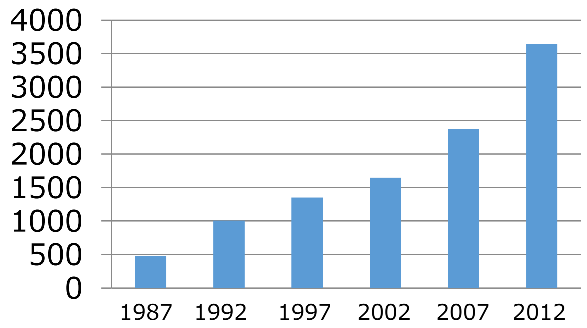
Current status of Fukushima Medical University in Radionuclide Therapy

- Perform approved radionuclide therapy
  - ^{131}I therapy for differentiated thyroid cancer (DTC) and Graves' disease
  - ^{90}Y-anti-CD20 Ab for low-grade B-cell non-Hodgkin's lymphoma (B-NHL)
  - ^{223}Ra-chloride for symptomatic bone metastases with hormone refractory prostate cancer
  - ^{89}Sr-chloride for relief of painful bone metastases
- Develop new radiopharmaceuticals for targeted radionuclide therapy
  - α, β-particle therapy
  - Produce ^{211}At with in-house cyclotron (MP-30)
- Develop molecular imaging for radionuclide therapy
  - Companion diagnosis with PET/SPECT for targeted therapy

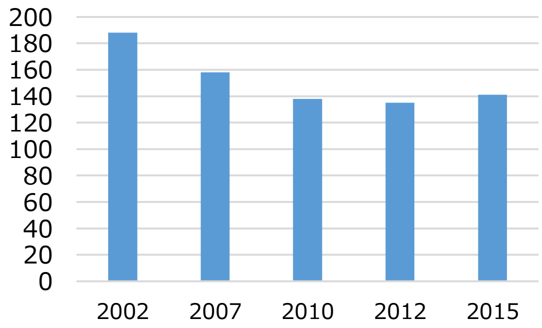
Domestic status of radionuclide therapy for DTC in Japan

(1) Increased performance
(2) Shortage of beds for therapy
(3) Long waiting period
(4) Poor survival

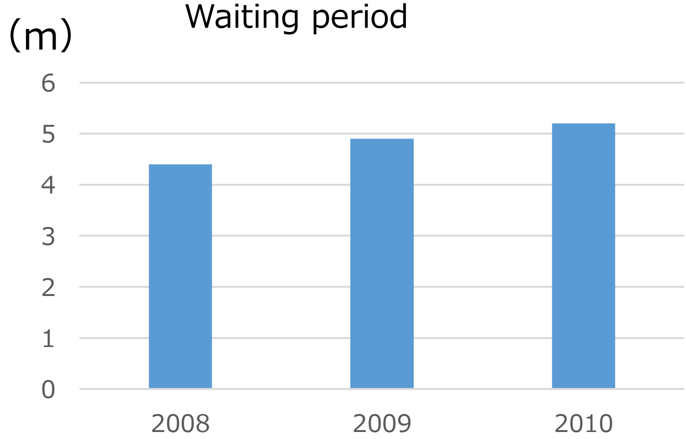
Number of therapy



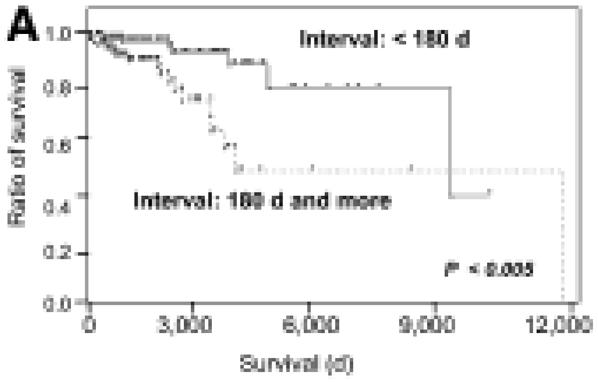
Number of beds for therapy



Waiting period



Shorter survival with longer waiting period



Higashi T, et al. J Nucl Med 2011;52:683-9

^{131}I-MIBG therapy for malignant pheochromocytoma and paraganglioma in Japan

《Summary》

- ✓ Rarely "effective"
- ✓ Stable disease in majority
- ✓ Less side effects

Endocrine Journal 2014, **61** (12), 1171-1180

ORIGINAL

Effects and safety of ^{131}I-metaiodobenzylguanidine (MIBG) radiotherapy in malignant neuroendocrine tumors: Results from a multicenter observational registry

Keiichiro Yoshinaga[1)], Noboru Oriuchi[2)], Hiroshi Wakabayashi[3)], Yuuki Tomiyama[4)], Megumi Jinguji[5)], Tetsuya Higuchi[2)], Daiki Kayano[3)], Makoto Fukuoka[3)], Anri Inaki[3)], Ayane Toratani[3)], Shozo Okamoto[4)], Tohru Shiga[4)], Yoichi M. Ito[6)], Masatoyo Nakajo[5)], Masayuki Nakajo[5)], Seigo Kinuya[3)] and Drafting Committee for Guidelines on Internal Radiotherapy with ^{131}I-MIBG, Japanese Society of Nuclear Medicine in Oncology and Immunology, Japanese Society of Nuclear Medicine

Table 2
(A) Treatment-based response to ^{131}I-MIBG radiotherapy

Disease	Response				Total
	CR	PR	SD	PD	
Pheochromocytoma	0	1	40	9	50
Paraganglioma	0	0	14	1	15
Total	0	1	54	10	65

CR, complete remission; MIBG, metaiodobenzylguanidine; PD, progressive disease; PR, partial remission; SD, stable disease.

Table 4 Details of bone marrow suppression in adult neuroendocrine tumors
(A) Treatment number-based analysis

