REVIEW OF CYCLOTRONS USED IN THE PRODUCTION OF RADIO-ISOTOPES FOR BIOMEDICAL APPLICATIONS

P W SCHMOR
AAPS INC.
TRIUMF

Historical Perspective

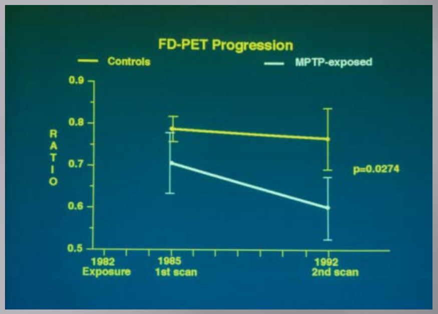
- 1931 Lawrence demonstrates first Cyclotron
- 1936 Lawrence produces ^{32}P for injection to patient with leukemia
- 1941 Washington University, St. Louis, USA installs first cyclotron for medical isotope production
- 1955 Hammersmith Hospital, London, UK begin operation of first cyclotron wholly dedicated to medical isotope production
- 1961 Scanditronix is founded

Uses of Cyclotron Produced Isotopes

- *Medicine (Diagnostics and Therapy)*
- *Agriculture (Tracers for bio-kinetics in plants and soil)*
- *Biology (Tracers for bio-chemical and toxicological studies)*
- *Ecology (pollution, environmental impact studies)*
- *Geology (migration of elements in soils and waters)*
- *Pharmacology (metabolic studies)*

Life Sciences Examples (TRIUMF/UBC)

PET Program

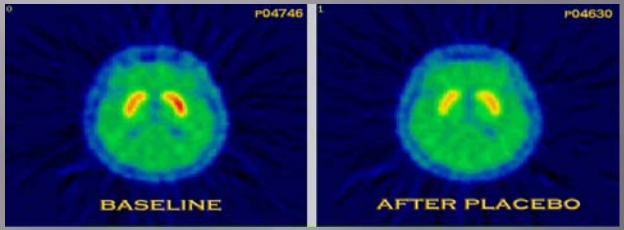


Preclinical changes
Progression

TR13

Botany (^{13}N)

Barley

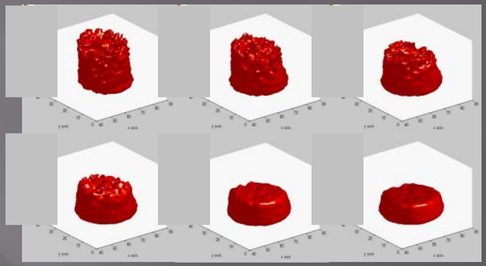


Placebo
measured

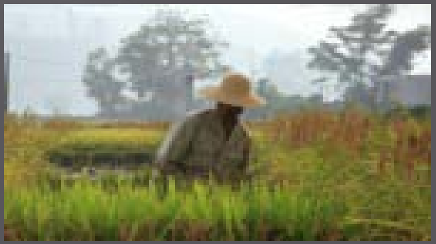
Old growth forest

^{18}F-fibers

PET
scan



Pulp & Paper



Protein content of rice

Primary Uses of Cyclotron Produced Radio Isotopes for Medicine

- *Diagnostics*
  - *PET/CT (Positron Emission Tomography)*
    - *Short-lived positron emitters*
    - ^{11}C, ^{13}N, ^{15}O and ^{18}F
  - *SPECT (Single Photon Emission Computed Tomography)*
    - *Medium Half-Lives*
    - *Single photon emitters*
- *Therapy*

  Isotopes with longer lives that form molecules that preferentially attach to tumour sites

  Decay products have high linear-energy transfer

Generalized Cyclotron Specifications for Producing Medical Radioisotopes

- *Cyclotrons for PET/CT Radionuclides*
  - *Energies < 20 MeV*
  - *Currents $\approx 50\ \mu$A per target*
  - *Located near user*
- *Cyclotrons for SPECT Radionuclides*
  - *Energies ≈ 20 MeV to 35 MeV*
  - *Currents $\approx 500\ \mu$A to 1.5 mA*
  - *Half lives permit distant delivery*
- *Cyclotrons for Therapeutic Radionuclides*
  - *Energies ≈ 35 MeV to 70 MeV*
  - *Currents $\geq 500\ \mu$A*
  - *Half lives permit distant delivery*

Cyclotrons Producing Medical Radio Isotopes

- > 600 world wide in 2006
- > 850 predicted by 2012
- Sales about 50/year

TABLE 2.1 Procedures per Medicare Fee-for-Service Beneficiary, by Imaging Modality

	2000	2005	Average Annual Growth Rate (%)	Share of All Imaging (%) 2000	Share of All Imaging (%) 2005
All	3.83	4.99	5	100	100
CT	0.35	0.57	11	9	10
MRI	0.10	0.19	13	3	3
Nuclear Medicine					
Non-PET	0.21	0.33	9	5	6
PET and PET/CT	0.00	0.01	80	0.02	0.05
Ultrasound	0.84	1.14	6	22	22
Interventional	0.17	0.26	8	5	5
Mammography	0.21	0.33	9	6	6
X-ray, excluding mammography	1.94	2.14	2	51	49
Other	0.01	0.03	37	0.2	0.2

SOURCE: Data from American College of Radiology Research Department.

Advancing Nuclear Medicine Through Innovation
http://www.nap.edu/catalog/11985.html

Nuclear Medicine USA Growth

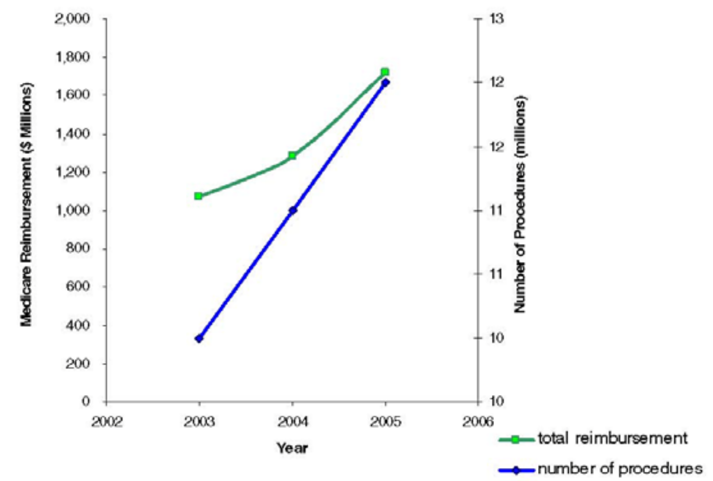


FIGURE 2.1 Number of nuclear medicine procedures that were approved for reimbursement by the Center for Medicare and Medicaid Services and total reimbursement for 2003–2005. SOURCE: Data provided by CMS.

