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RCNP
大阪大学 核物理研究センター

YITP International Workshop:
Biological & Medical Science based on Physics:
Radiation and physics, Physics on medical science,
Modeling for biological system

Activities of the consortium for medicine, mathematics, chemistry, and physics at Osaka University

Research Center for Nuclear Physics(RCNP),
Osaka University

Mitsuhiro FUKUDA

November 7, 2015

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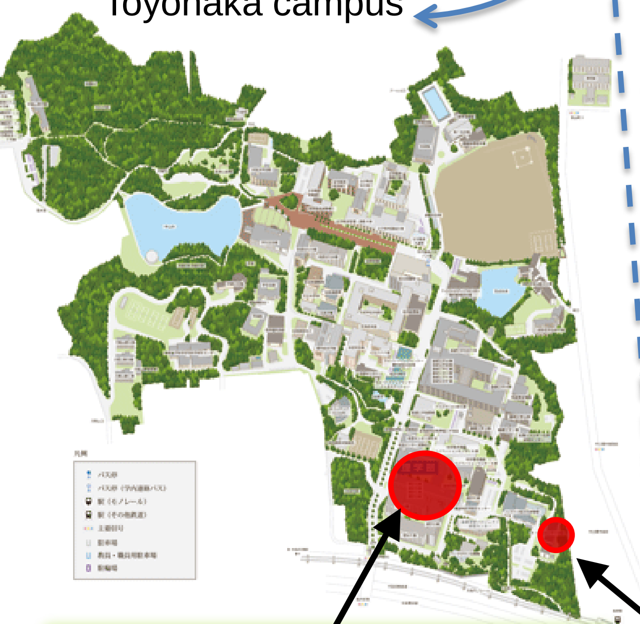
Contents

1. Introduction

Complete facilities for the research in medicine, chemistry, nuclear and accelerator physics at Osaka University

～20 min.

Toyonaka campus

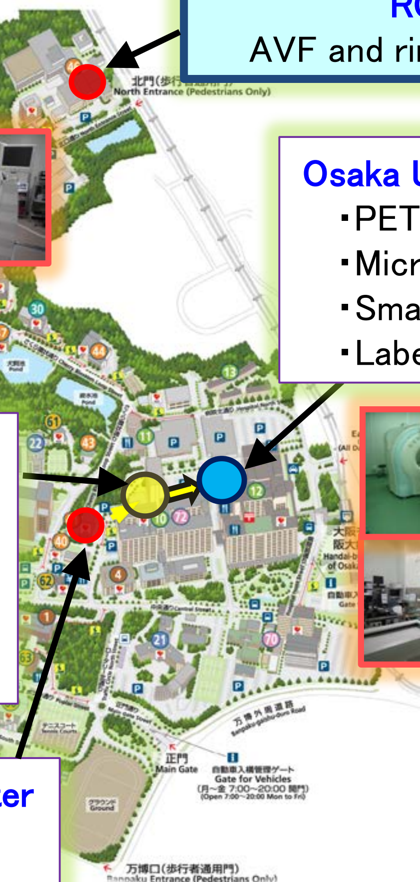


Graduate School of Science

・RI experiment facility

・Molecular synthesis equipment

Suita campus



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AVF and ring cyclotrons

Osaka University Hospital

・PET/CT, SPECT/CT

・Microdose PET/CT

・Small cyclotrons

・Labeling/synthesis

Graduate School of Medicine

PET molecular imaging center

・Positron camera

・Gamma camera

・PET/MR, PET/CT for animals

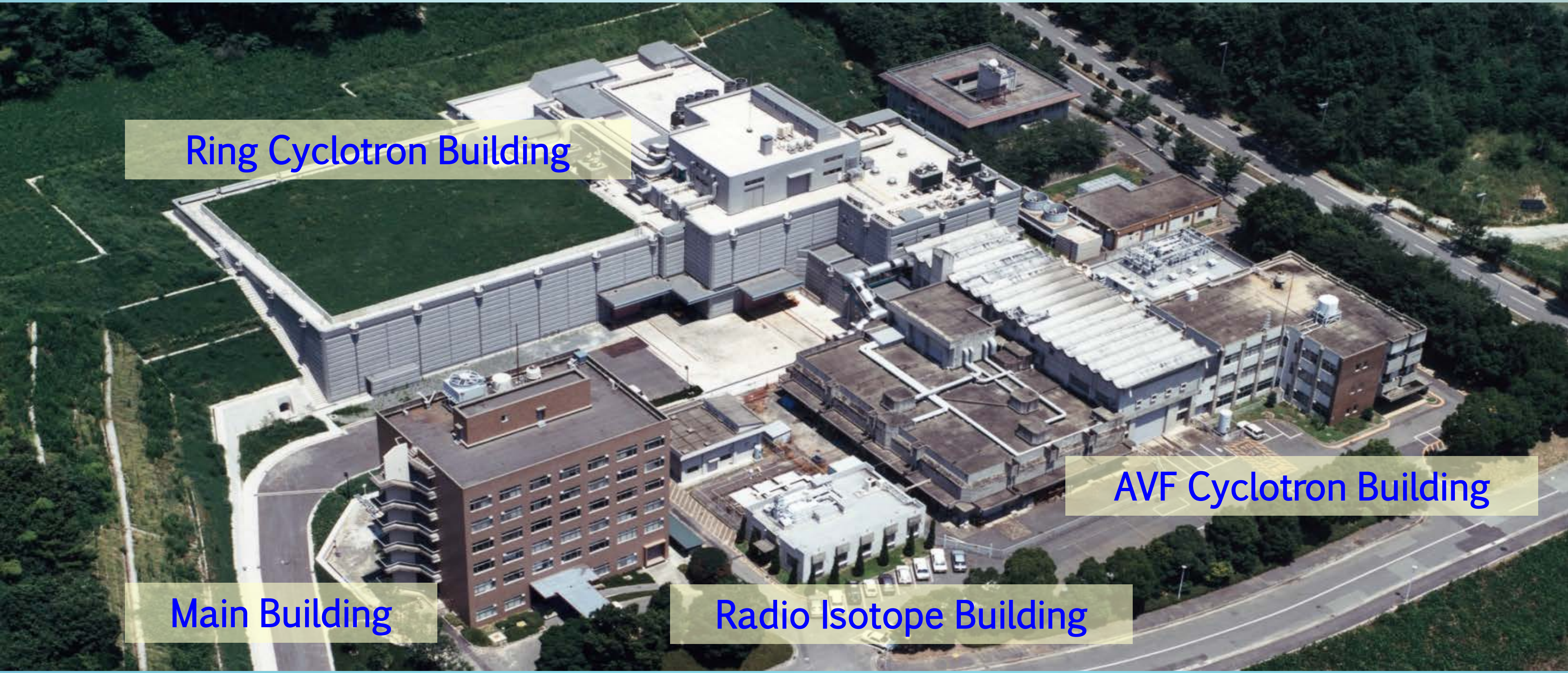
Radioisotope Research Center

・RI production equipment

・PET/MR for small animals

Research Center for Nuclear Physics (RCNP)

- 1971 Foundation of RCNP
- 1973 Completion of the AVF cyclotron facility (42 years old)
- 1976 Experiments started.
- 1991 Completion of the Ring cyclotron facility



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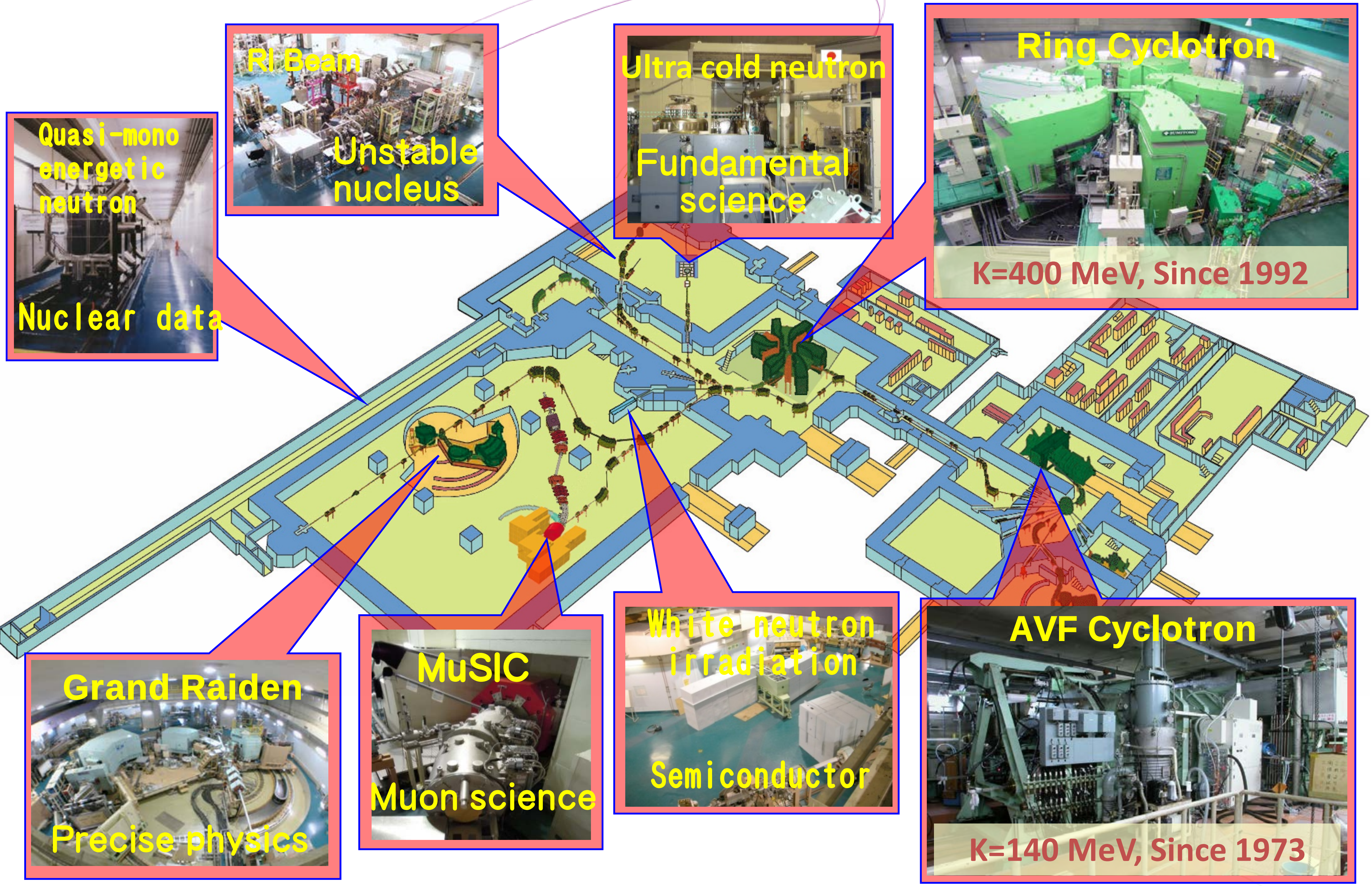
RCNP Cyclotron Facility