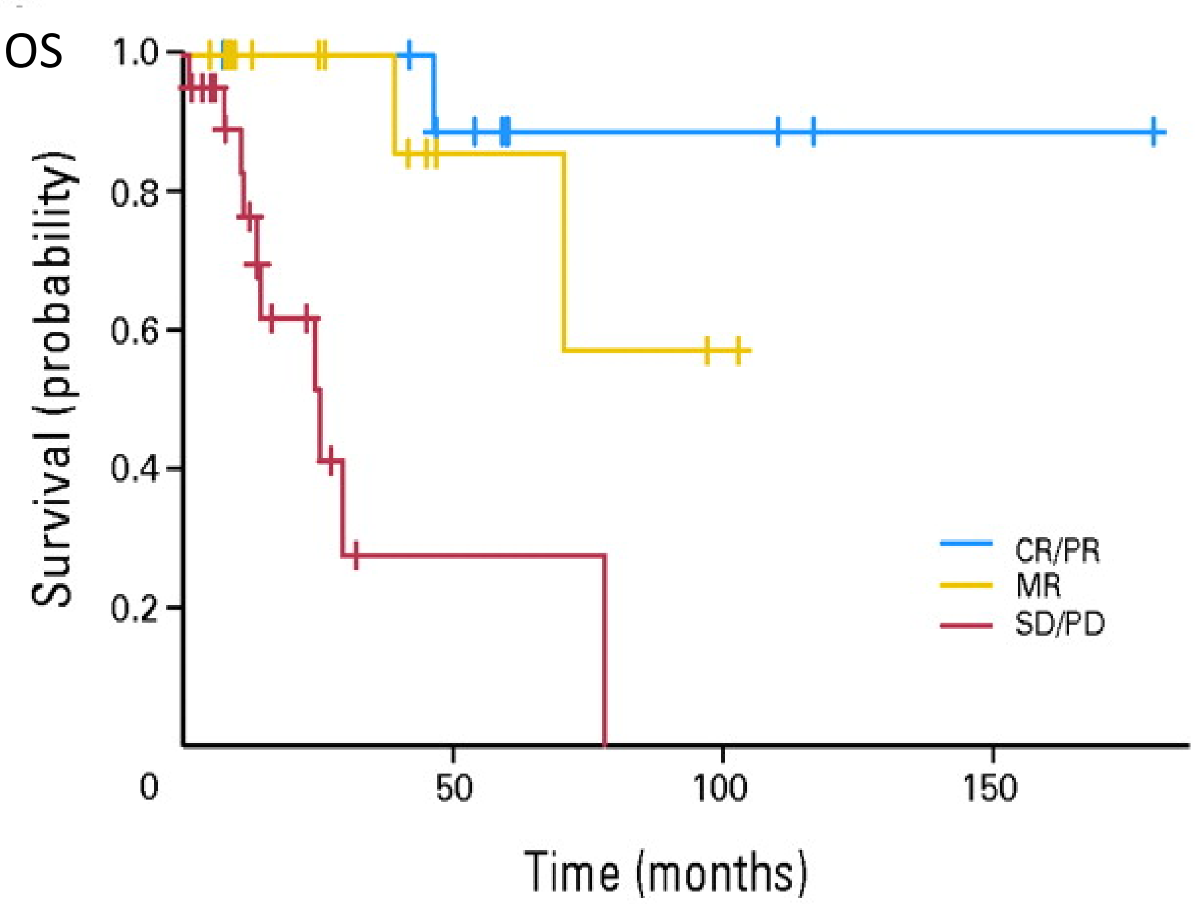
	NCI toxicity grade			
	I	II	III	IV
Thrombocytopenia	0	0	0	0
Anemia	0	1	0	0
Leukopenia	0	12	2	0
Total number of patients	0	13	2	0

Yoshinaga K, et al. Endocrine Journal 2014, 61, 1171

^{131}I-MIBG therapy for malignant pheochromocytoma in the USA

	Dose (mCi)	(mCi/kg)
1st	492-1,160 (av. 818)	9-19
Total	492-3,191	

Effectiveness	Total		2nd (vs 1st)	
	No.	%	No.	%
CR	4	8	1	7
PR	7	14	5	33
MR	17	35	5	33
SD	4	8	1	7
PD	17	35	3	20



Gonias S, et al. J Clin Oncol 2009; 27: 4162

Radionuclide therapy ward in Fukushima Medical University

Radionuclide therapy ward in Fukushima "Life and Future" Medical Center

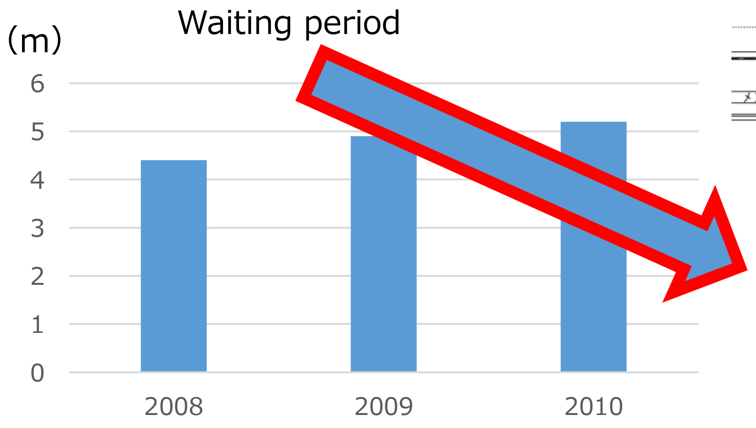
37.0 GBq:　(#3)

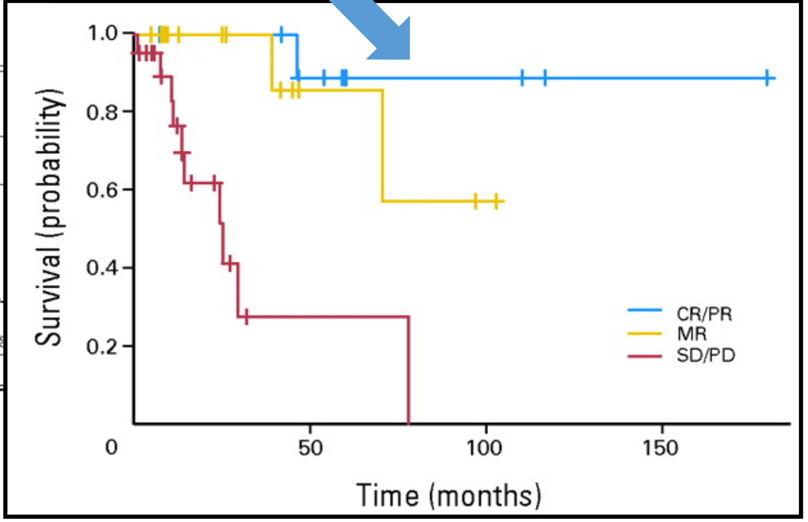
22.2 GBq:　(#2)