AAPS Advanced Applied Physics Solutions ETPP Exploitation des Techniques de Pointe en Physique

Medical Isotope Cyclotrons Worldwide (from IAEA-DCRP/2006)

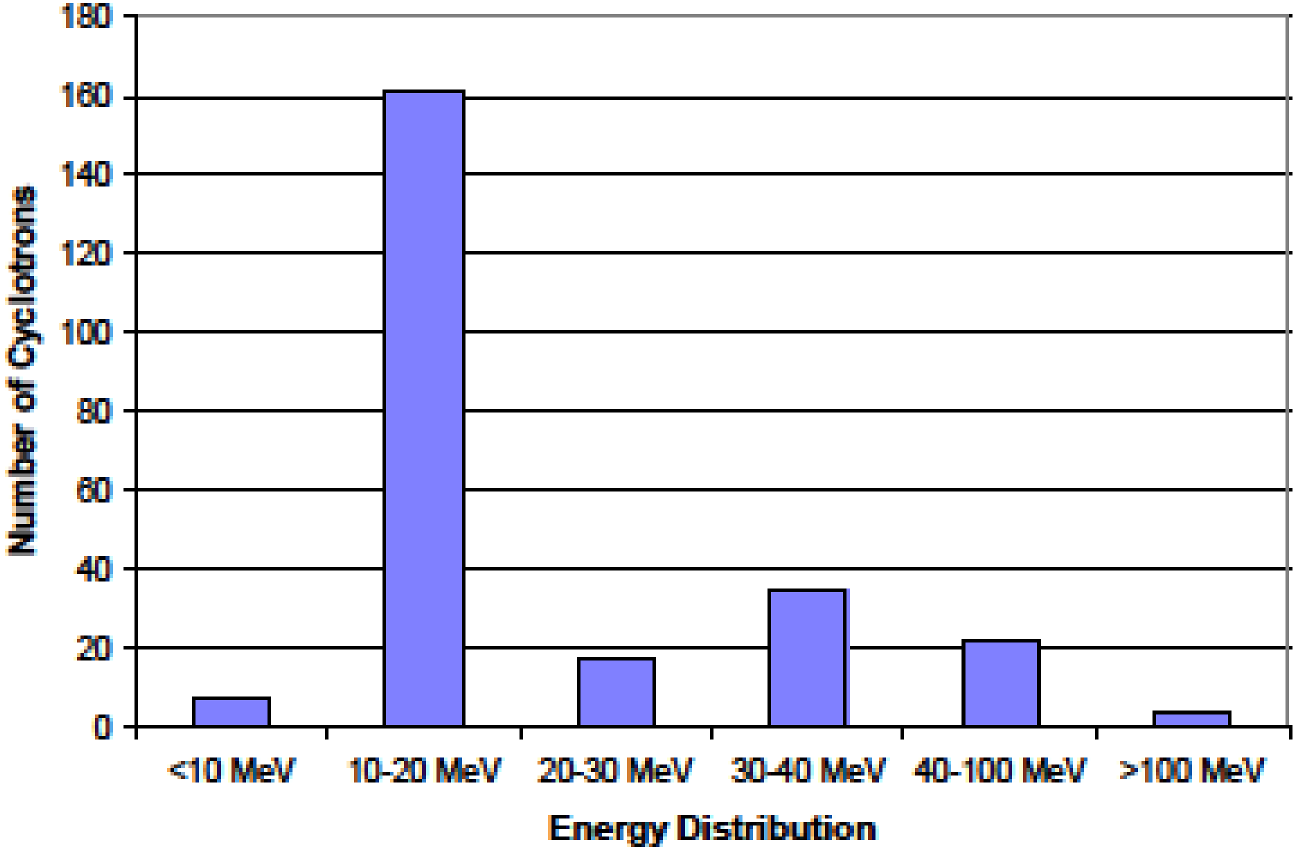


FIG. 1. Distribution of proton energies as reported by respondents to the IAEA survey.

Cyclotron PET Compounds
(from IAEA-DCRP/2006)