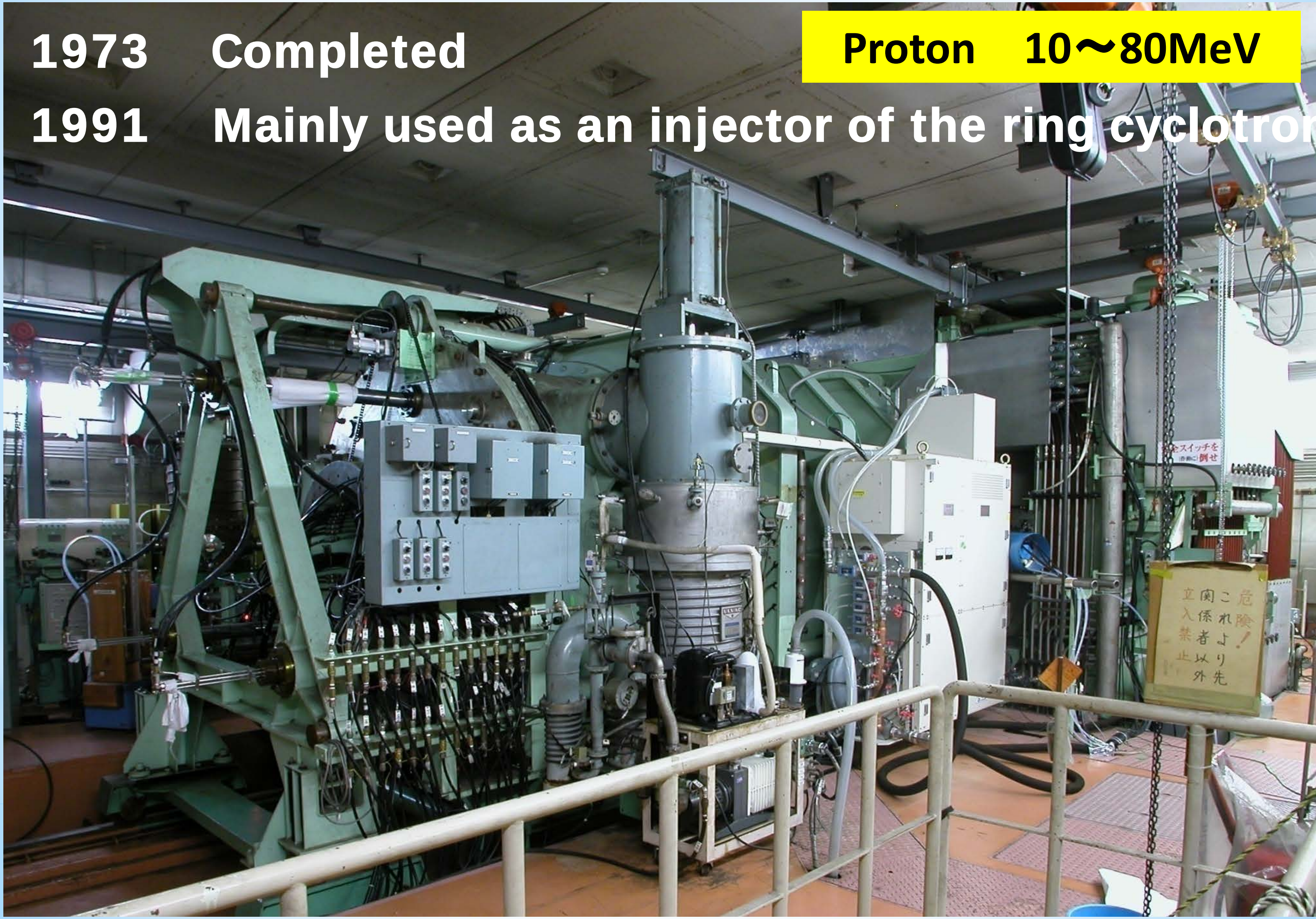


*RCNP K140 AVF Cyclotron

1973 Completed

1991 Mainly used as an injector of the ring cyclotron

Proton 10～80MeV



Operation Parameters of K140 AVF Cyclotron

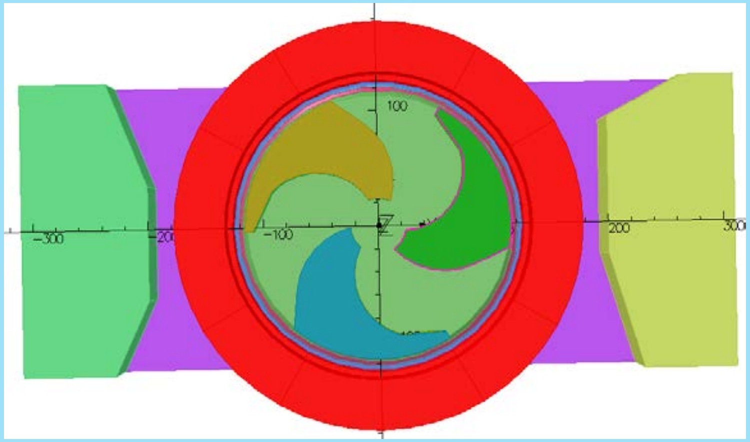
【Specifications】

- Energy of ions with M/Q≦5

proton	≦ 80 MeV
D^+, $^4He^{2+}$	≦ 35 MeV/n
$^3He^{2+}$	≦ 180 MeV
Heavy Ion	≦ $140 \times (Q/A)^2$

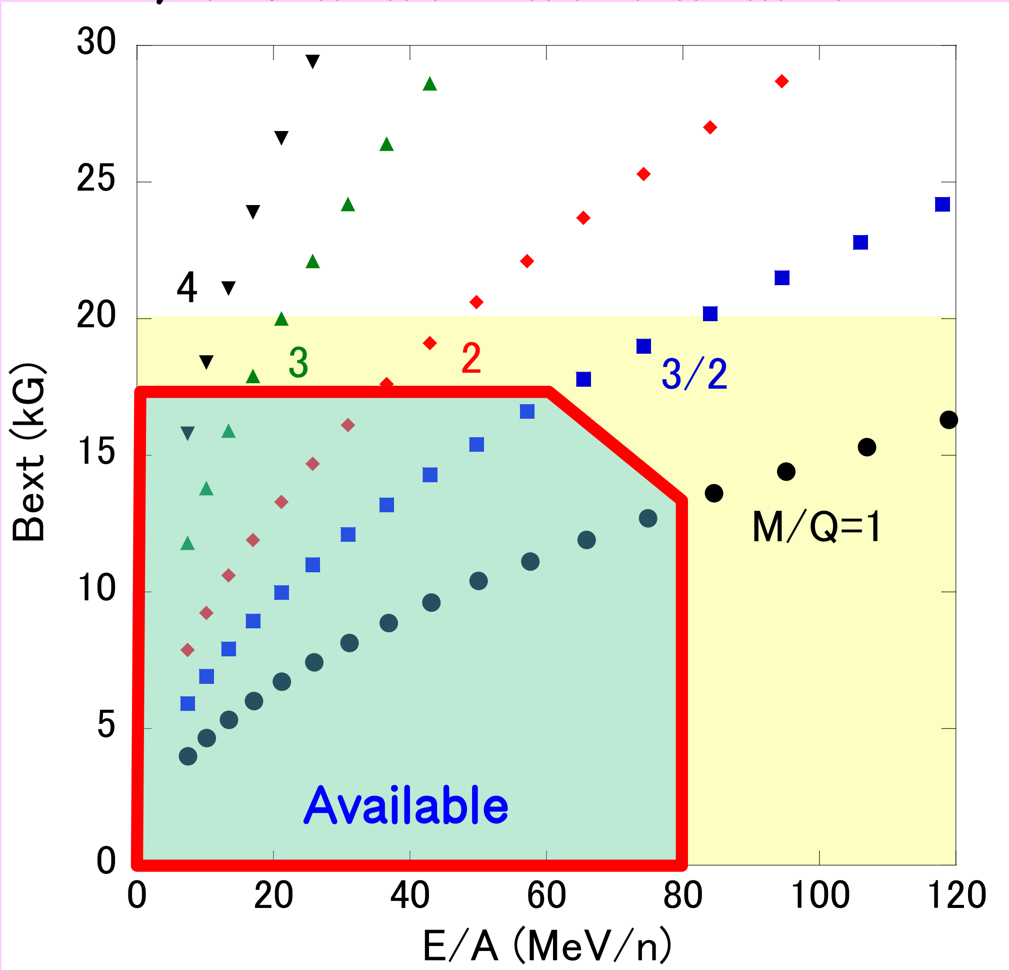
- RF 6～19 MHz
- Acc. harmonics 1, 3
- Average field ≦ 1.7 T

Magnet of 3-sector type



●Characteristics

- Variable energy and multi-particle
- Operation mode : injector of the ring cyclotron and stand-alone mode

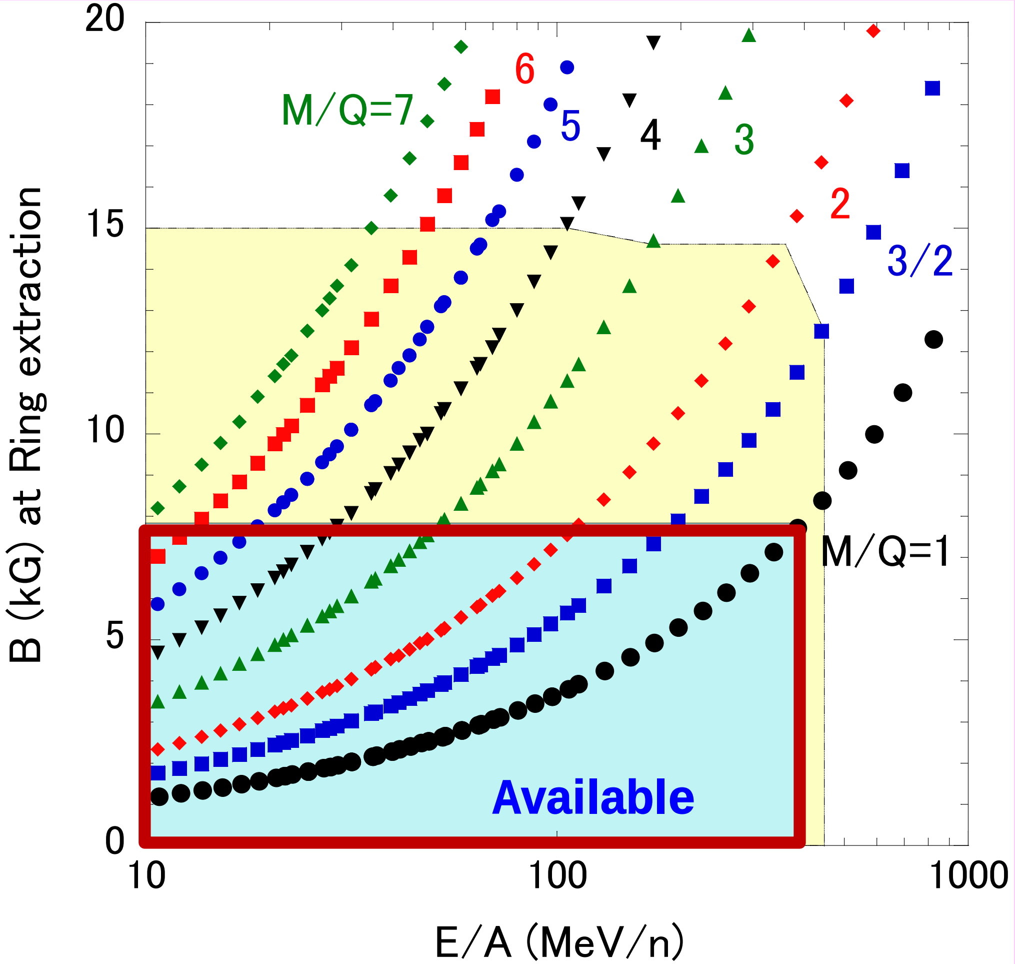


*RCNP K400 Ring Cyclotron

* RCNP K400 Ring Cyclotron

【Specifications】
- Energy Designed for light ions with M/Q≦3
  - proton ≦ 420 MeV
  - D^+, $^4He^{2+}$ ≦ 100 MeV/n
  - $^3He^{2+}$ ≦ 170 MeV/n
  - Heavy Ion ≦ $400\times(Q/A)^2$
- RF 30～52 MHz
- Acc. harmonics 6, 10, 12, 18
- Average field 8 kG(max.17.5)

● Characteristics
- Beam power : 0.44kW for proton
- Energy spread : $\Delta E/E \sim 0.01\%$
- Mag. Field stability : $\Delta B/B < 0.001\%$