7.4 GBq:　(#4,5,6)

3.7 GBq :　(#1,7,8,9)

Sufficient dose for efficacy



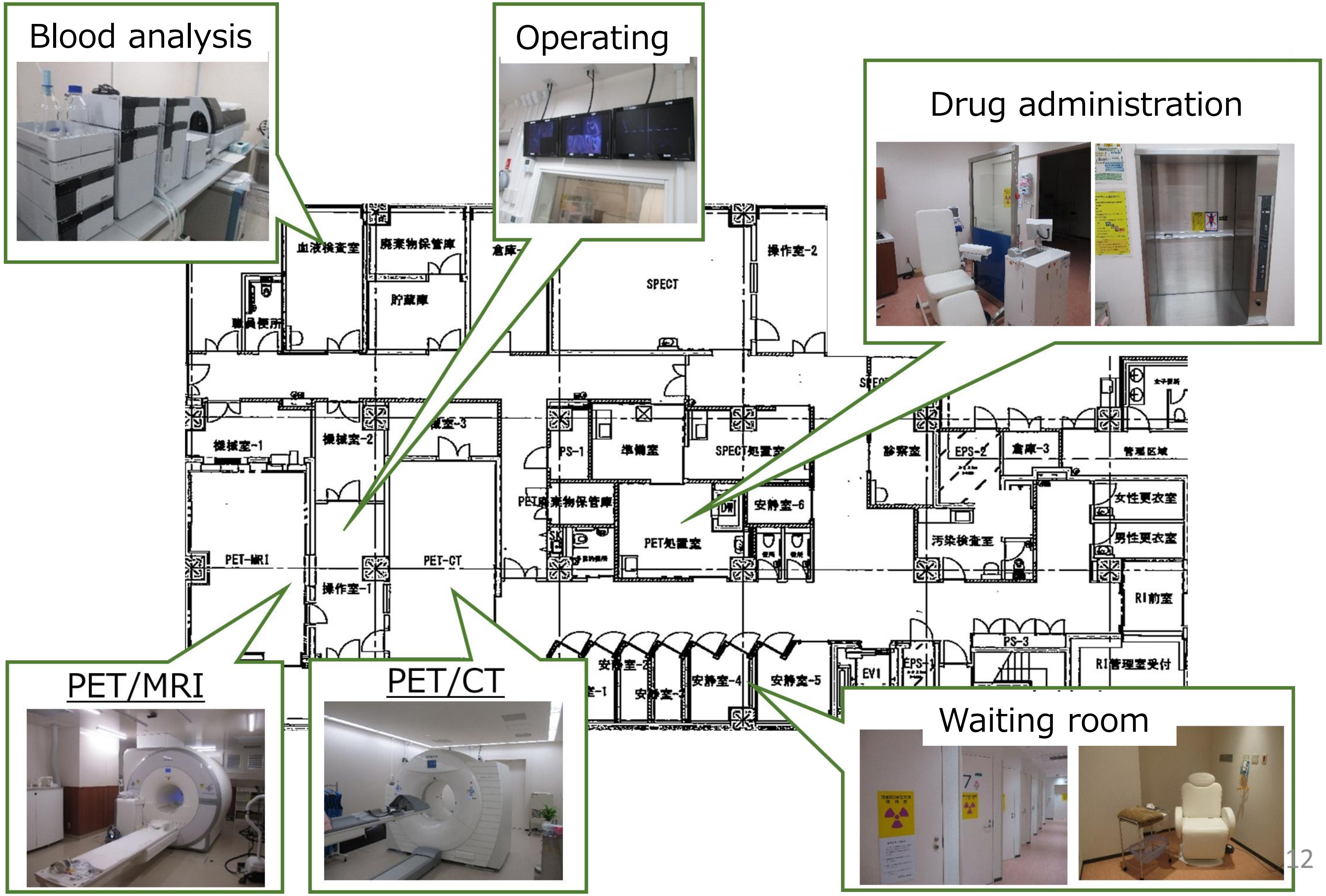


Theranostics = Therapy + Diagnostics

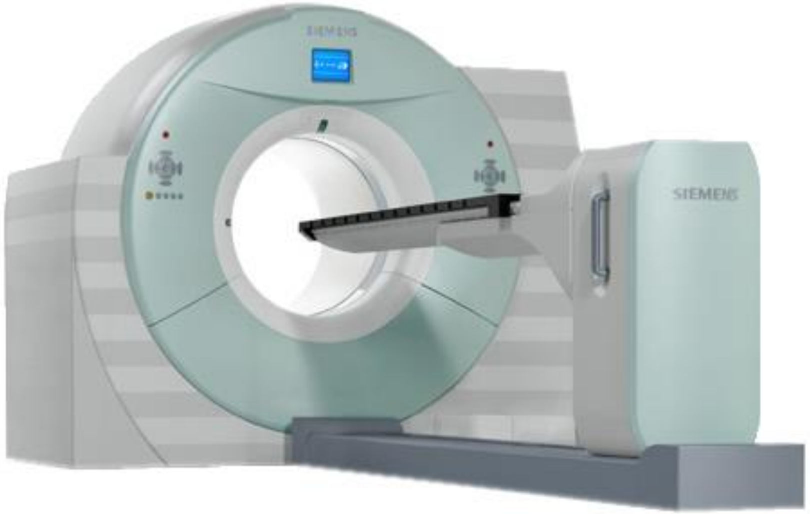
- Specific targets for radionuclide therapy
- Same target for diagnostic imaging
  - Indication
  - Therapeutic effectiveness and toxicity
  - Dosimetry

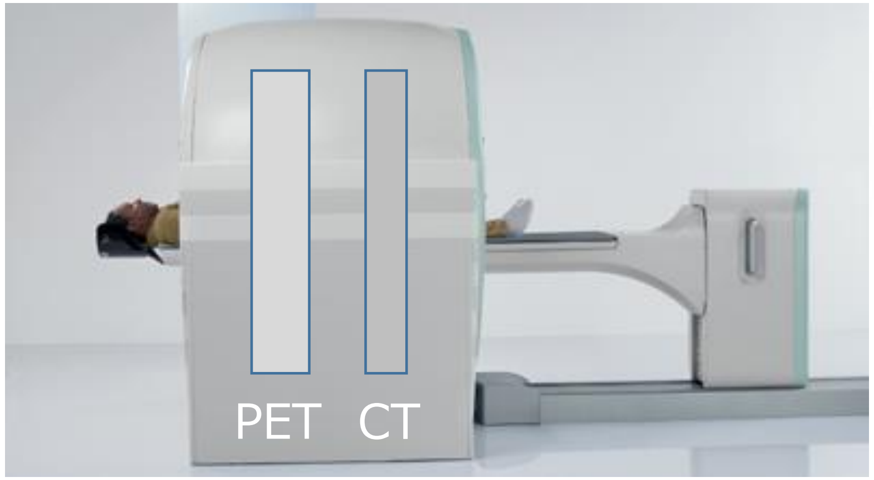
PET/SPECT imaging $\xrightarrow{\textbf{Targets}}$ Radionuclide therapy

Clinical PET/CT and PET/MRI facility



PET/CT



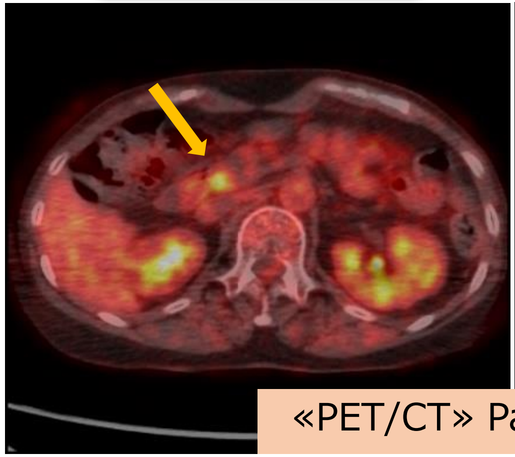


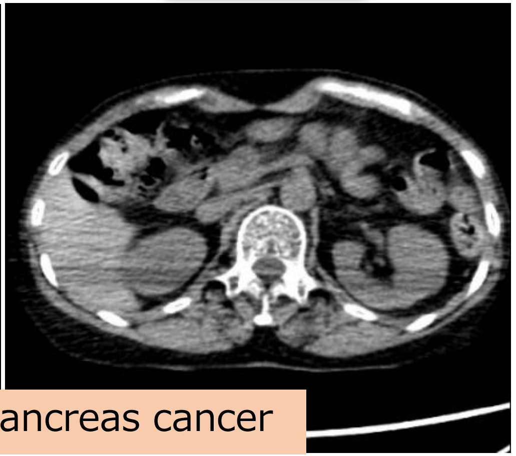
(Biograph mCT, Siemens)