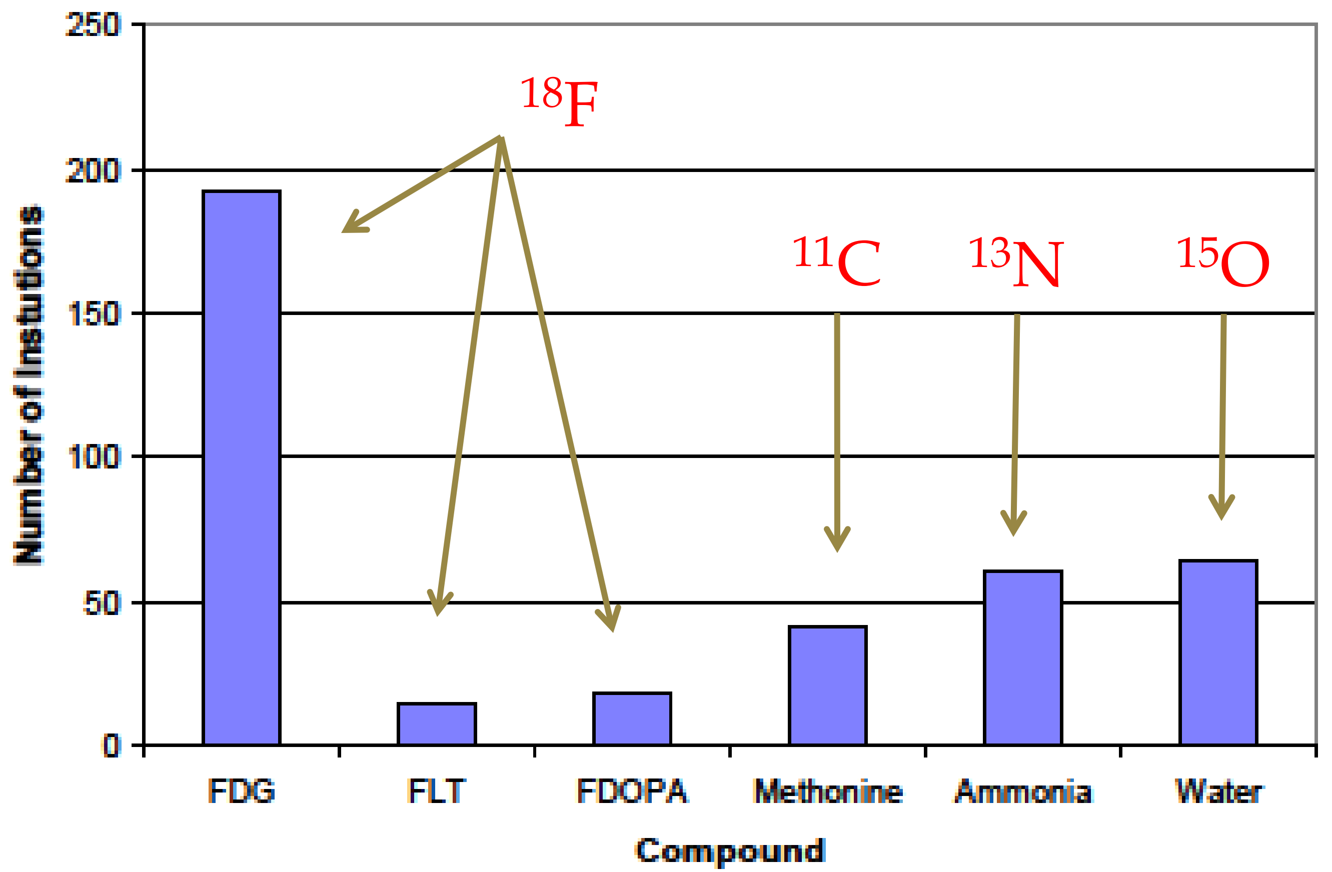
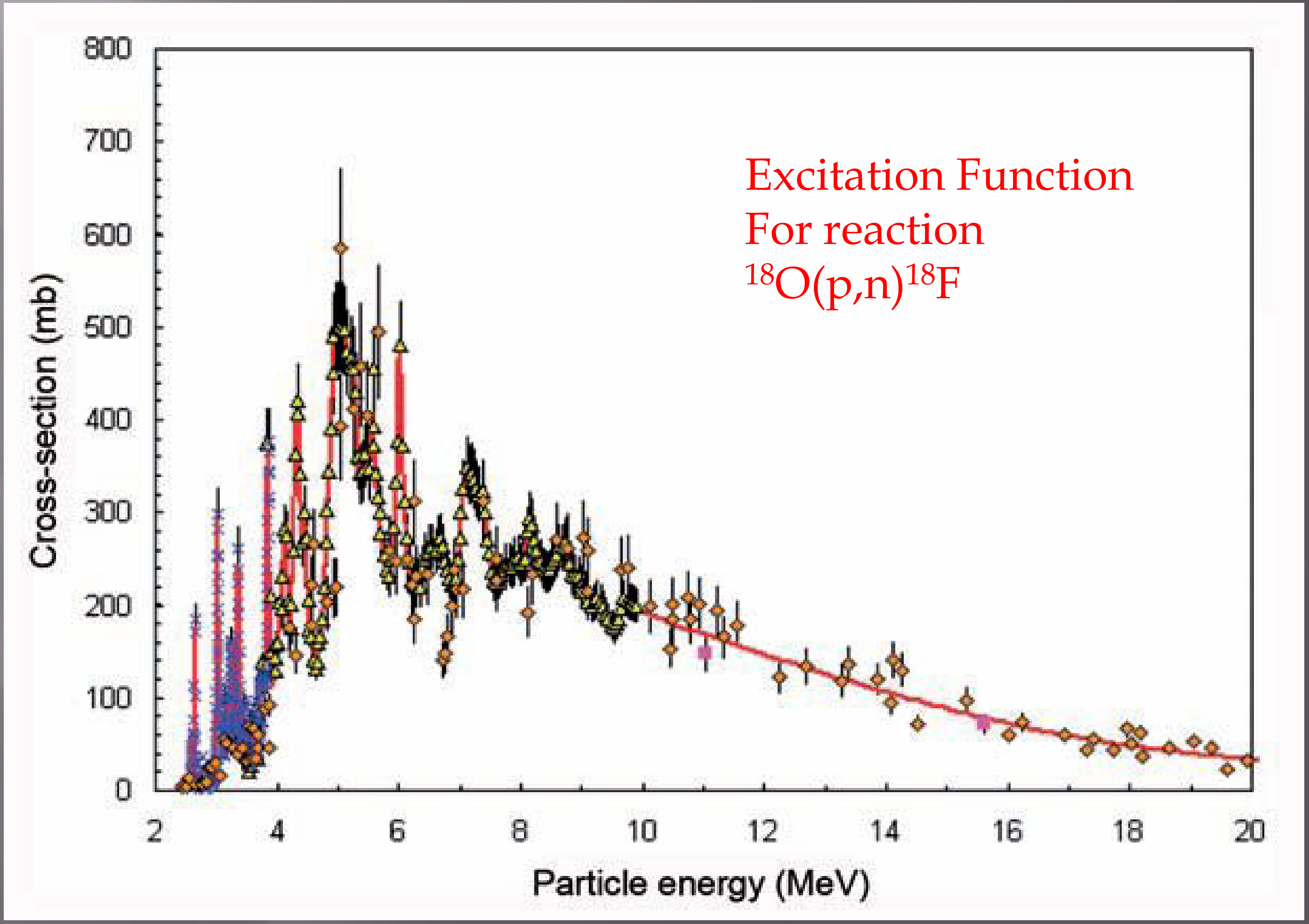


FIG. 3. Number of reporting institutions that use a particular compound.

AAPS Advanced Applied Physics Solutions ETPP Exploitation des Techniques de Pointe en Physique

Nuclear Reactions used for Production of Radionuclides

- *(p,n)*
- *(p,2n)*
- *(p,a)*
- *(p,xn)*
- *(d,n)*
- *(d,2n)*
- *(α,n)*



AAPS Advanced Applied Physics Solutions ETPP Exploitation des Techniques de Pointe en Physique

Selected Medical Radioisotopes, some of their properties, possible nuclear reactions, and yields.

From

T. J. Ruth et al Nucl. Med. Biol. Vol 16, No. 4, pp. 323 – 336 (1989)

Medical Isotope	Lifetime $T_{1/2}$	Use	Nuclear Reaction	Target Abundance (%)	Energy Range (MeV)	Production Yield (mCi @ sat)	Typical Dose (mCi)
^{11}C	20.4m	PET	^{11}B(p,n)	80.3	8 - 20	40/µA	
^{11}C	20.4m	PET	^{14}N(p,α)	99.6	12	100/µA	
^{11}C	20.4m	PET	^{10}B(d,n)	19.7	7	10/µA	
^{13}N	9.96m	PET	^{13}C(p,n)	1.1	5 - 10	115/µA	
^{13}N	9.96m	PET	^{12}C(d,n)	98.9	2 - 6	50/µA	
^{13}N	9.96m	PET	^{16}O(p,α)	99.8	8 - 18	65/µA	
^{15}O	2m	PET	^{15}N(p,n)	0.36	10 - 15	47/µA	
^{15}O	2m	PET	^{16}O(p,pn)	99.8	>26	25/µA	
^{15}O	2m	PET	^{14}N(d,n)	99.6	8 - 6	27/µA	
^{18}F	109.8m	PET	^{18}O(p,n)	0.20	8 - 17	180/µA	5 - 20
^{18}F	109.8m	PET	^{20}Ne(d,α)	90.5		82/µA	
^{64}Cu	12.7h	SPECT	^{64}Ni(p,n)	0.93	5 - 20	5/µA	
^{67}Cu	61.9h	SPECT	^{68}Zn(p,2p)	19.0	>40	0.02/µA	
^{67}Ga	78.3h	SPECT	^{68}Zn(p,2n)	19.0	20 – 40	4.5/µA	10
^{82}Sr/^{82m}Rb	25d/5m	PET	^{85}Rb(p,4n)^{82}Sr Produces Rb	72.2	50 -70	0.18 /µAh	
^{99m}Tc	6h	SPECT	^{100}Mo(p,2n)	9.7	19	14/µAh	20
^{103}Pd	17.5d	Therapy	^{103}Rh(p,n)	100	10 -15	0.52/µAh	
^{111}In	67.2h	SPECT	^{112}Cd(p,2n)	24.1	18 - 30	6/µAh	3
^{123}I	13.2h	SPECT	^{124}Xe(p,2n)^{123}Cs →^{123}Xe→^{123}I	0.10	25 - 35	27/µAh	
^{123}I	13.2h	SPECT	^{123}Te(d,2n) ^{123}I	0.89	10 - 15	20/µAh	
^{124}I	4.1d	PET	^{124}Te(p,n)	4.7	10 - 18	0.1/µAh	
^{124}I	4.1d	PET	^{124}Te(d,2n)	4.7	>20	0.15/µAh	
^{186}Re	90.6h	Therapy /SPECT	^{186}W(p,n)	28.4	18		
^{201}Tl	73.5h	SPECT	^{203}Tl(p,3n)^{201}Pb →^{201}Tl	29.5	27 - 35	0.7/µAh	4
^{211}At	7.2h	Therapy	^{209}Bi(α,n)	100	28	1/µAh	0.05-.01