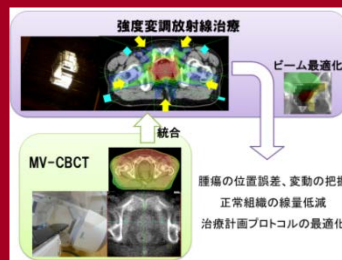


Cooperation among Graduate Schools of Medicine and Science, RCNP

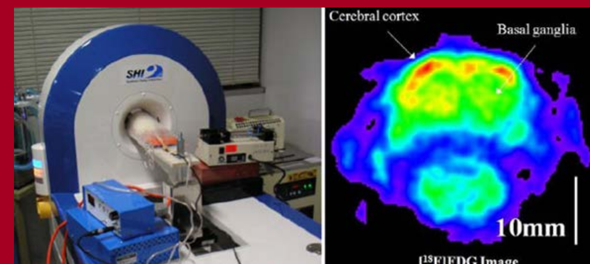
Accelerator phys.
Nuclear physics
Radiation physics

Medicine and clinic

Graduate School of Medicine



Rad. Therapy



PET and SPECT

Education for medical physicists

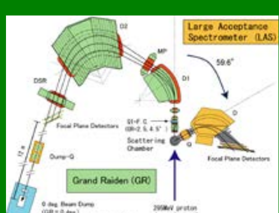
- Gantry for heavy particle therapy
- Next generation BCNT
- Compact accelerator for therapy and RI production

- Diagnostics
- Nuclear data

Molecular materials synthesized and labelled with RI

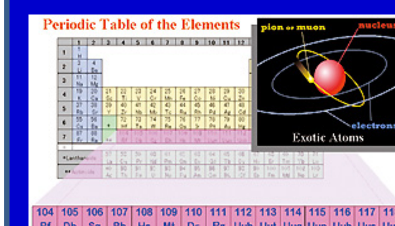
RI production

RCNP



Nuclear Physics Accelerator

Graduate School of Science



Nuclear chem. Organic Chem.

2. R&D for particle therapy

Collaboration history of a campaign to construct the particle therapy facility in Osaka

- 1995 Fundamental research on particle therapy started at RCNP.
- 2005 OPTA（大阪粒子線がん治療研究会）start-up

  [Candidate site] Osaka station north yard, Saito near RCNP、・・・

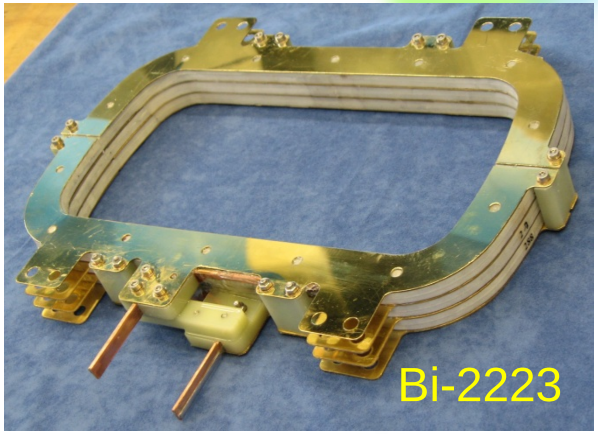
  ※Profs. Toki and Hatanaka supported the project

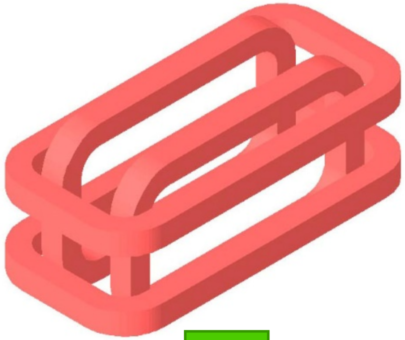
  ※Lectures for citizens, symposium, etc.

- 2006～ Development of high temperature superconducting scanning coils, bending magnets

HTS Scanning Coils

Coils	Inner size	B_x: 150 mm × 300 mm, B_y: 150 mm × 380 mm
	Cross section	30 mm × 30 mm
	Separation	70 mm
	Max. field	0.6 T
	Superconductor	Bi-2223/Ag alloy wire
	Total length	B_x: 412 m × 2, B_y: 460 m × 2
	Number of turns	420 × 2 coils for both B_x and B_y
	Winding construction	3 double pancakes/coil
	Inductance of single coil	B_x: 75mH, B_y: 92 mH
	Critical current at 77 K	40-43 A
	Rated current	200 A
	Operating temperature	20 K
Cryostat	Cooling method	Conduction cooling by two GM refrigerators
	Thermal insulation	Vacuum isolation, 80 K shield, super-insulation
	Cooling power of the GM refrigerator	45 W at 20K, 53 W at 80 K



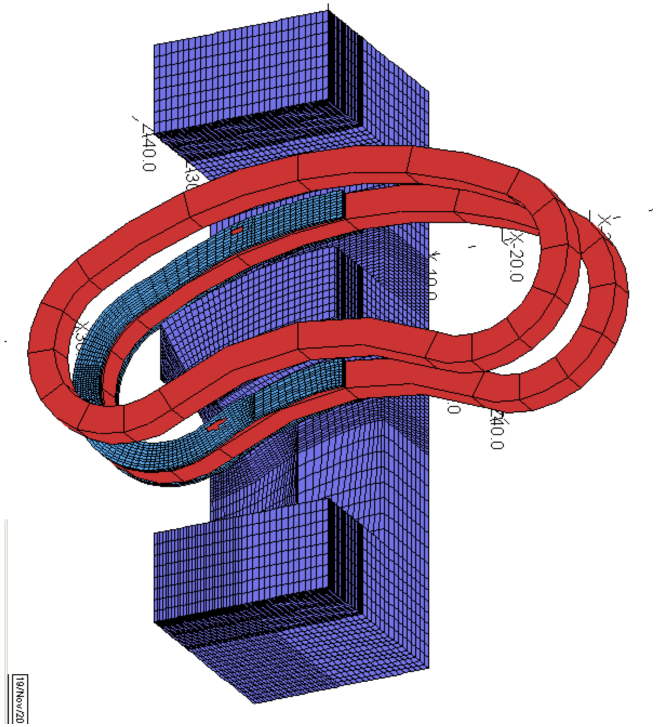


K. Hatanaka, J. Nakagawa, M. Fukuda, T. Yorita, T. Saito, Y. Sakemi, T. Kawaguchi, N. Noda, "A HTS scanning magnet and AC operation", Nucl. Instrum. Methods in Phys. Res. A, Vol.616, pp.16-20 (2010)

HTS Dipole magnet

【Parameters】
- Max. magnetic field : 3 T
- Orbit radius : 400 mm
- Deflection angle : 60 °
- Pole gap : 30 mm
- Laminated pole and yoke for AC operation

Bi-2223

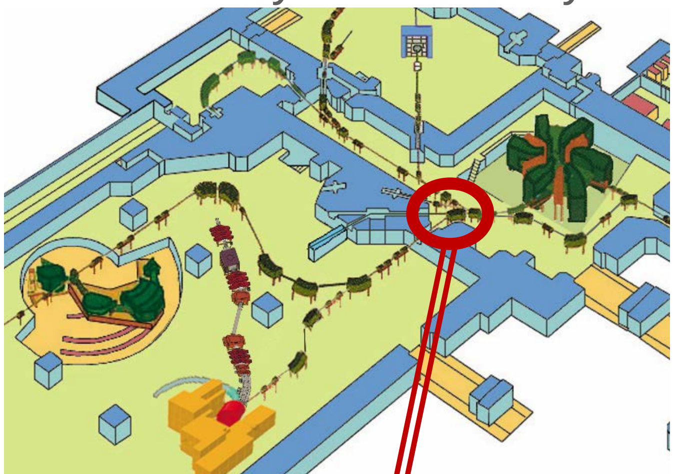


Three double-pancakes and cooling plates are stacked and fixed with epoxy resin in vacuum.

K. Hatanaka, M. Fukuda, K. Kamakura, S. Takemura, H. Ueda, Y. Yasuda, K. Yokoyama, T. Yorita, "Developments of HTS magnets at RCNP", Proceedings of Cyclotrons2013, Vancouver, BC, Canada

HTS Beam Switching magnet

RCNP cyclotron facility



HTS Wire:

- Type : SEI, DI-BSCCO TYPE Hti-CA50
- Size : W 4.6 mm × t 0.41 mm
- Ic : ≧180 A @ 77 K, self field

Double Pan Cake (DPC):

- Turn # : 64 × 2 = 128
- Size : L 920 mm × W 750 mm
- Wire length : 855 m
- Total DPC # : 4 = 2 × 2
- Operating temperature : < 20 K
- Operating current : < 200 A

3. RI production for PET/SPECT imaging and cancer therapy

Collaboration of RI production with Graduate Schools of Medicine and Science

- 2005 Fundamental research on PET started

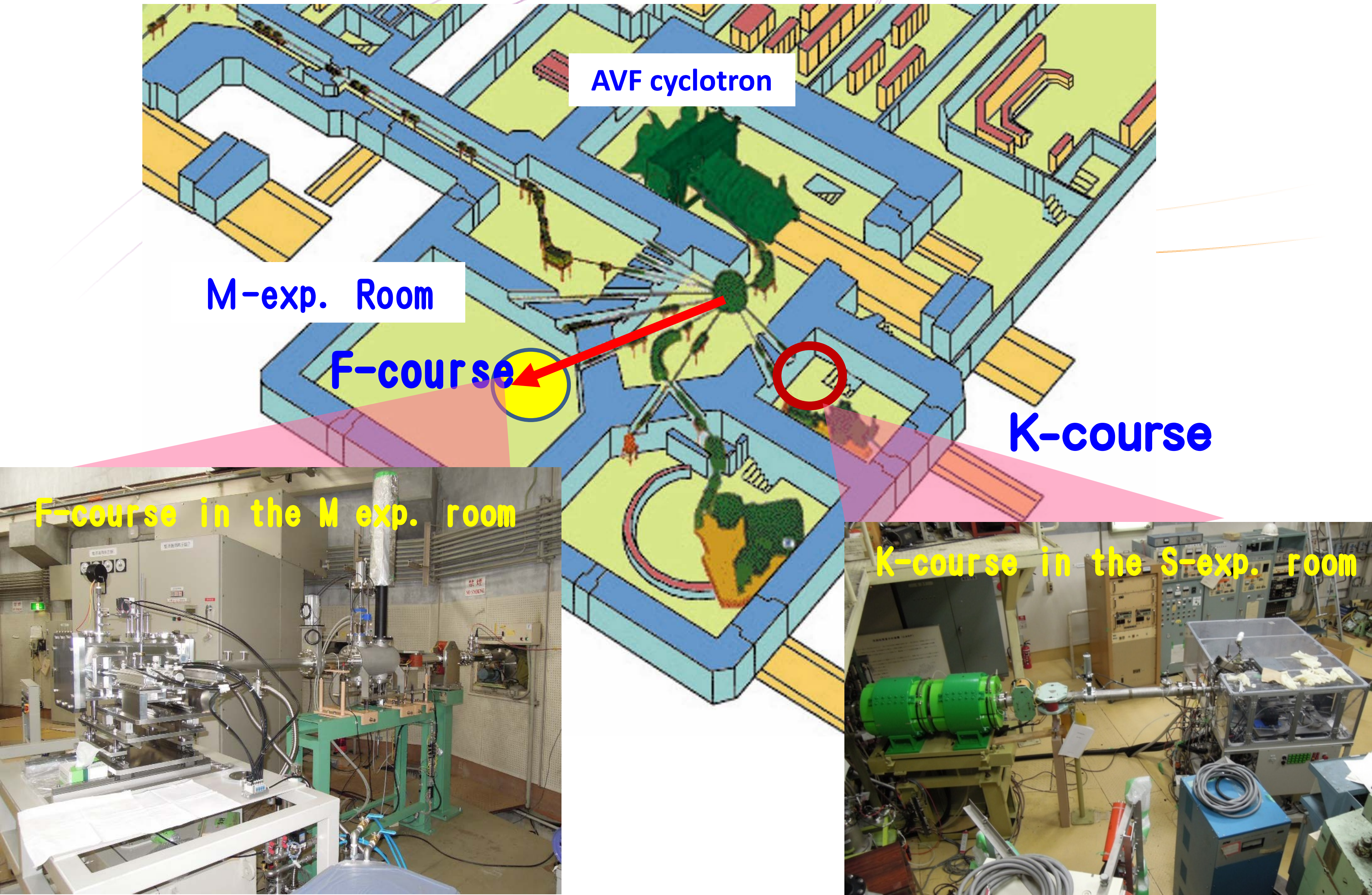
  by the collaboration among Graduate Schools of Medicine and Science, and RCNP.