Pancreas cancer

PET/CT

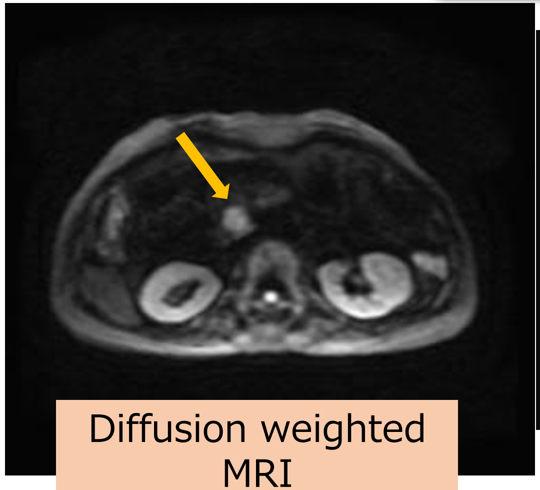
CT



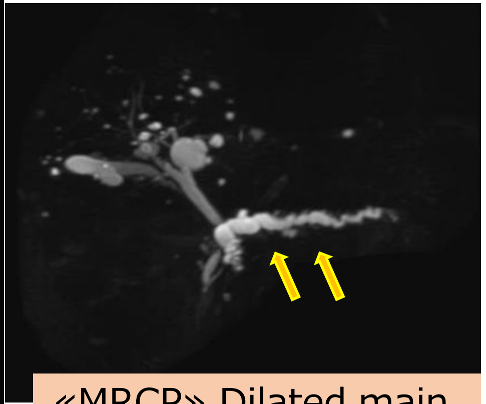


«PET/CT» Pancreas cancer

MRI

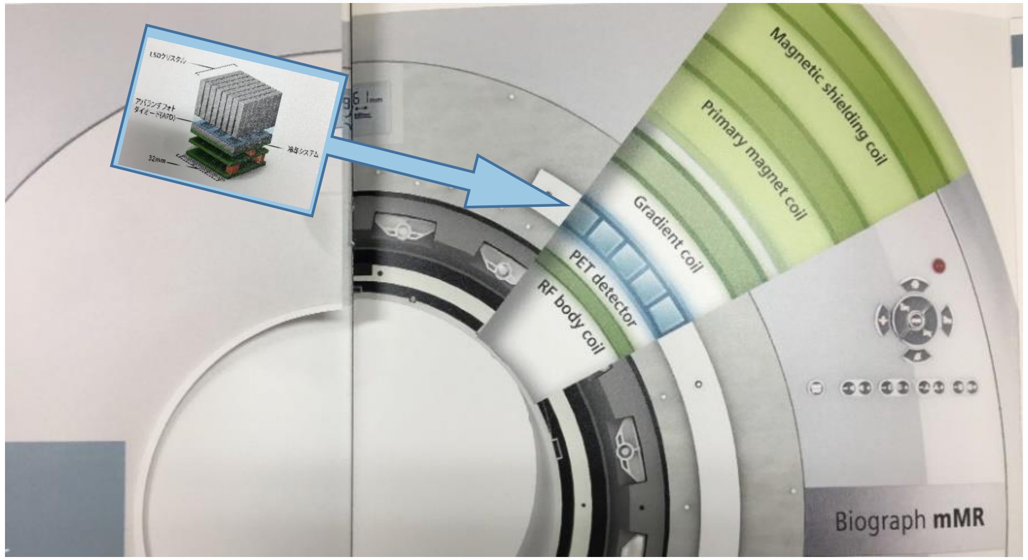


Diffusion weighted MRI



«MRCP» Dilated main pancreatic duct

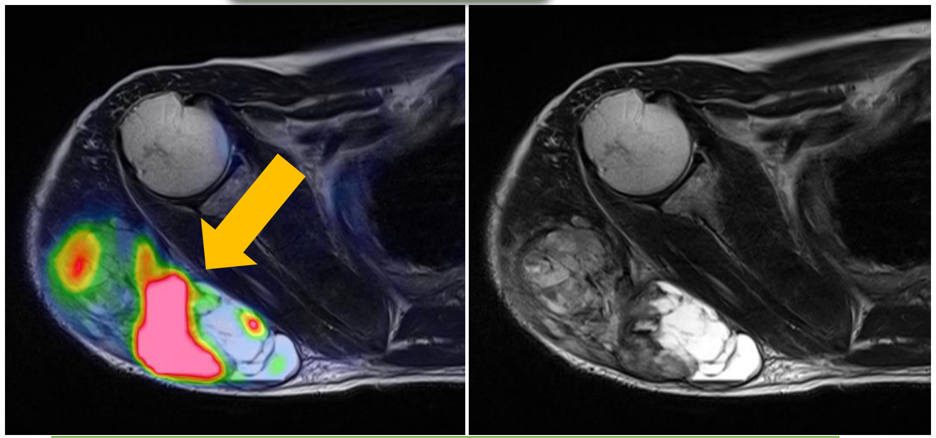
PET/MRI



(Biograph mMR, Siemens)