Medical Isotopes of Interest

- PET
  - ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{82}Rb (from ^{92}Sr parent)
- SPECT
  - ^{99m}Tc, ^{57}Co, ^{67}Ga, ^{111}In, ^{123}I, ^{81m}Kr, ^{201}Tl
- Therapy
  - ^{77}Br, ^{103}Pd, ^{186}Re, ^{211}At

CYCLOTRON PROVIDERS

- **Currently**
  - *Advanced Cyclotron Systems Inc (ASCI)*
  - *Advanced Biomarkers Technology (ABT)*
  - *Best Cyclotrons Systems Inc (BSCI)*
  - *China Institute of Atomic Energy (CIAE)*
  - *Efremov (NIIEFA)*
  - *EuroMeV*
  - *GE Healthcare*
  - *IBA*
  - *KIRAMS*
  - *Siemens*
  - *Sumitomo*
- **Previously**
  - *Scanditronix (MC series cyclotrons)*
  - *The Cyclotron Corporation (TCC/CP series cyclotrons)*
  - *Japan Steel Works (JSW/BC series cyclotrons)*
  - *Computer Technology and Imaging Inc (CTI with their CTI-RDS, Radio Isotope Delivery System cyclotrons)*
- **Others**
  - *PSI Injector*
  - *TRIUMF*

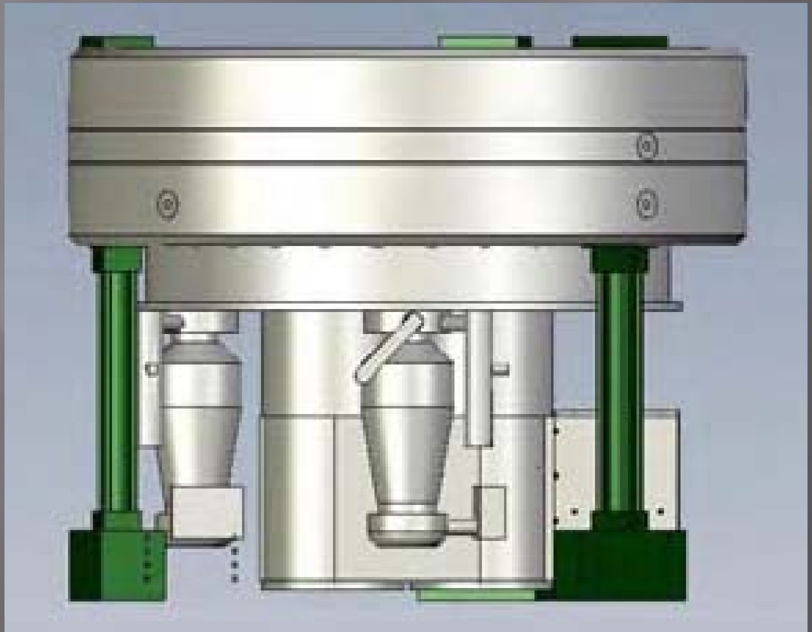
Advanced Cyclotron Systems Inc ASCI

- Cyclotron models
  - TR14 (H-, 14 MeV, self-shielded option)
  - TR18/9 (H-/D- , fixed energy)
  - TR19 (H-, fixed or variable energy)
  - TR24 (H-, variable energy, 15 – 24 MeV)
  - TR30 (H- variable energy, 15 – 30 MeV, I ≤ 1.2 mA)
  - TR30/15 (H-/D-, Variable energy, 15 – 30 /7.5 – 15 , I ≤ 1.2 mA)

AAPS Advanced Applied Physics Solutions · ETPP Exploitation des Techniques de Pointe en Physique

Advanced Biomarkers Technology Inc (ABT)

- NEW - 'Table-top' Cyclotron
  - 7.5 MeV, fixed-energy, self-shielded
  - 1-5 μA, internal targets & self-shielded
  - Produces 'single-dose' on demand
  - Weight = 11 ton [Cyclotron weight = 3.2 ton]