  A new beam line K-course and RI production equipment was constructed in the S-exp. Room.

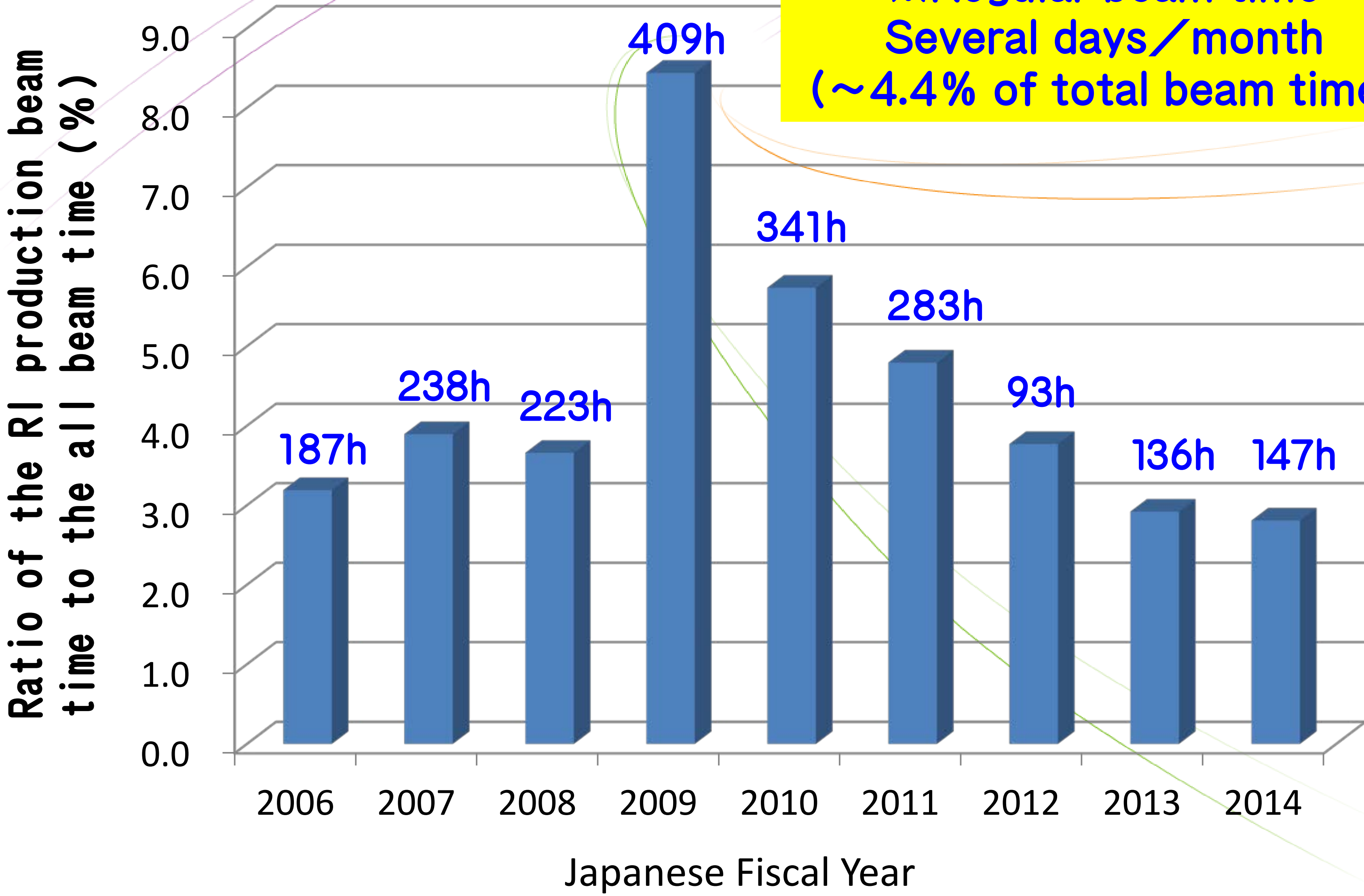
※Profs. Shinohara and Hatanaka promoted the project

- 2006 The new project for development of production of PET RI such as I-124, F-18, C-11, etc.
- 2013 A new beam line F-course for medical-use RI production was constructed in the M-exp. Room

Construction of beam lines for medical use



Annual beam time for RI production



※Regular beam time
Several days／month
(～4.4% of total beam time)

3－1. ^{99}Mo-^{99m}Tc production

Prof. Nakai (RCNP)

Prof. Takahashi (Graduate School of Science, Department of Chemistry)

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Fundamental research for ^{99}Mo-^{99m}Tc production

● RI use ratio for SPECT and PET at domestic medical institutions

SPECT: Single Photon Emission (Neutron rich)		PET: Positron Emission (Proton rich)	
^{99m}Tc	87%	^{15}O	2%
^{67}Ga	3%	^{11}C	Research
^{201}Tl	4%	^{13}N	Research
^{111}In	1%	^{18}F	98% (^{18}FDG 0.3M/year)
^{123}I	4%	^{82}Rb	Research
^{131}I	1%	^{124}I	Research
^{133}Xe	1%	^{62}Zn	Research
		^{64}Cu	Research

※87% of ^{99}Mo ($T_{1/2}$=66h) decays to ^{99m}Tc: 143 keV isomeric state of ^{99}Tc

【Serious issue】 Stable supply of RI for SPECT imaging

Radioactive medicine	Annual amount of supply（TBq）	Parent nucleus	Half life	Production method	Supply method
Tc-99m	**334**	**Mo-99**	**65.9 h**	**reactor**	**import**
Mo-99/ Tc-99m	**178**				
Tl-201	26	Tl-201	72.9 h	accelerator	domestic
I-123	24	I-123	13.3 h	accelerator	domestic
Ga-67	16	Ga-67	3.3 d	accelerator	domestic
In-111	9	In-111	8.0 d	reactor	import
Xe-133	7	Xe-133	5.2 d	reactor	import

In 2016, all the supply from Canada will be stopped due to shut down of the old reactor using highly condensed uranium fuel.