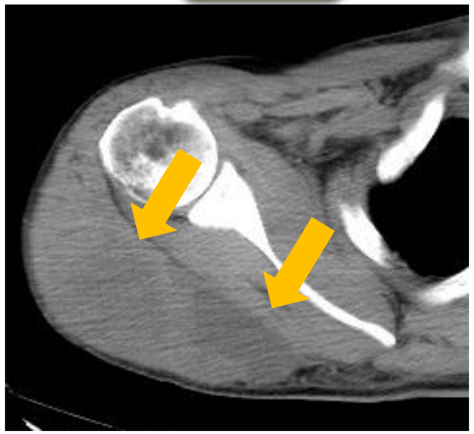
Undifferentiated pleomorphic sarcoma

PET/MRI

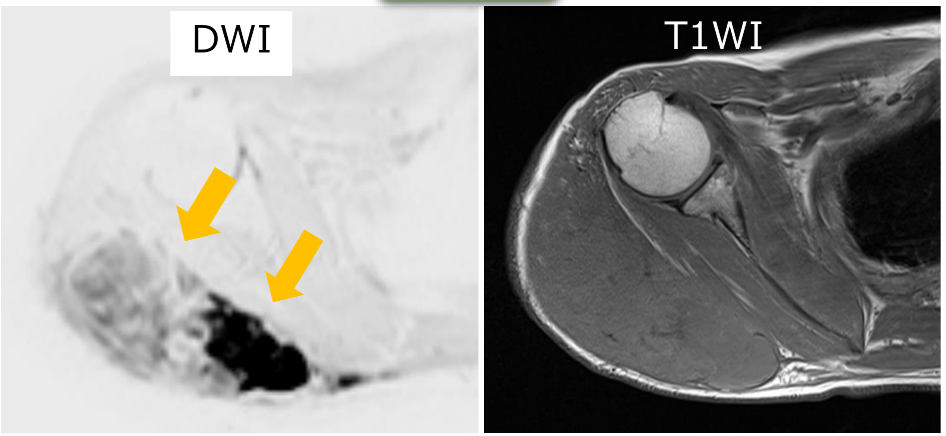


«PET/MRI» Heterogeneouly increased FDG uptake in the tumor

CT



MRI



«CT» Low density area in the right deltoid muscle

«MRI» Heterogeneous signal intensity on diffusion-weighted MRI

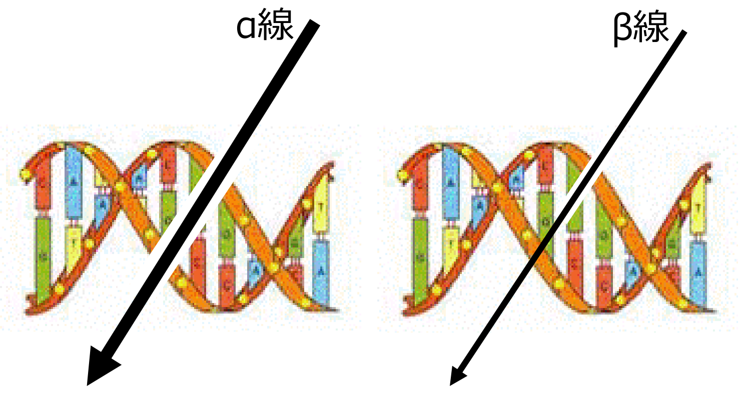
Radionuclides for theranostics

Therapy			Diagnosis	
Radionuclides	**$T_{1/2}$ (days)**	**Radiation**	**Radionuclides**	**$T_{1/2}$ (days)**
^{67}Cu	2.58	β^-	^{64}Cu	0.53
^{77}Br	2.42	EC, Auger	^{76}Br	0.68
^{131}I	8.02	β^-	^{124}I	4.17
^{177}Lu	6.73	β^-	^{68}Ga	68 (min)
^{211}At	0.3	α	^{124}I	4.17

Characteristics of α-particle and β-particle

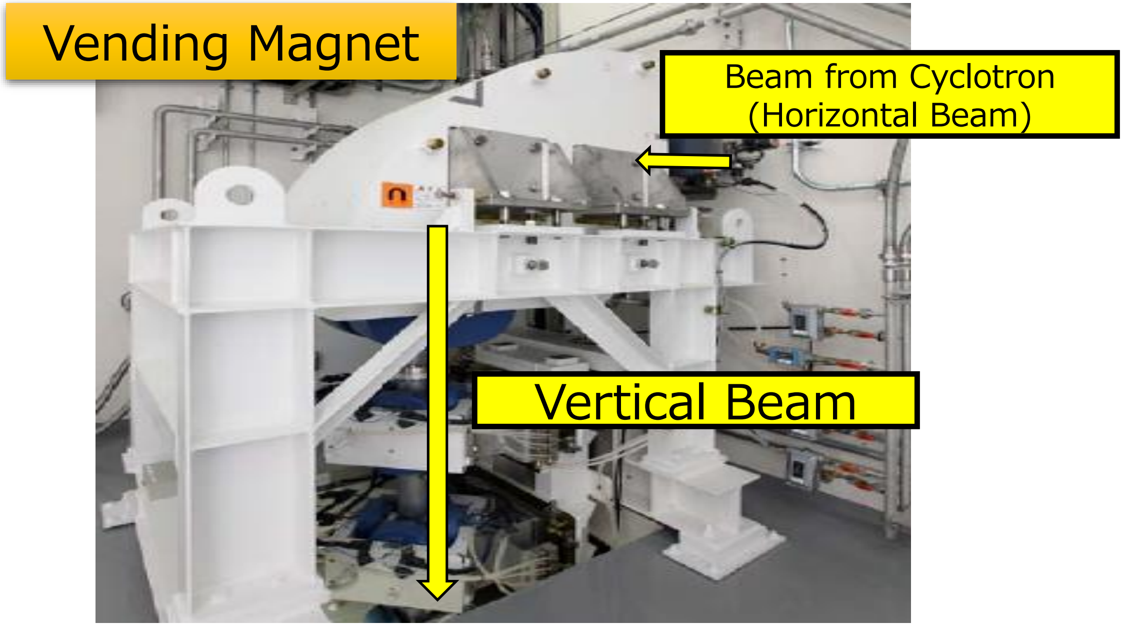
α-emitters are more capable comparing with β-emittes for therapy

- Increased cellular damage
  - High LET (Linear energy transfer)：97 (^{211}At) vs. 0.2 keV/μm (^{90}Y)
  - High RBE (Relative biological effectiveness) ：5-20 (α) vs. 1 (β)
- Low toxicity
  - Short path length：<100 μm (^{211}At) vs. 11 mm (^{90}Y)
  - Limited radiation to adjacent normal organs, BM



RI	Radiation	γ	T1/2	Energy (MeV)	Path length (mm)
^{67}Cu	β	+	62.1 h	0.39	1.1
^{89}Sr	β		50.5 d	1.49	8
^{90}Y	β		64.1 h	2.28	11
^{131}I	β	+	8.0 d	0.61	2
^{177}Lu	β	+	6.7 d	0.5	1.5
^{211}At	α	+	7.2 h	5.58	<0.1
^{223}Ra	α	+	11.4 d	26.5	<0.1

Characteristics of MP-30 Cyclotron



Special Features:

Vertical Irradiation System

Automatic Target Transport System

Advantage of vertical irradiation system

→ Easy material fixing

for low melting point target materials

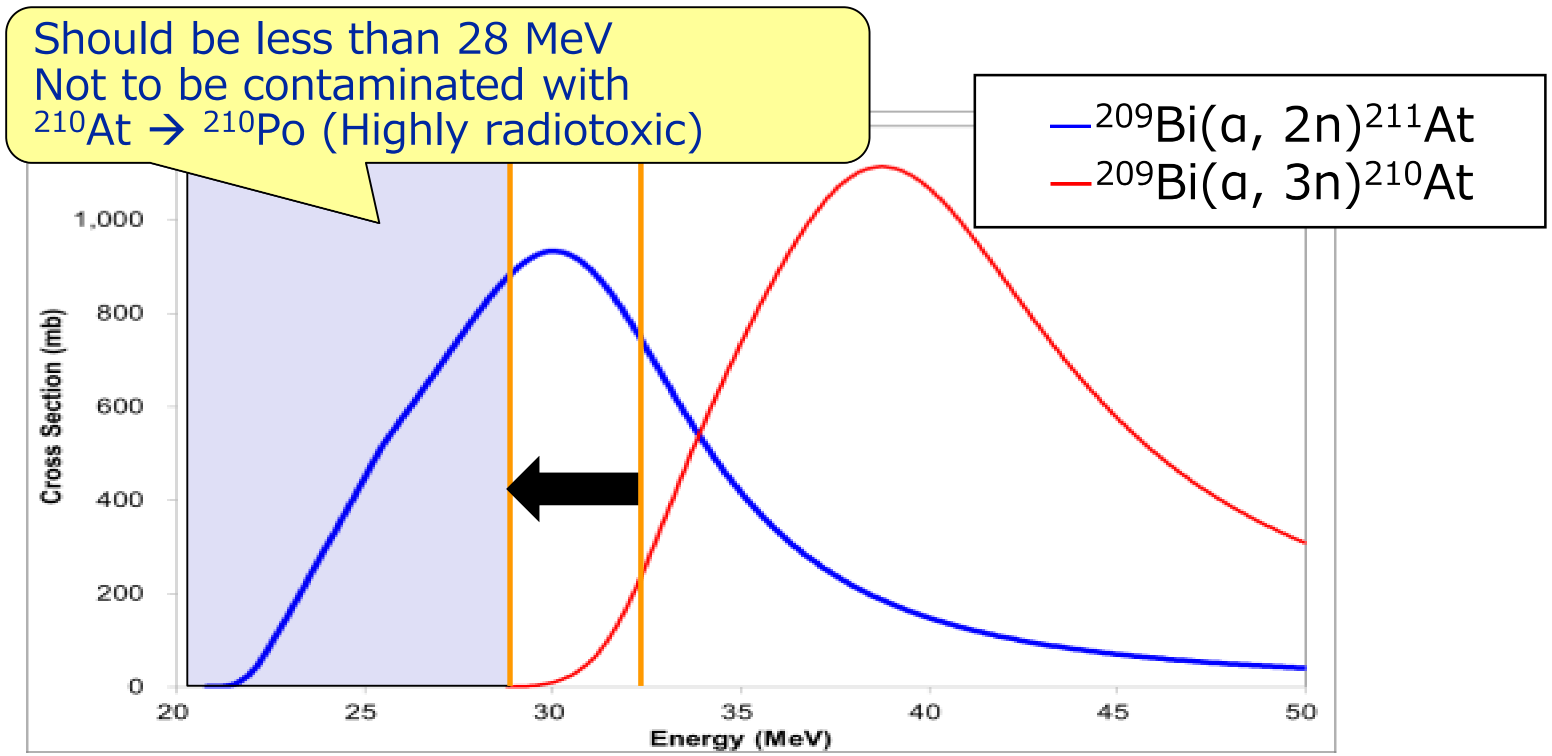
ex. Gallium, Bismuth

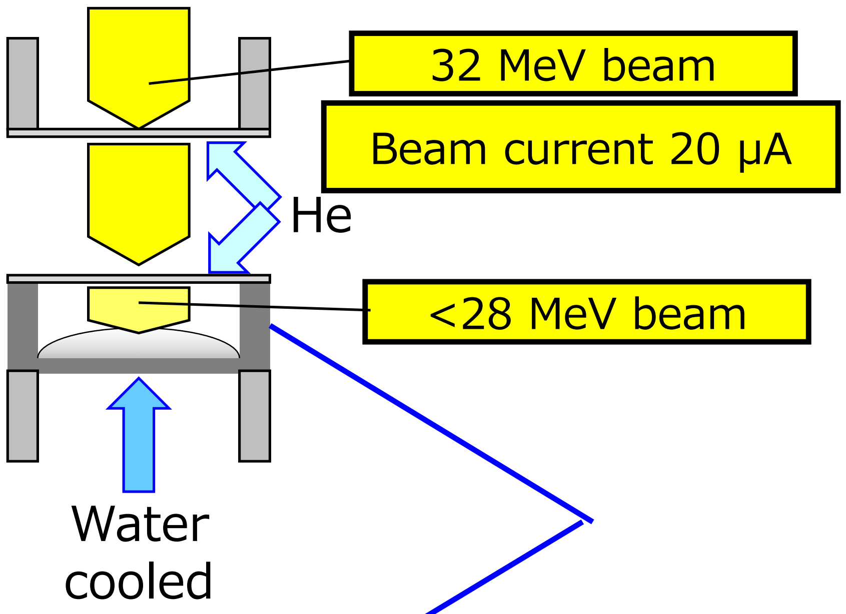
for powder or lump target materials

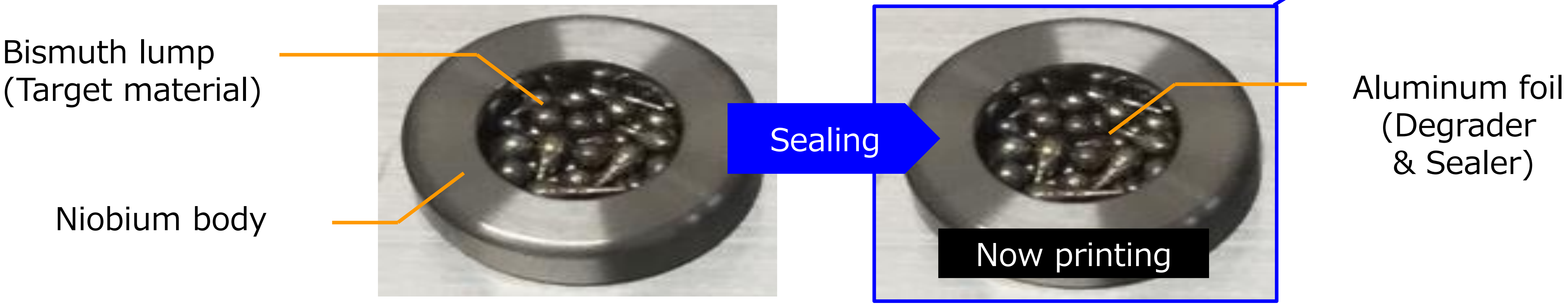
ex. Oxide, Enrichment powder

6 target ports system

Production of ^{211}At with MP-30 Cyclotron





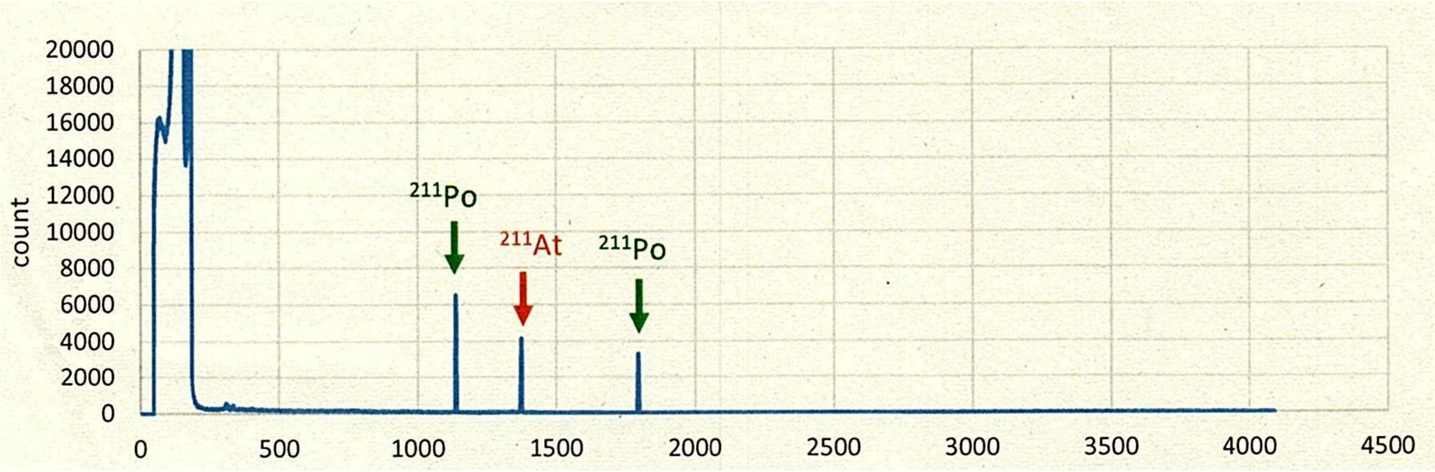


Production of At-211 at Fukushima Medical University

At-211 production
$^{209}Bi(\alpha, 2n)^{211}At$
Projectile energy <28 MeV