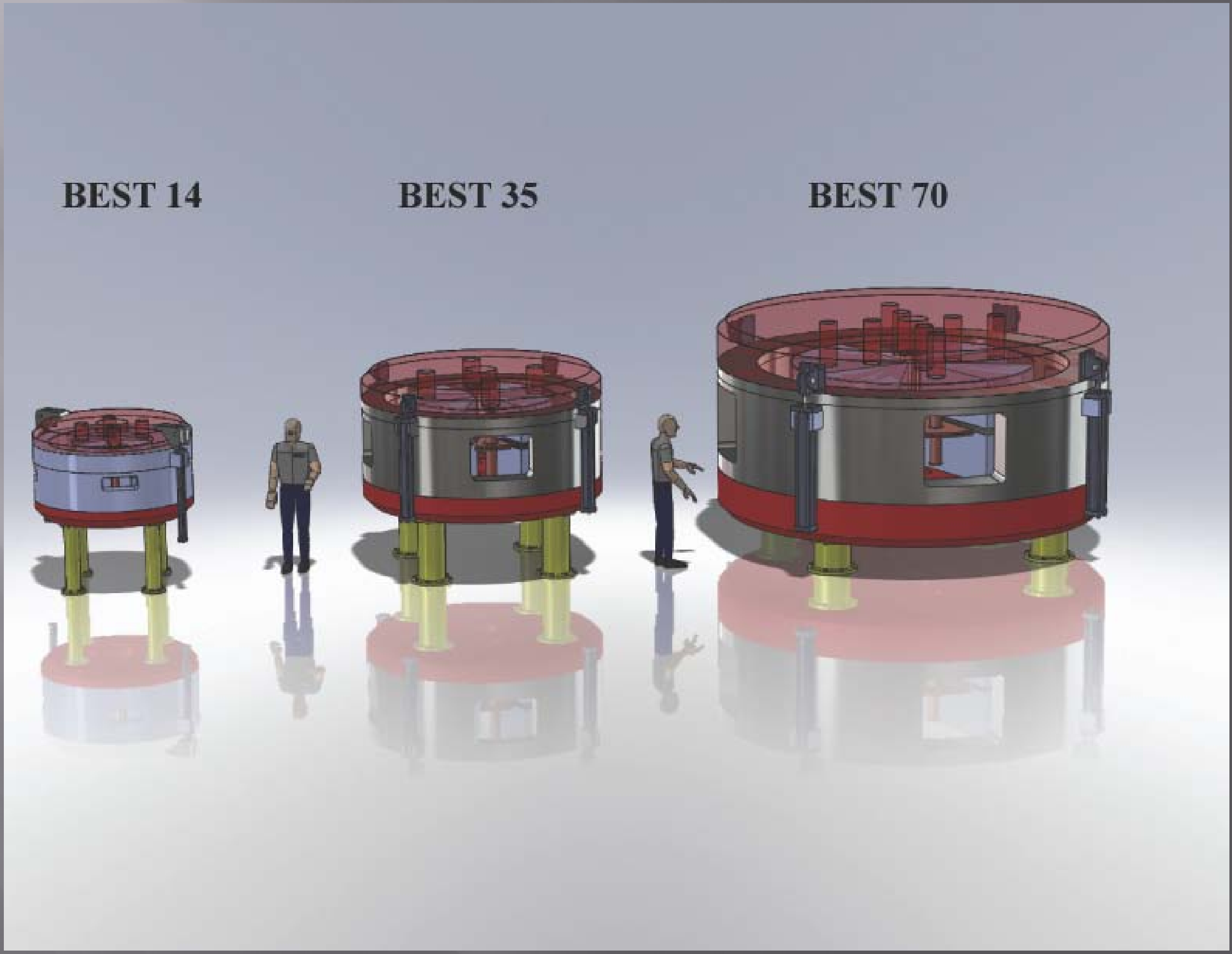


AAPS Advanced Applied Physics Solutions
ETPP Exploitation des Techniques de Pointe en Physique

Best Cyclotron Systems, Inc [poster MOPC017]

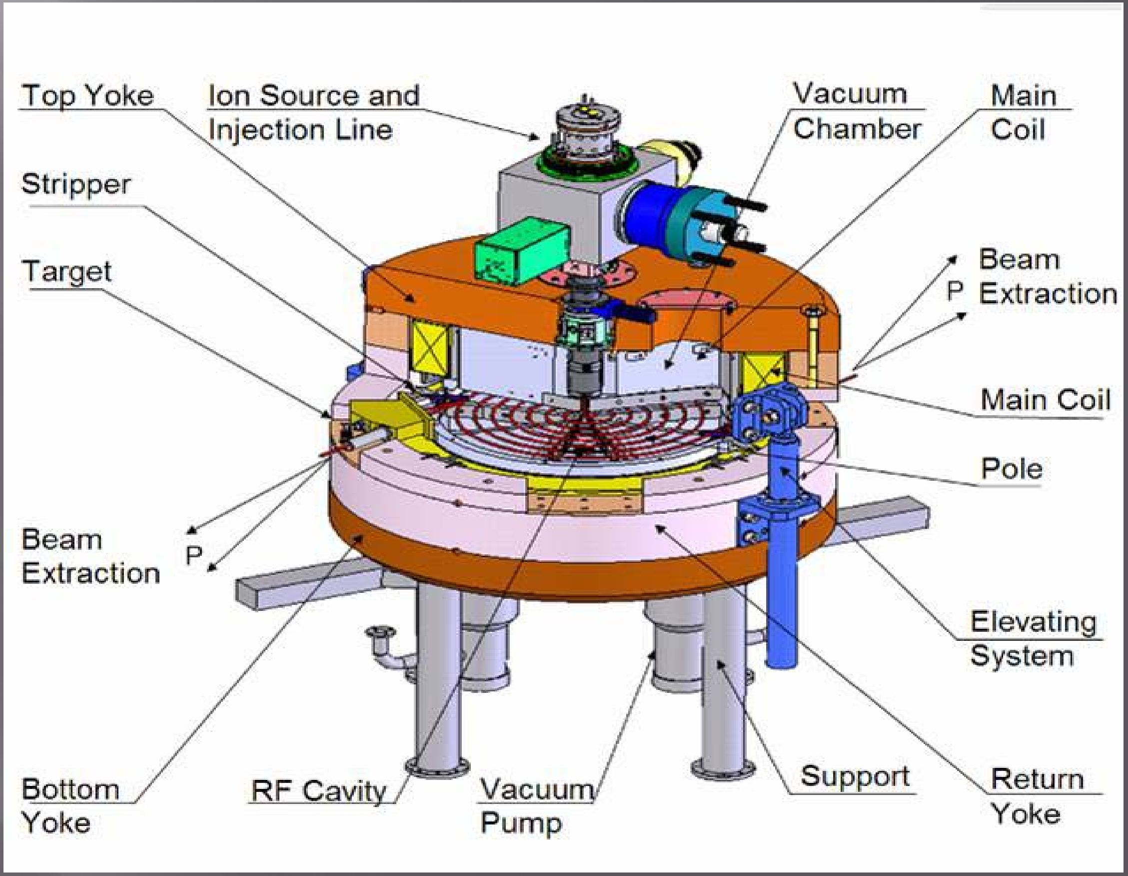
- BEST 14
  - Fixed Energy 14 MeV, 100 µA
- BEST 35
  - Variable Energy 15 – 35 MeV, 1,500 µA
- BEST 70
  - Fixed Energy 70 MeV, 800 µA

Best Cyclotron Systems, Inc
[poster MOPC017]



China Institute of Atomic Energy (CIAE)