⬇

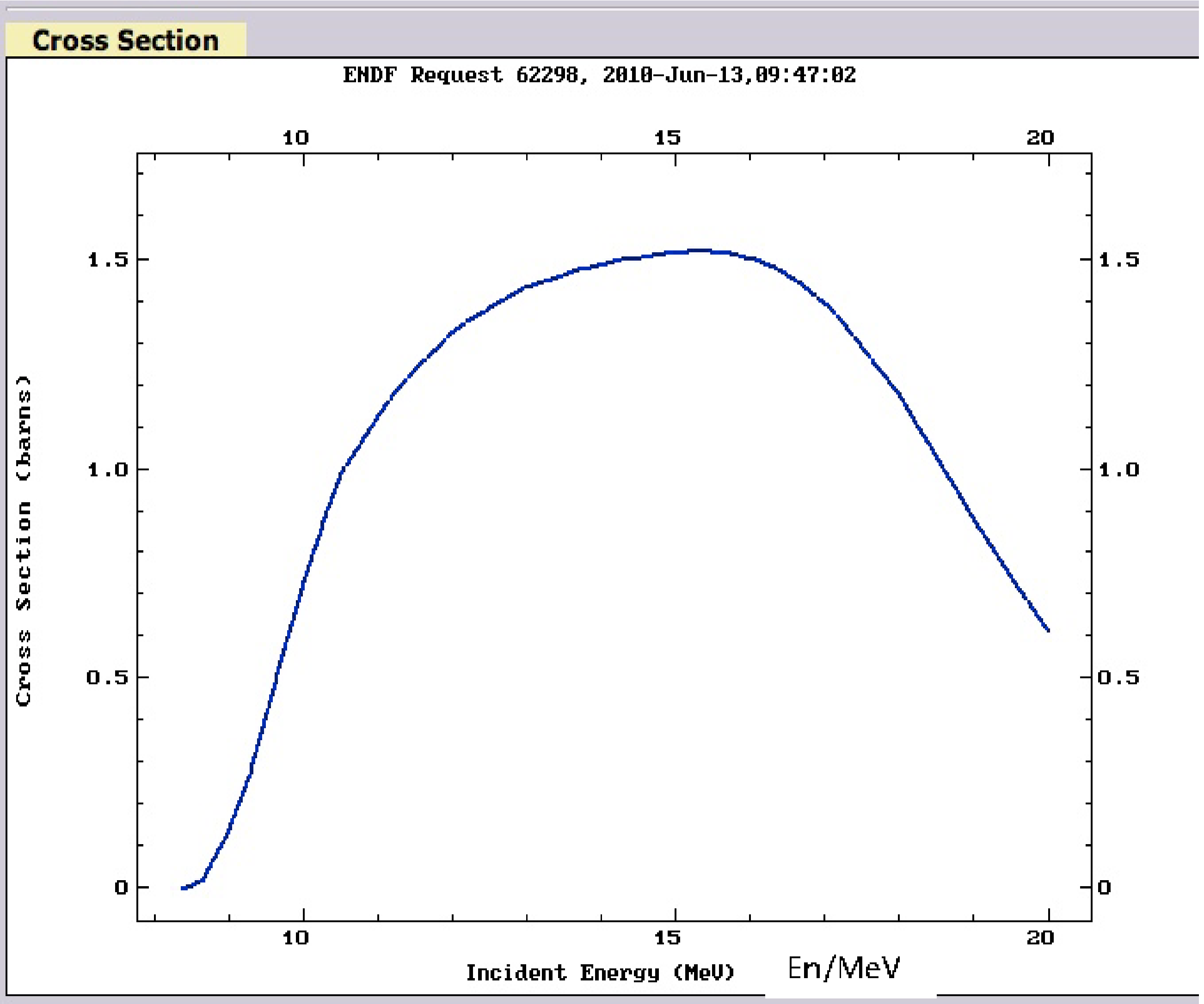
Crisis in nuclear medicine

$^{100}Mo(n,2n)^{99}Mo$ reaction

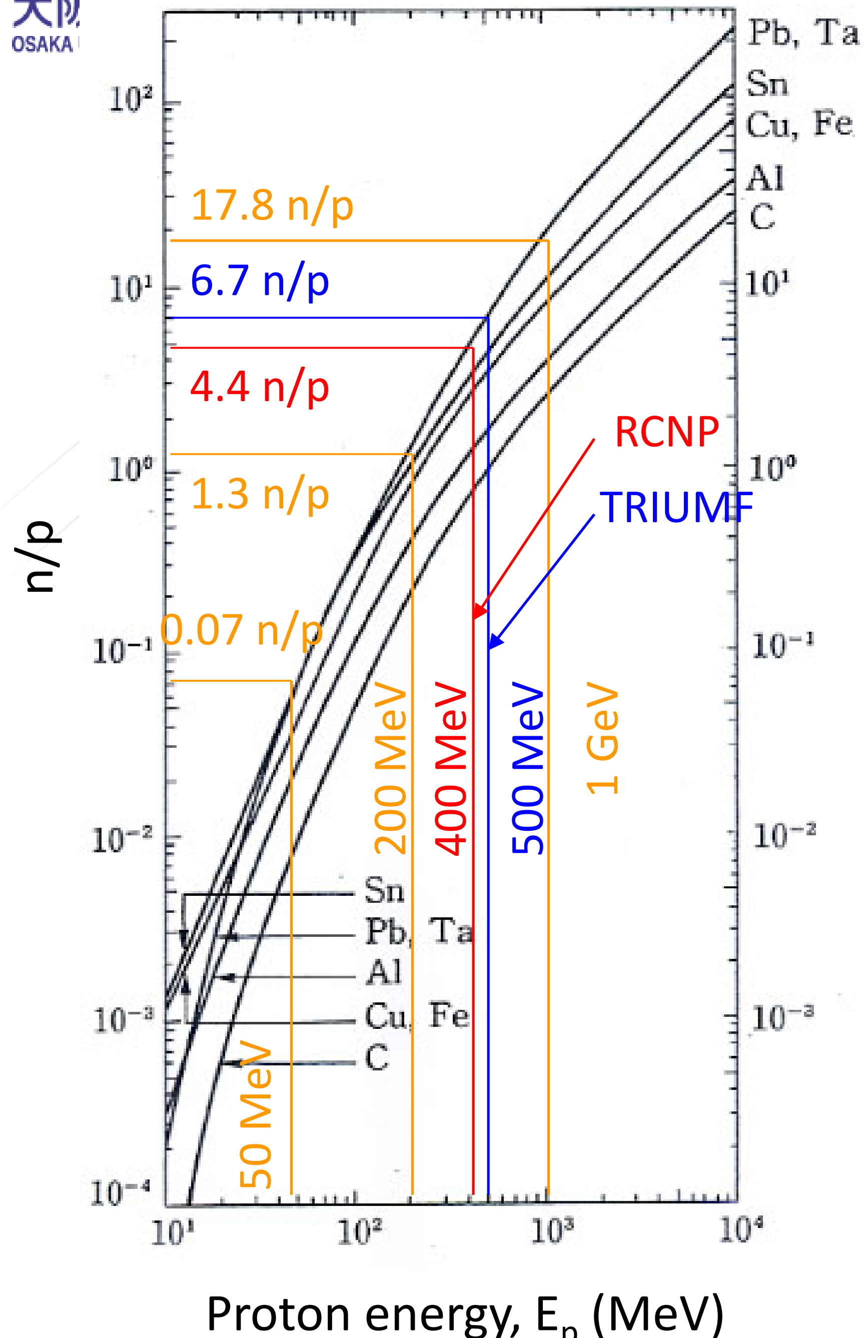
10MeV＜En＜17MeV

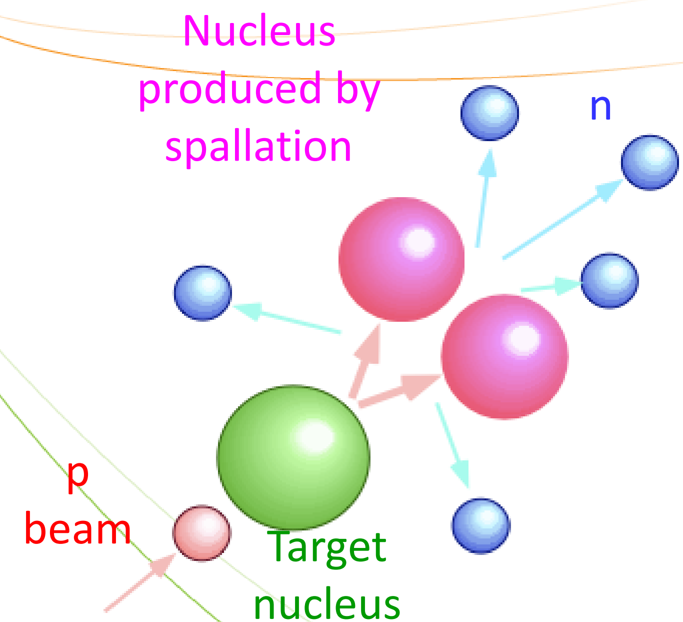
$\sigma > 1.0$ b

$\sigma_{MAX} = 1.5$ b



Neutron production





K. Tesch (1985)

^{99}Mo-^{99m}Tc production test at RCNP

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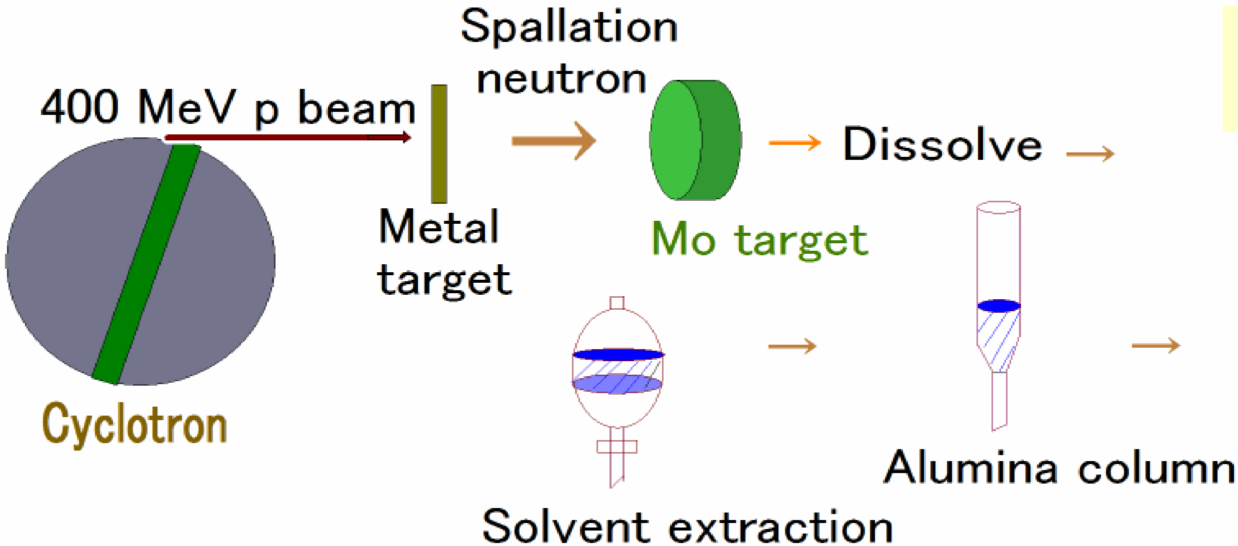
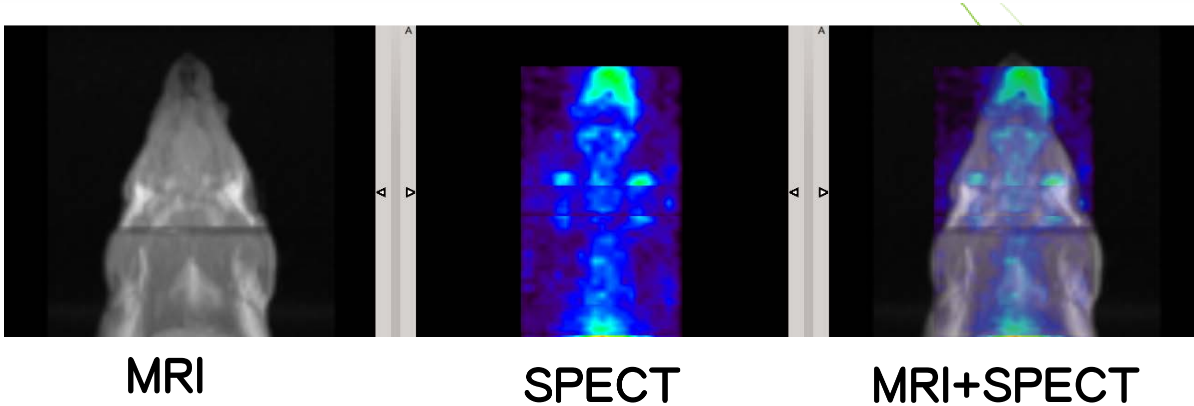
Schematic diagram for the production of ^{99m}Tc and the chemical separation

$^{100}Mo(n,2n)^{99}Mo \rightarrow {}^{99m}Tc$
$^{100}Mo(p,pn)^{99m}Tc$





Bone scintigraphy with ^{99m}Tc-MDP using rat

Production rate

^{nat}Mo 1g

↓

^{99}Mo: 3MBq/mA·h

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3－2. ^{211}At production

Prof. Hatazawa, Kaneda (G.S. Medicine)

Prof. Shinohara, Takahashi (G.S. Chemistry)

Prof. Fukase (G.S. Chemistry)

Prof. Nakano, Fukuda (RCNP)

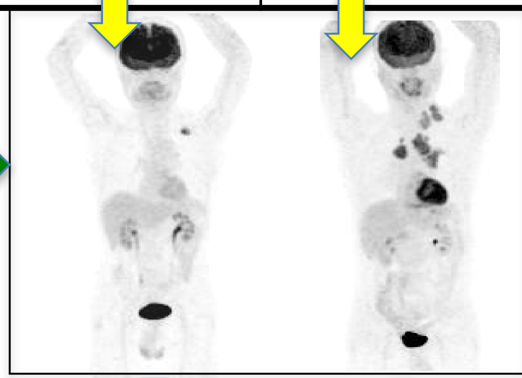
Application of targeted alpha therapy to the advanced cancer

大阪府におけるがん登録年報　第67報
（大阪府健康福祉部、大阪府医師会、大阪府成人病センター）

1/3 of cancer patients has advanced cancer at the 1st medical examination.

Ratio of cancer type at the 1st medical examination	Primary organ localization	Belonging lymph node change	Next organ permeating	Remote change
	47%	22%	12%	19%

- Removal by surgery
- Radiation therapy
- Chemotherapy
- Immunity method of treatment



- Chemotherapy
- Immunity method of treatment

5-years relative survival rate	74.5%	47.2%	17.9%	6.1%

Very low survival rate

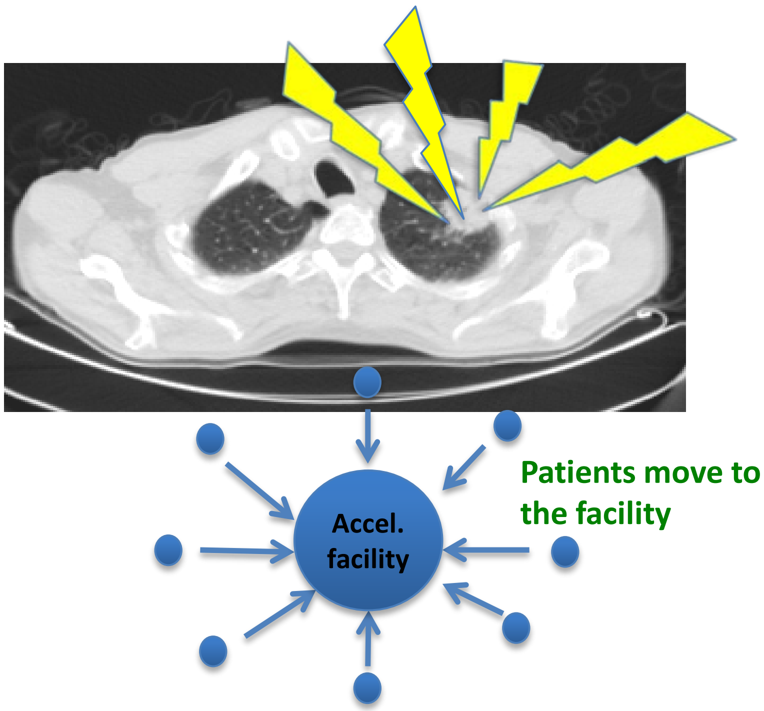
Application of the targeted alpha therapy

Difference between the heavy particle therapy and the targeted alpha therapy

Conventional heavy particle therapy:

External irradiation of heavy particles from an accelerator

- targeting the tumor from outside by suppressing the damage to normal tissues
- effective to the cancer that other radiation is useless

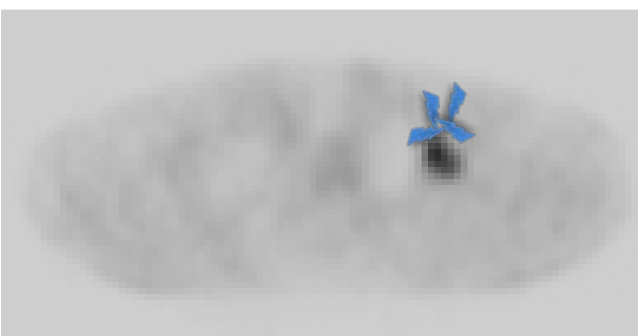


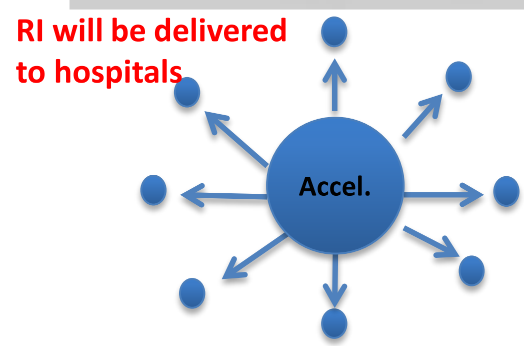
Treatment at accelerator facility

Targeted alpha therapy:

Administration of molecules labelled by alpha-emitting-RI and pinpoint irradiation of a cancer cell from inside.