Approximately 1.5 GBq (EOB) of ^{211}At
No production of At-210

MP-30, Sumitomo Heavy Industry



γ-ray spectrometry analysis

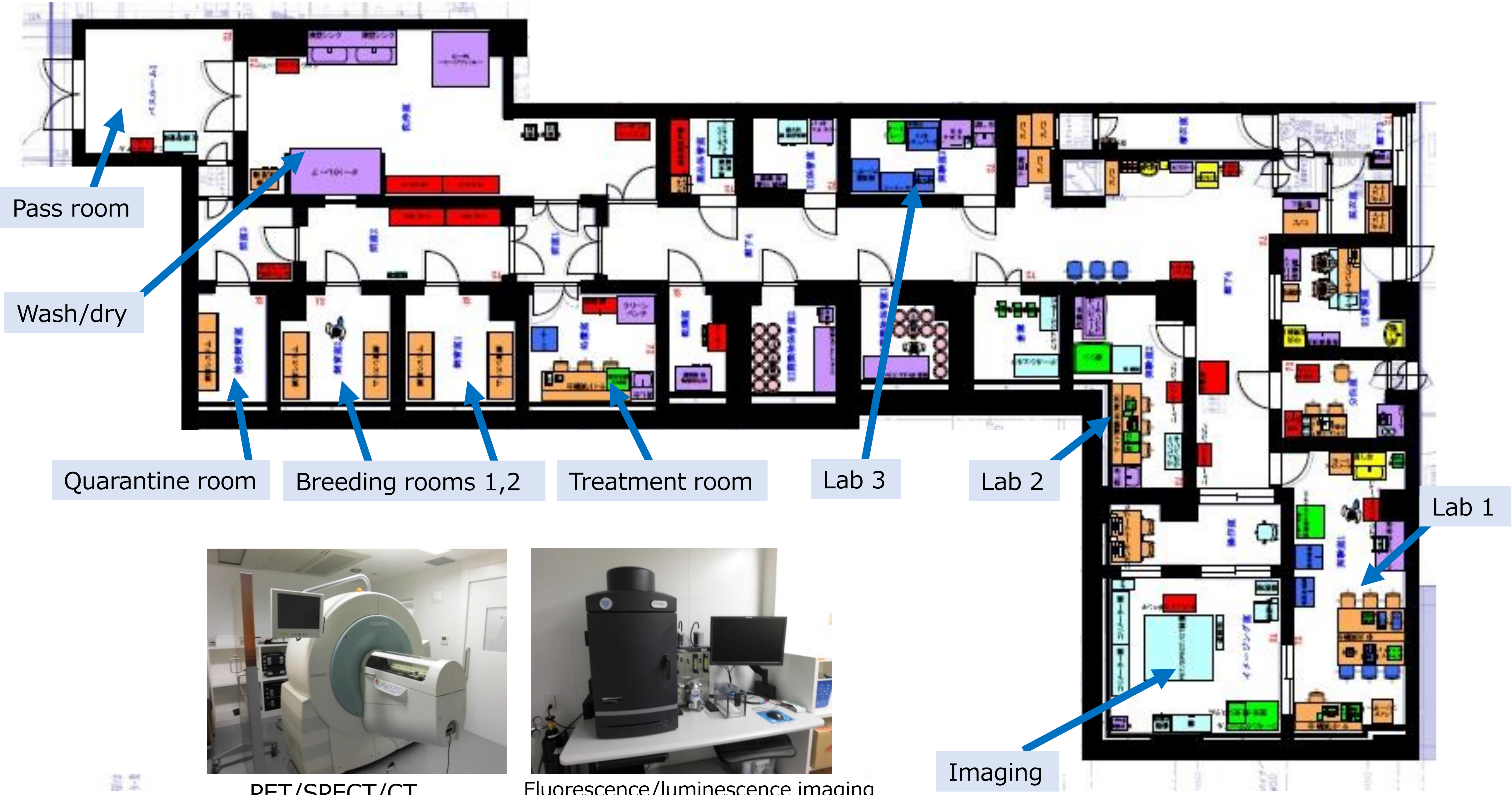
Hot labs: Production of radioactive compound and quality control

Hot Lab　＃3, 4, 5

Chemical black box
（Automatic synthesis device）

Quality control device

Animal facility for preclinical study with radionuclide

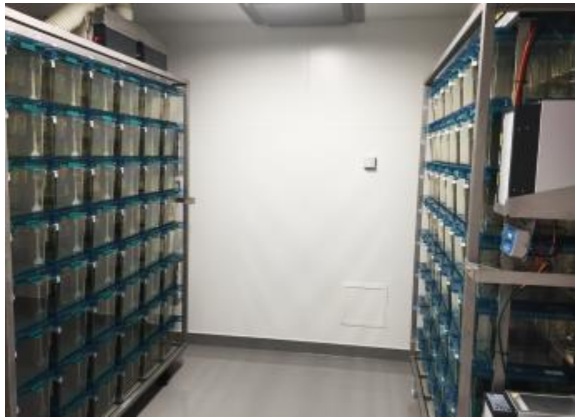


PET/SPECT/CT

Fluorescence/luminescence imaging

Animal breeding facilities

Isolated housing



Automatic
cage washer

Autoclave

- Three breeding rooms including quarantine inspection room
- Isolated 240 cages for rodent