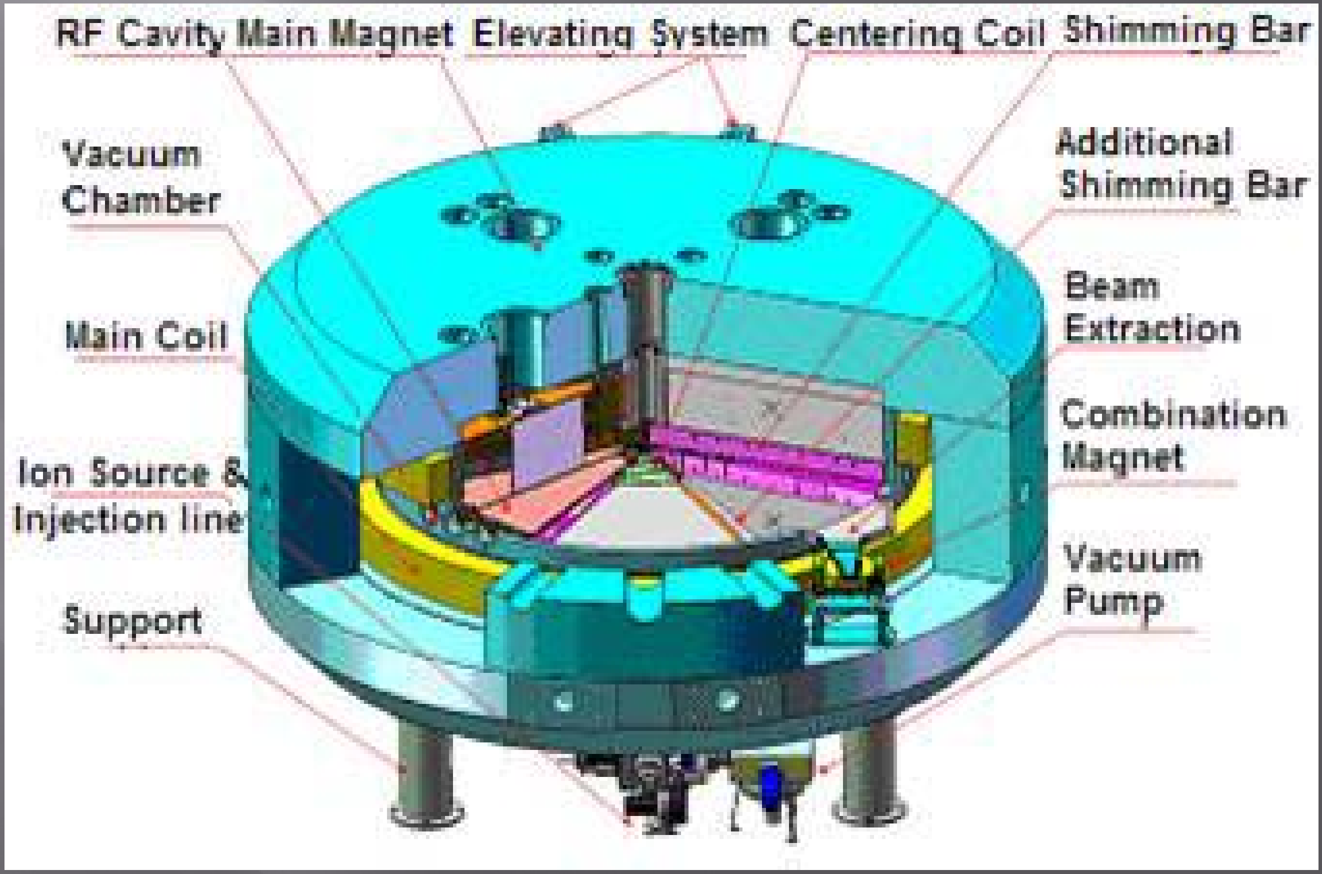
- CYCCIAE- 14 [poster MOPCP030]
  - 14 MeV, 400 μA



AAPS Advanced Applied Physics Solutions | ETPP Exploitation des Techniques de Pointe en Physique

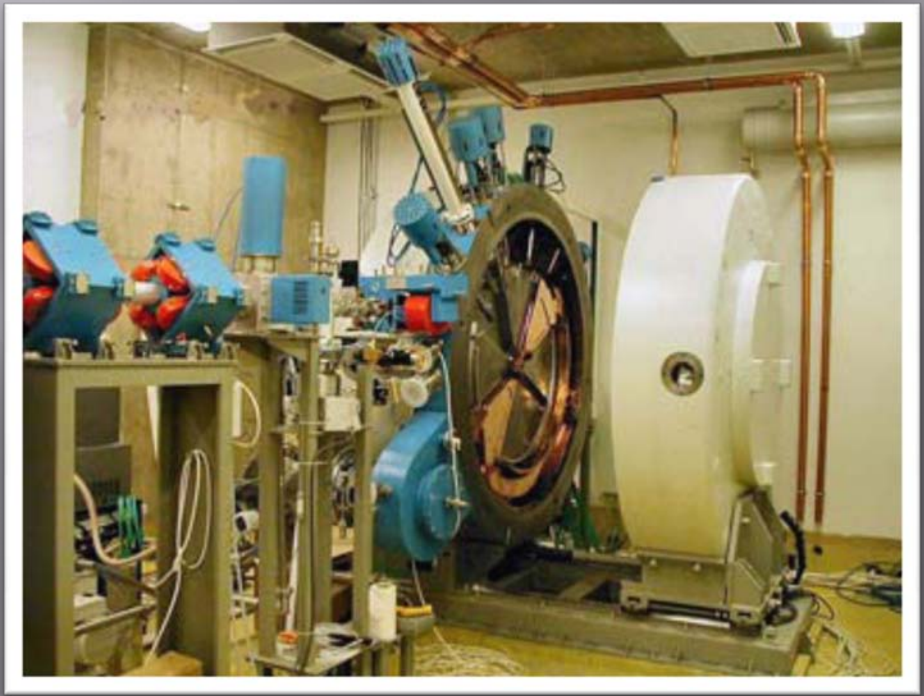
China Institute of Atomic Energy (CIAE)

- CYCCIAE- 70 [posters MOPC030 & MOPC031]
  - 70 MeV, 750 μA



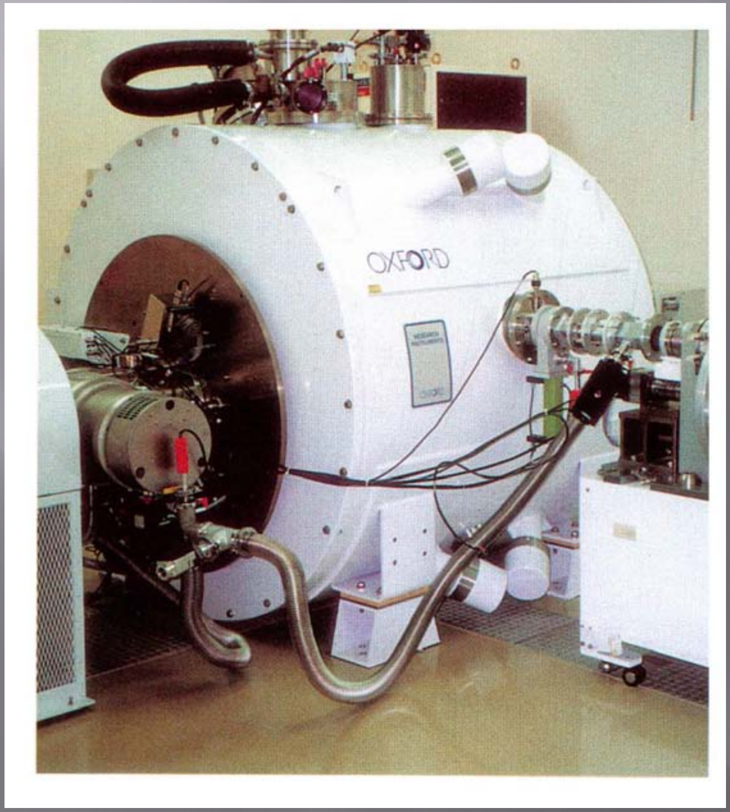
Efremov Institute (NIIEFA)