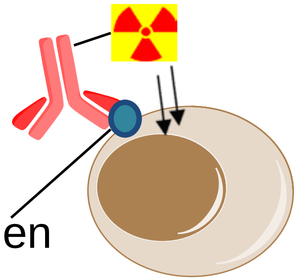
- Attacking only to cancer cells by highly efficient targeting
- smaller invasion to surrounding organ due to short range
- effective to the advanced cancer like remote change cancer





Treatment at a hospital

Targeted RI Therapy



- Utilization of targeting molecule like antibody
- Pinpoint radiation irradiation and cell-death leading

⇒ no side effect and maximization of treatment effect

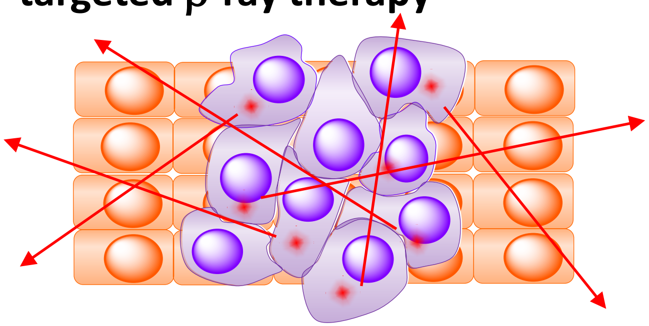
- Practically used targeted beta-ray therapy ⇒ **β-ray utilization**

- ゼヴァリン（^{90}Y-抗CD20抗体）：B細胞性非ホジキンリンパ腫
- ベキサール（^{131}I-抗CD20抗体）：B細胞性非ホジキンリンパ腫
- ^{177}Lu-DOTA-[Tyr3]-octreotide（ソマトスタチンアナログ）：神経内分泌腫瘍

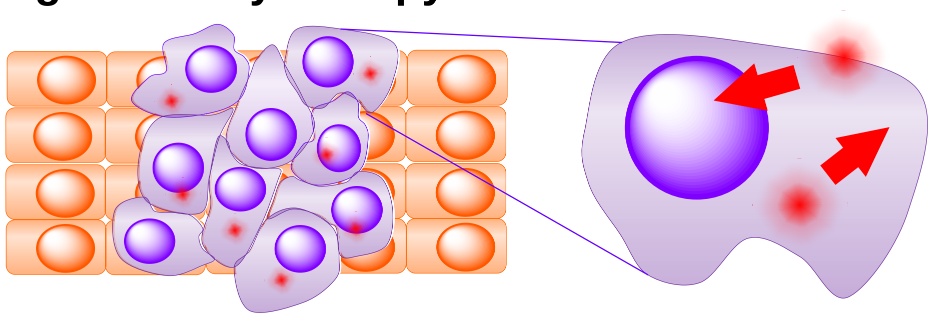
Issues: not so effective for a solid cancer, side effect caused by radiation exposure to normal tissues around the tumor

α–ray | Short range, high LET, short half life ⇒ decrease of side effect, enhanced effect

・targeted β-ray therapy



・targeted α-ray therapy



Alpha-emitter suitable for targeted therapy

Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_α mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219 Po-215 *Pb-211* Bi-211	4 s 1.8 ms *0.6 h* 130 s	4	6.59	>50
Ra-224	3.66 d	Rn-220 Po-216 *Pb-212* Bi-212	56 s 0.15 s *10.6 h* 1.01 h	4	6.62	>50
Ac-225	10.0 d	Fr-221 At-217 *Bi-213* Po-213	294 s 32 ms *0.76 h* 4 μs	4	6.88	>50

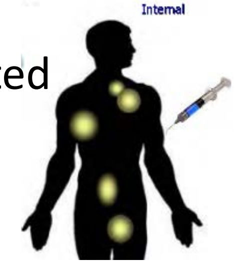
Collaboration for realizing the targeted alpha therapy at Osaka University

Graduate Schools of Science,
Department of Chemistry and Macromolecular Science,
Radioisotope Research Center

Radioactive materials synthesis technology

Certification facility for radioactive medicine

Targeted alpha therapy



Clinic
- Treatment by the targeted alpha therapy

Labeling/Synthesis
- High efficient targeting at tumor

Radio nucleus separation technology

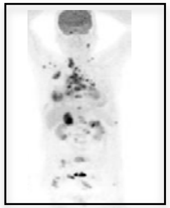
Separation
- Automatic separation system

Skeleton cyclotron

Production
- Large amount of RI production

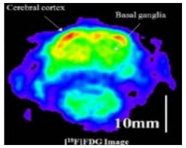
RCNP
Graduate Schools of Science, Department of Physics

Graduate Schools of Medicine



Advanced cancer

Imaging



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High intensity compact accelerator for RI production
− Air-core type HTS Skeleton Cyclotron −

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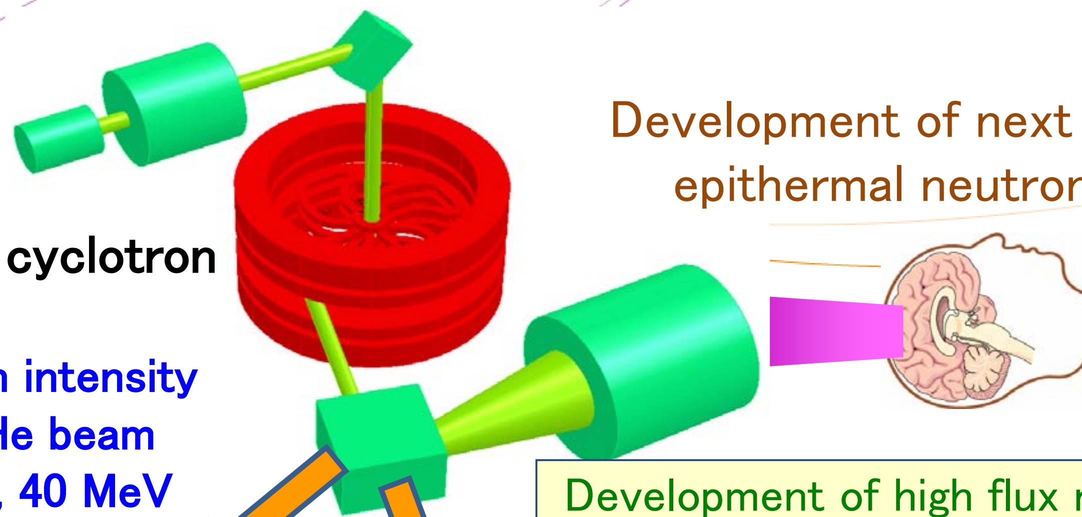


Skeleton cyclotron

High intensity
^{4}He beam
28, 40 MeV

Development of next generation epithermal neutron source

Fundamental research on BNCT

Mass product of RI in a hospital for targeted therapy
Alpha emitter : At-211

For therapy

$$^{209}Bi(\alpha,2n)\,^{211}At \qquad E_\alpha \leq 28MeV$$

$$^{209}Bi(\alpha,3n)\,^{210}At \qquad E_\alpha \geq 40MeV$$

For imaging

Development of high flux neutron source

- Spallation neutron： proton 30 MeV
- breakup reaction：deuteron 40MeV
- Inverse kinematics using heavy ions： 12C2+/3+

RI production for PET/SPECT imaging

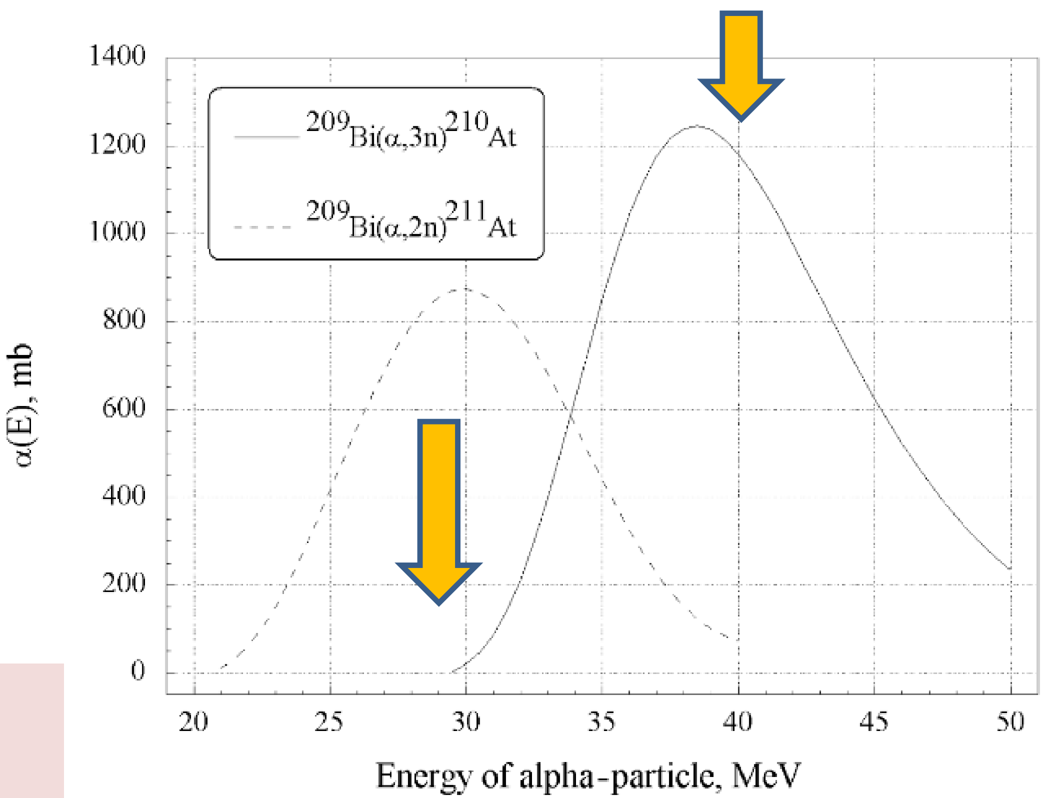
- PET（F-18, O-15, etc）： proton 18MeV
- SPECT（Mo-99/Tc-99m, etc.）： proton use→Tc-99m
  ※High purity Mo-100 is required

At-211 for targeted alpha therapy

Alpha emitter and energy

RI	$T_{1/2}$	Eα (MeV)
Tb-149	4.2 h	4.0
Bi-212	61 min	8.8
Bi-213	46 min	8.4
At-211	7.2 h	5.9, 7.5
Ra-223	11.4 d	5.8
Ra-224	3.66 d	5.8
Ac-225	10 d	5.9

- ^{210}At for SPECT imaging
  produced by $^{4}He^{2+}$ 40～50MeV
- ^{211}At for targeted α-ray therapy
  produced by $^{4}He^{+/2+}$ 28～30MeV



...the cross section data taken from the literature for the ^{209}Bi(α,2n)^{211}At and ^{209}Bi(α,3n)^{210}At reactions[6,7]

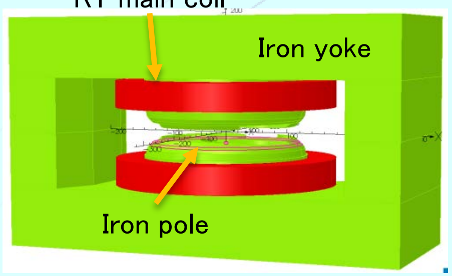
^{211}At of several tens GBq can be produced by 400～500μA, 28MeV $^{4}He^{2+}$ beam

大阪大学
OSAKA UNIVERSITY

What's Skeleton cyclotron ?