Cell culture equipment

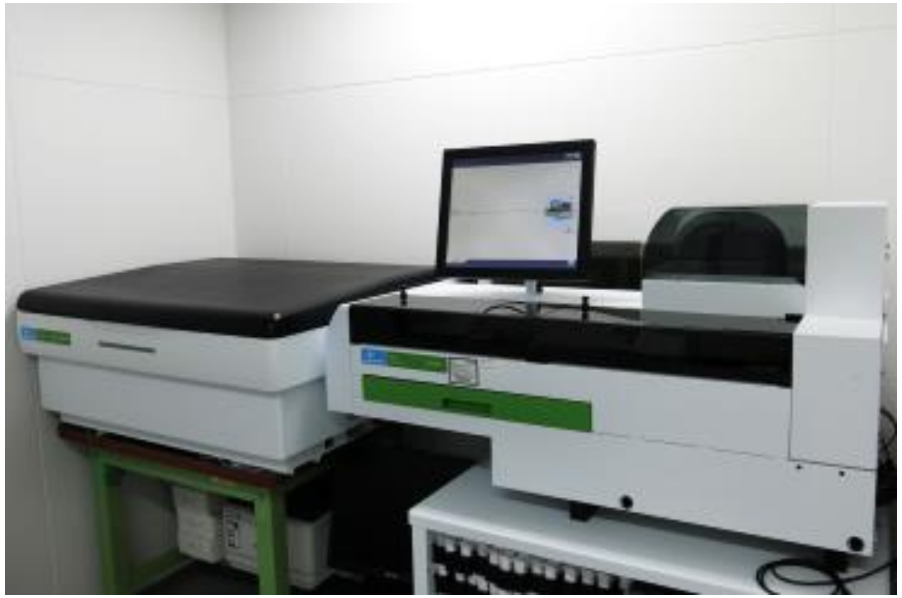
CO_2 incubator

Safety cabinet

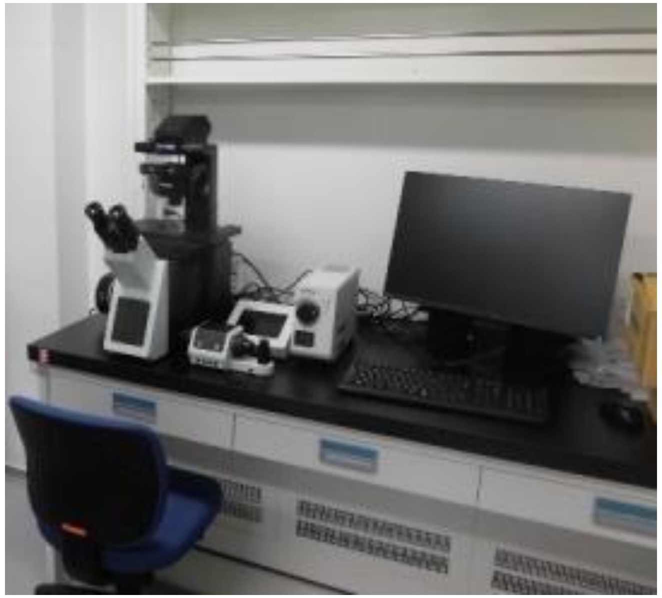
Microscope, cell counter

●Cell culture for in vitro exam and preparation for tumor model in immunodeficiency mice
●Specific pathogen free status is secured

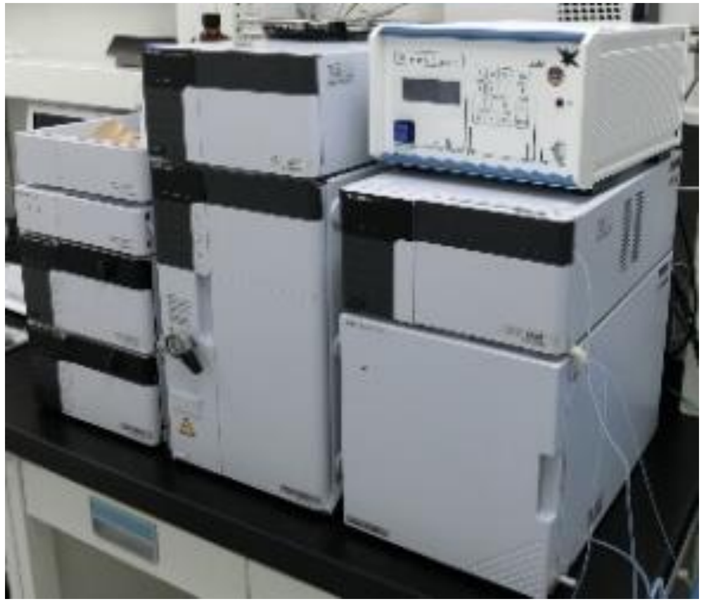
Radioactivity measurement and analyses



Liquid scintillation counter
Gamma counter



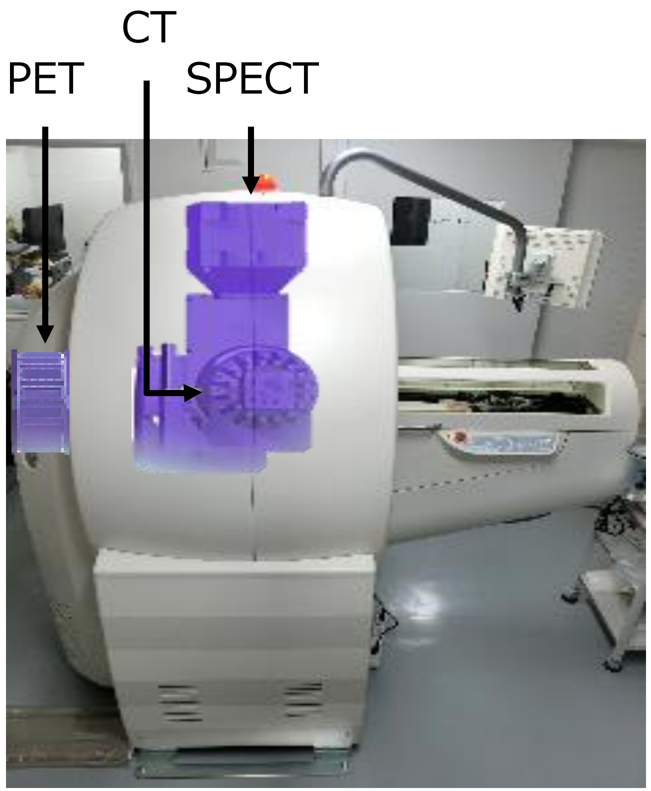
Fluorescence and
luminescence microscope



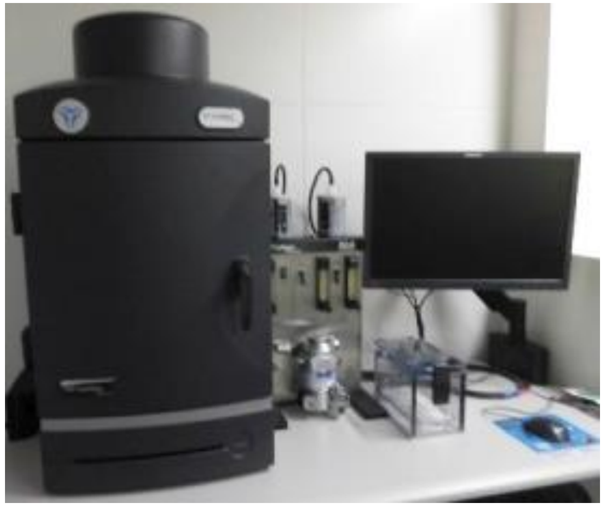
HPLC for radioactive
compounds

- High spec analytical instruments for radioactive compounds and there metabolites
- Pharmacokinetic and pharmacodynamic study for drug development

Imaging apparatus for small animal



PET/SPECT/CT



Fluorescence and luminescence imaging

MRI

Autoradiography

- Molecular imaging apparatus can be used for in vivo analysis of radioactive compounds
- Pharmacokinetic and pharmacodynamic study for drug development

Development of novel radionuclide therapy in Fukushima

- Develop new treatment
  - Investigate target-oriented therapeutic strategy
  - Produce novel radiolabeled compounds
  - Preclinical study and clinical trials for approval
- Targeted α-particle therapy
  - ^{211}At-labeled compounds
  - Stable and constant production with safety
- Collaboration with researchers, clinical practitioners
- Cooperation with pharmaceutical companies, machinery companies

Thank you for your attention

Future
From
Fukushima.

ふくしまから
はじめよう。