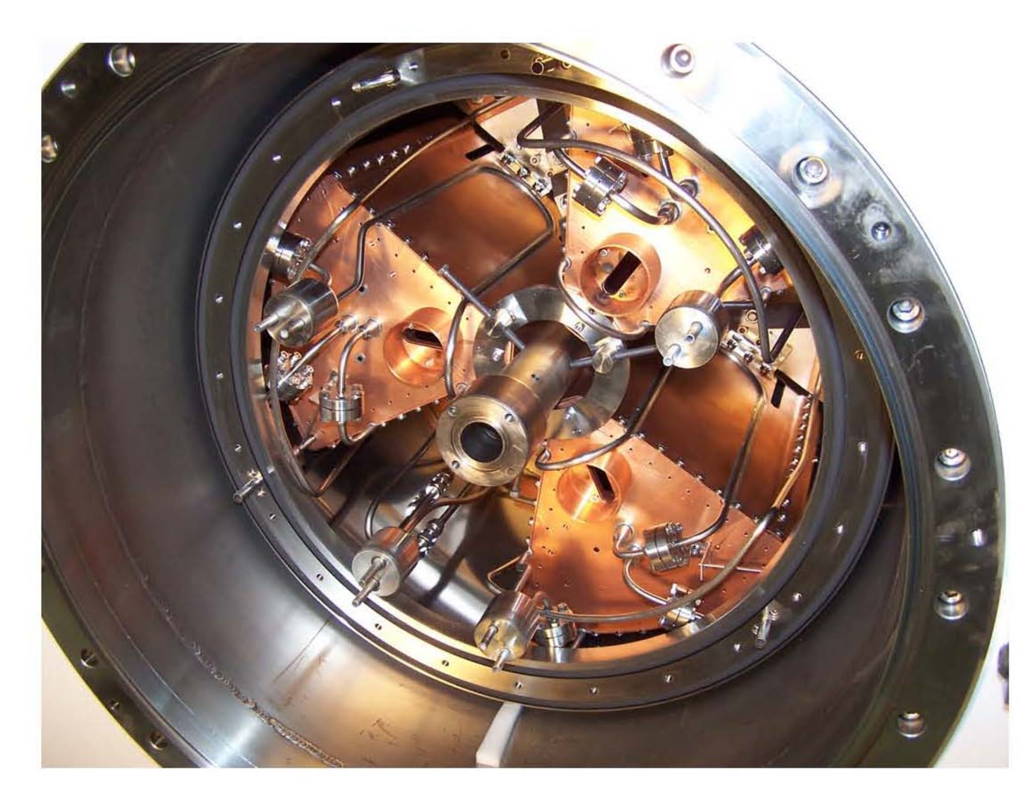
- CC 18/9
  - H-/D-, 18/9 MeV, 100/50 μA
  - External Ion Source & Vertical Acceleration Plane



EuroMeV

- ISOTRACE
  - 12 MeV, 100 µA, Superconducting, 40 kW, 3.8 ton





GE Healthcare

- MiniTrace
  - H-, 50 μA, 9.6 MeV
- PetTrace
  - H-/D-, 18.5/8.6 MeV, 100/65 μA

Ion Beam Applications (IBA)

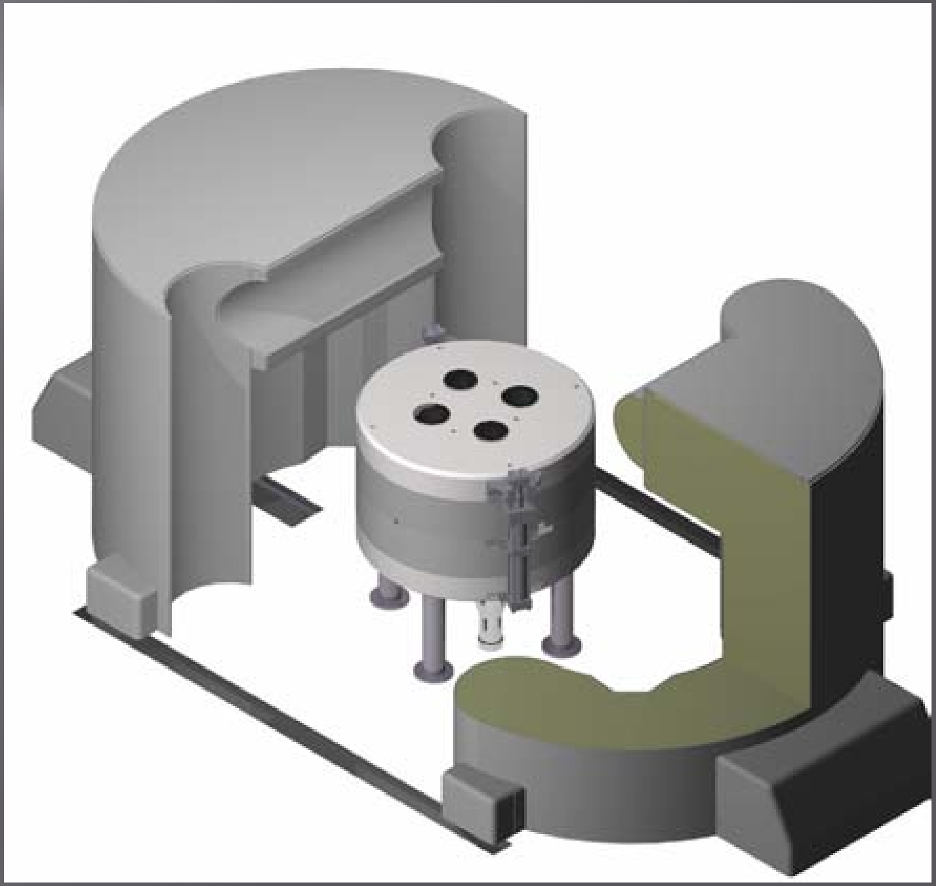
- Cyclone 3D
- Cyclone 10/5
- Cyclone 11
- Cyclone 18/9
- Cyclone 18 Twin
- Cyclone 30
- Cyclone 30 XP
- Cyclone 70

Ion Beam Applications (IBA)

- Cyclone 3D [poster MOPCP074]
  - D, 3.6 MeV, 70 μA
  - MOPC074
- Cyclone 10/5
  - H-/D-, 10/5 MeV, 100/35 μA

Ion Beam Applications (IBA)

- Cyclone 11
  - H+, 11 MeV, 120 μA
  - Self-shielded
  - [poster MOPCP072]



AAPS Advanced Applied Physics Solutions | ETPP Exploitation des Techniques de Pointe en Physique

Ion Beam Applications (IBA)