Next generation hight power compact HTS cyclotron with very low weight, low consumption power, high stability, high reproducibility, high controllability

Conventional AVF cyclotron



【Problems】

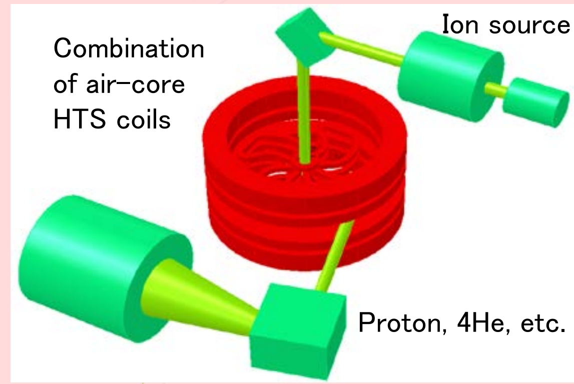
①Combination of RT coils and iron core
→ Large consumption power and low magnetic field

②Stability or beam intensity
→ sensitive to variation of the iron core temperature

③Reproducibility of operation parameters
→ depending on hysterisis

④Existence of iron pole
→ lost of special freedom
→ Beam current <100 μ A

Skeleton cyclotron



Amount of RI is proportional to the beam current.

Innovation of cyclotron technology

【Solutions】

★Adopt of HTS coils
→ ①save power (1/10) and high magnetic field
→ ②highly stable magnetic field without dependence of room temperature

★Air-core cyclotron (first trial)
→ ③good reproducibility of magnetic field, simple operation
→ ④Compact, space-saving-type, increase of freedom for equipment layout, high intensity beam increased 10 times will be available.

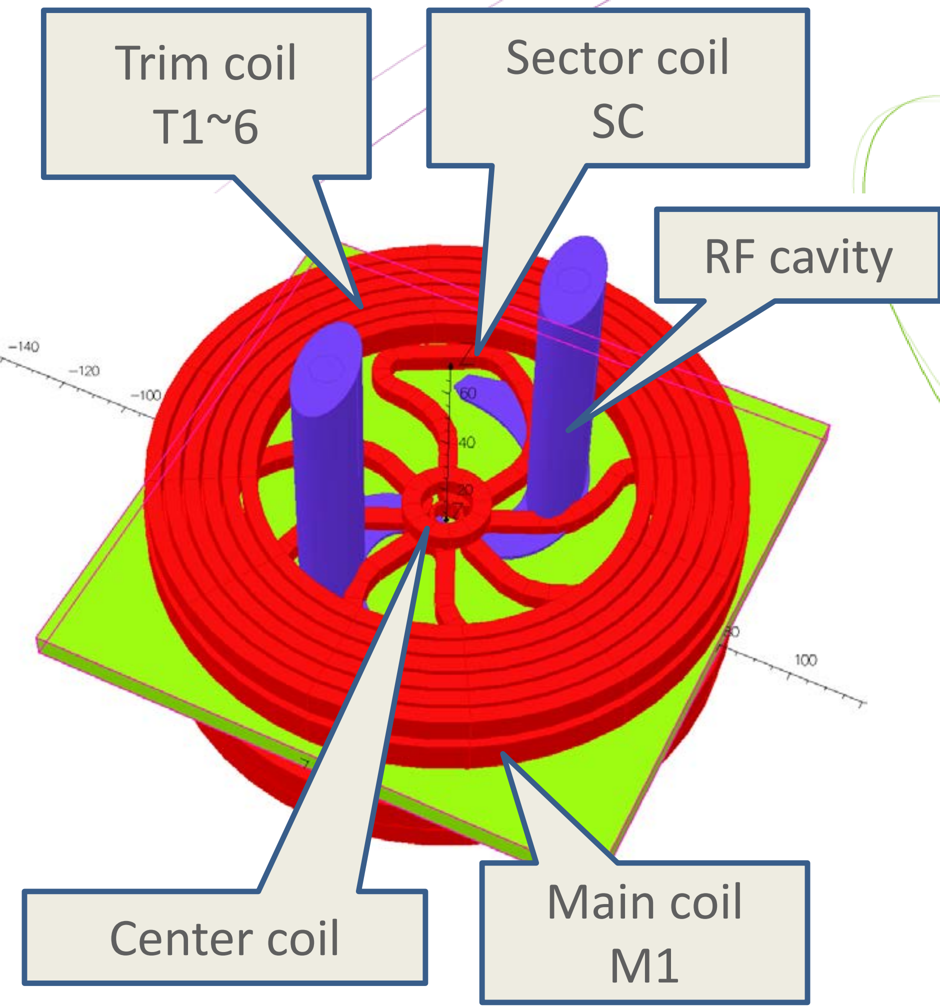
Parameters of the Skeleton cyclotron

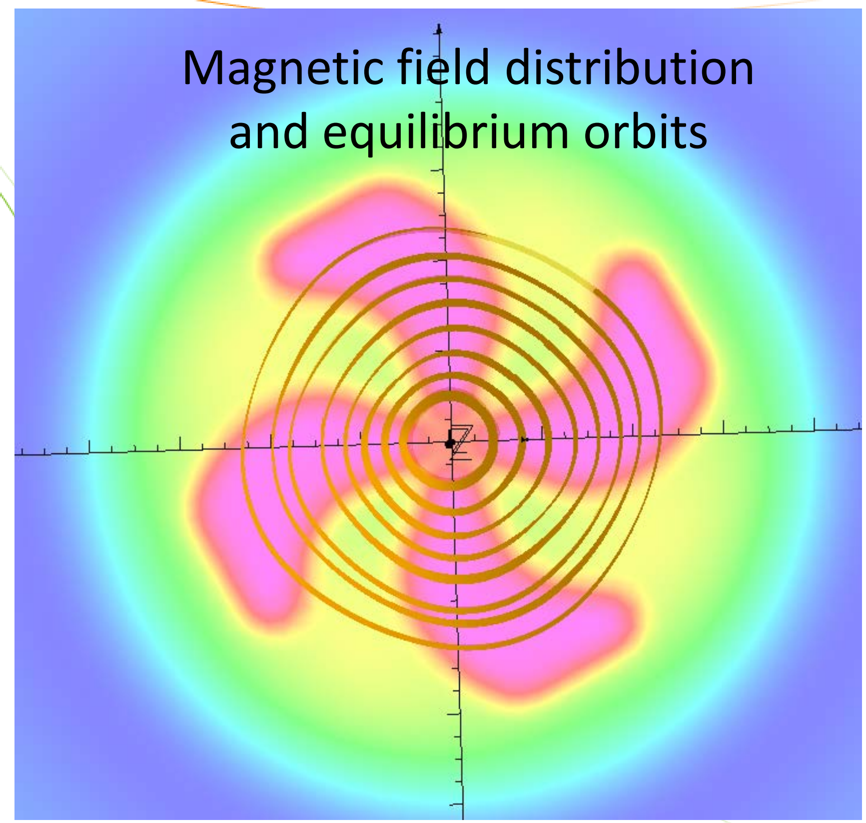
- Extraction radius : 50 cm ←compact
- max. magnetic field : 3.2 (T) ←HTS coils
- **K-number : 120 MeV**
- acceleration harmonics : 3, 5 ←36, 45° two Dee electrodes
- RF frequency : 55〜95 MHz

Ion	Energy (MeV)	B_{av} (T) @50cm	B_0 (T) @center	f_{RF} (MHz)	h	Applications
$^4He^+$	30	3.160	3.135	60.189	5	^{211}At α-therapy
$^4He^{2+}$	50	2.043	2.016	77.400	5	^{210}At γ-SPECT
$^4He^{2+}$	120	3.179	3.080	70.964	3	K-number
H^-	18	1.232	1.209	92.140	5	PET-CT, $^{225}Ac/^{213}Bi$
H^-	30	1.596	1.546	70.710	3	BNCT, ^{99}Mo-^{99m}Tc
H^+	50	2.071	1.966	89.906	3	BNCT, ^{99}Mo-^{99m}Tc
D^+／H_2^+	40	2.598	2.535	58.396	3	^{99}Mo-^{99m}Tc

Design of the Skeleton Cyclotron

※Collaboration with SHI
※Design collaboration with Waseda Univ., Hokkaido Univ., Chubu electric power co.





放射性核種の自動分離装置の開発

多量のRIによる被ばくを防ぐために自動化は必須！

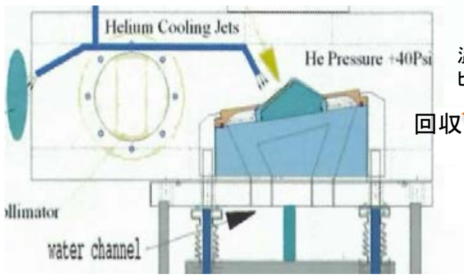
手動分離

動作原理は実証済

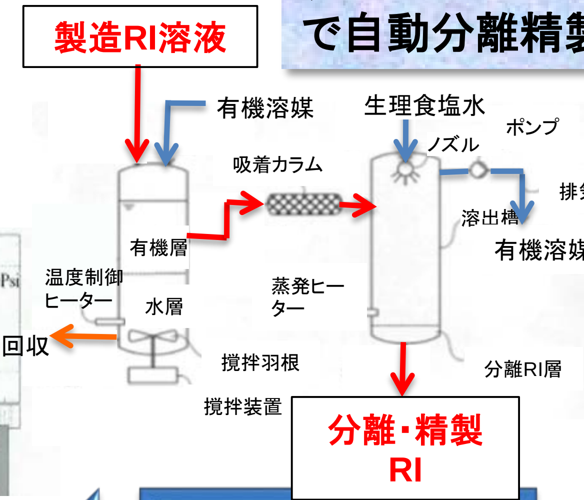
抽出分離

大強度ビームによる多量のRI製造

αビーム

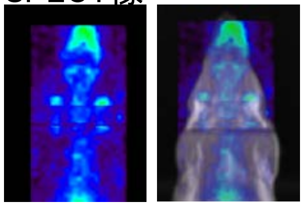


製造RIをon-lineで自動分離精製



新RI製造装置

^{99m}Tcによるラットの SPECT像



ターゲットの開発

実証

^{211}At等の自動製造

薬剤合成へ

開発

照射→分離・精製の自動化

実績２

医療用ラジオアイソトープの製造

単一光子放射断層撮影（SPECT）用
^{99}Moと^{99m}Tcの自動分離精製に成功!
PET核種^{62}Zn,^{124}Iの製造とPET撮影済

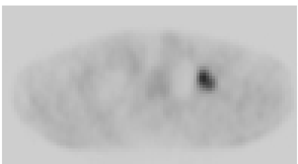
実績１

様々なα放出核の製造

アルファ線内用療法の実現に向けたターゲティング戦略と放射線医薬化

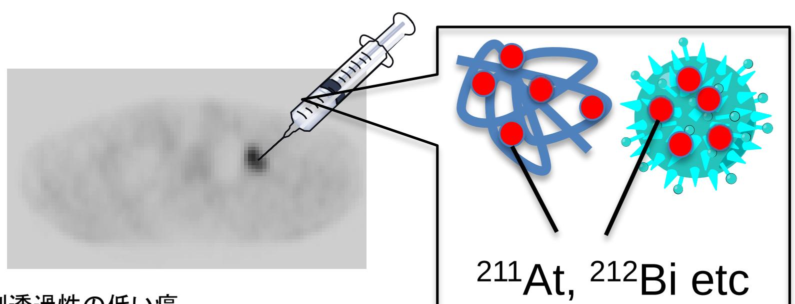
①診断と物理的ターゲティング

1. PETイメージングによるがん患部の特定



新規PET核種^{62}Zn、^{124}Iを開発、新規プローブ開発
^{68}Gaを用いた生体分子イメージング法を開発

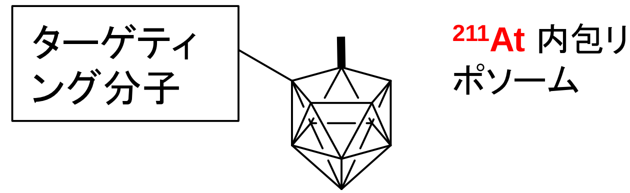
2. ウイルス様粒子等を担体とするα放出核種含有放射線医薬の腫瘍領域への仲人

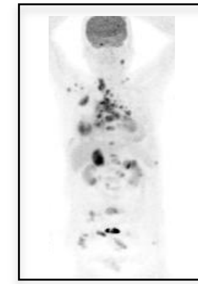


薬剤透過性の低い癌
浸潤がん、膵臓がん

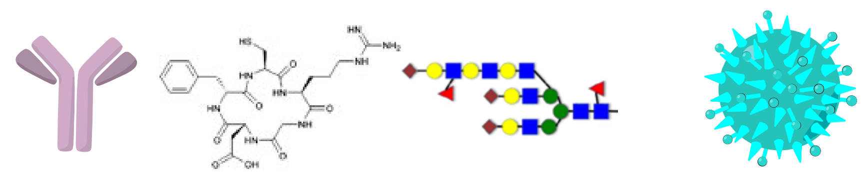
放射能比　がん組織：正常臓器=4:1を目指す

②α放出核種含有抗体（抗体によるターゲティング）





③新しいがんターゲティング分子の開発



抗体　ペプチド低分子医薬　糖鎖　ウイルス様粒子ナノメディシン

機能集積複合分子の合成

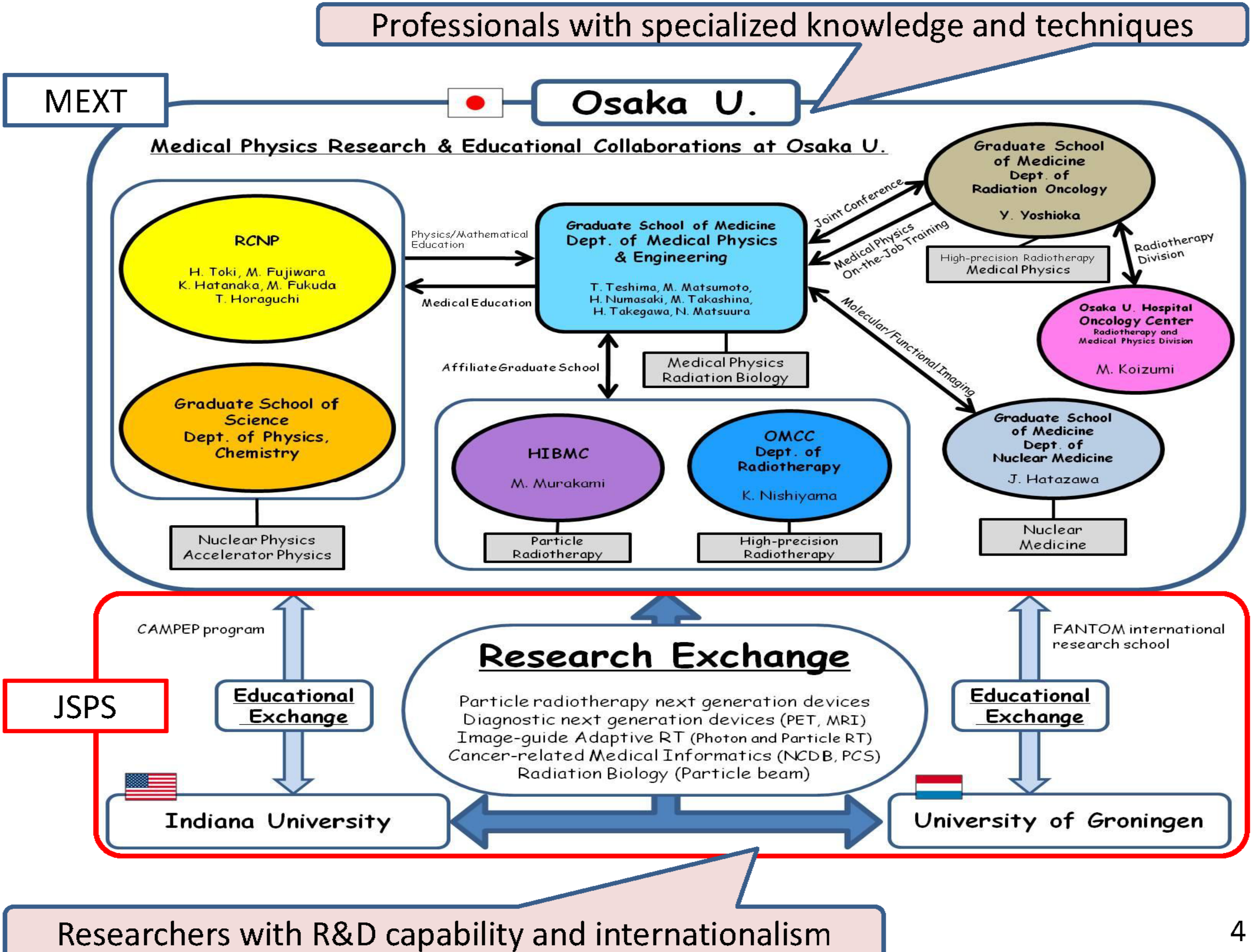
極めて簡便な生体分子複合化法を開発！
世界最先端の生体分子複合体の合成技術

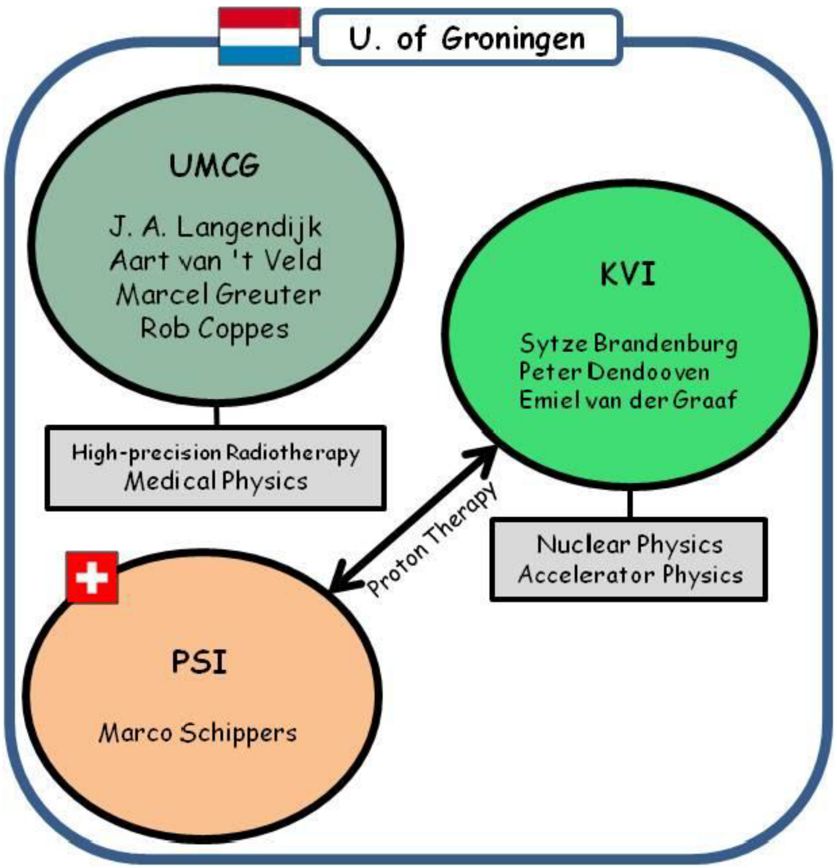
治療効果の検証、副作用の検証、周囲の被曝の有無の検証
難治性がん（転移がん、がん幹細胞、膵臓がん、肝臓がん、脳腫瘍）への適用

理学研究科
化学専攻
高分子科学専攻
医学系研究科

5. Education for medical physicists

	Japan (2009)	USA (2004)
Population (M citizens)	127.8	293.9
Radiation Oncologist	～900	～4000
Medical Physicist	～150	～4000


Professionals with specialized knowledge and techniques
MEXT
Osaka U.
Medical Physics Research & Educational Collaborations at Osaka U.
RCNP
H. Toki, M. Fujiwara
K. Hatanaka, M. Fukuda
T. Horaguchi
Graduate School of Science
Dept. of Physics, Chemistry
Nuclear Physics
Accelerator Physics
Physics/Mathematical Education
Medical Education
Graduate School of Medicine
Dept. of Medical Physics & Engineering
T. Teshima, M. Matsumoto, H. Numasaki, M. Takashina, H. Takegawa, N. Matsuura
Medical Physics
Radiation Biology
Affiliate Graduate School
HIBMC
M. Murakami
Particle Radiotherapy
OMCC
Dept. of Radiotherapy
K. Nishiyama
High-precision Radiotherapy
Joint Conference
Medical Physics
On-the-Job Training
Graduate School of Medicine
Dept. of Radiation Oncology
Y. Yoshioka
High-precision Radiotherapy
Medical Physics
Radiotherapy Division
Osaka U. Hospital Oncology Center
Radiotherapy and Medical Physics Division
M. Koizumi
Molecular/Functional Imaging
Graduate School of Medicine
Dept. of Nuclear Medicine
J. Hatazawa
Nuclear Medicine
JSPS
CAMPEP program
Educational Exchange
Research Exchange
Particle radiotherapy next generation devices
Diagnostic next generation devices (PET, MRI)
Image-guide Adaptive RT (Photon and Particle RT)
Cancer-related Medical Informatics (NCDB, PCS)
Radiation Biology (Particle beam)
FANTOM international research school
Educational Exchange
Indiana University
University of Groningen
Researchers with R&D capability and internationalism



- The UMCG and KVI are setting up the Particle Therapy Research Center (PARTEC).

  The first particle therapy center in the Netherlands

- The first PET camera was developed at KVI in the world.

  (leading institution of the development of innovative imaging technology in the world)

- FANTOM International Research School

  → Educational program for scientific trainee researchers of nuclear and atomic physics

- Agreement

  between universities (2002-), and between departments (RCNP and School of Medicine)

  Osaka U. Groningen Center has been established since 2005.

- Expected Matching Fund

  ESF: Research Networking Programes

  NWO : Cooperation Japan

5. Summary

● Status of cooperation among Graduate Schools of Medicine and Science, RCNP

- Regular beam time for RI production: ～4% of total
- Fundamental research on production of alpha emitting RI for targeted therapy
- ^{4}He ion beam for production of At-211

  Beam current ≦ 6 pμA → 37MBq／patient／day
- New beam line for medical-use RI production
- Fundamental research on BNCT
- collaboration for educating students of medical physics course