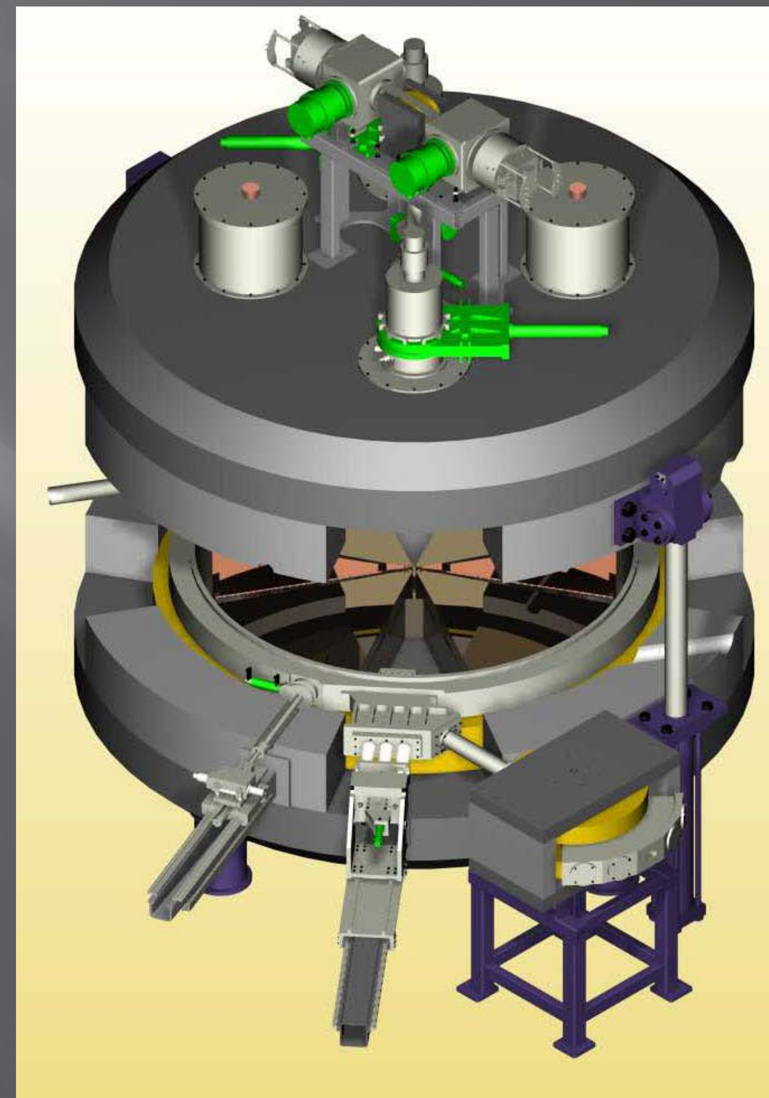
- Cyclone 18/9
  - H-/D-
  - 18/9 MeV
  - 150/40 μA
- Cyclone 18 Twin
  - H-
  - 18 MeV
  - 2 PIG Ion Sources

Ion Beam Applications (IBA)

- Cyclone 30
  - LC
    - H-, 15-30 MeV, 400 μA
  - ST
    - H-, 15-30 MeV, 800 μA
  - HC
    - H-, 15-30 MeV, 1500 μA
  - XP
    - H-, 15-30 MeV, 400 μA
    - D-, 8-15 MeV, 50 μA
    - He++, 30 MeV, 50 eμA
    - [poster MOPCP070]

Ion Beam Applications (IBA)

- CYCLONE 70
  - H-, H++
  - 70 MeV, fixed-energy
- Cyclone -70 Arronax
  - H- 35-70, 750 µA
  - D-, 17-25 MeV, 50 µA
  - He++, 70 MeV, 35 µA
  - H_2+, 35 MeV, 50 µA



Cyclotron Application Laboratory (KIRAMS)

- KIRAMS-13
  - H-, PIG, 13 MeV, 80 μA
- KIRAMS-30
  - H-, CUSP, 30 MeV, 500 μA

Siemens

- Eclipse HP
  - 11 MeV, 60 mA, 2 beam lines
- Eclipse RD
  - 11 MeV, 40 μA

Sumitomo Heavy Industries

- HM-7
  - H-/D-, 7/3.5 MeV
- HM-10
  - H-/D-, 9.6/4.8 MeV
- HM-12/S
  - H-/D-, 12/6
- HM-18
  - H-/D-, 18/10

AAPS Advanced Applied Physics Solutions ETPP Exploitation des Techniques de Pointe en Physique

Comparison ($E_p \leq 20$ MeV)

Company Name	Cyclotron Model	Particles	Energy (MeV)	Beam Current (μA)	Ion Source Type	RF Freq. (MHz)	Plane Of Accel	Cyc. Weight (t)	Shield Weight (t)	Power (kW)
ACSI	TR14	H-	14	>100	Cusp	74	V	22	40	60
ACSI	TR19/(9)	H-/(D-)	19/(9)	>300/100	Cusp	74/37	V	22		65
ABT	TableTop	H+	7.5	5	PIG	72	H	3.2	7.6	10
Best	BSCI 14p	H-	14	100	PIG	73	H	14		60
CIAE	CYCCIAE14	H-	14	400	Cusp					
NIIEFA	CC-18/9	H-/D-	18/9	100/50	Cusp	38.2	V	20		60
EUROMEV	Isotrace	H-	12	100	Cusp	108	V	3.8		40
GE	MINItrace	H-	9.6	>50	PIG	101	V	9	40	35
GE	PETtrace	H-/D-	16.5/8.6	>100/65	PIG	27.2	V	22	47	70
IBA	Cyclone 3	D+	3.8	60	PIG	14	H	5		14
IBA	Cyclone 10/5	H-/D-	10/5	>100/35	PIG	42	H	12	40	35
IBA	Cyclone 11	H+	11	120	PIG	42	H	13	52	35
IBA	Cyclone 18/9	H-/D-	18/9	150/40	PIG	42	H	25		50
KIRAMS	Kotron-13	H+	40372	100	PIG	77.3	H	20	80	18?
Siemens	Eclipse RD	H-	11	2x40	PIG		H	11	39	35
Siemens	Eclipse HP/ST	H-	11	2x60	PIG	72				35
Sumitomo	HM-7	H-/D-	7.5/3.8				V		30	
Sumitomo	HM-10	H-/D-	9.6/4.8				V		52	
Sumitomo	HM-12/S	H-/D-	12/6	>60/30	PIG	45	V	11	56	45
Sumitomo	HM-18	H-/D-	18/10	>90/50	PIG	45	H	24	86	55

Comparison ($E_p \leq 20$ MeV)

Company Name	Cyclotron Model	Particles	Energy (MeV)	Beam Current (μA)	Ion Source Type	RF Freq. (MHz)	Plane Of Accel	Cyc. Weight (t)	Shield Weight (t)	Power (kW)
ACSI	TR14	H-	14	>100	Cusp	74	V	22	40	60
ACSI	TR19/(9)	H-/(D-)	19/(9)	>300/100	Cusp	74/37	V	22		65
ABT	TableTop	H+	7.5	5	PIG	72	H	3.2	7.6	10
Best	BSCI 14p	H-	14	100	PIG	73	H	14		60
CIAE	CYCCIAE14	H-	14	400	Cusp					
NIIEFA	CC-18/9	H-/D-	18/9	100/50	Cusp	38.2	V	20		60
EUROMEV	Isotrace	H-	12	100	Cusp	108	V	3.8		40
GE	MINItrace	H-	9.6	>50	PIG	101	V	9	40	35
GE	PETtrace	H-/D-	16.5/8.6	>100/65	PIG	27.2	V	22	47	70
IBA	Cyclone 3	D+	3.8	60	PIG	14	H	5		14
IBA	Cyclone 10/5	H-/D-	10/5	>100/35	PIG	42	H	12	40	35
IBA	Cyclone 11	H+	11	120	PIG	42	H	13	52	35
IBA	Cyclone 18/9	H-/D-	18/9	150/40	PIG	42	H	25		50
KIRAMS	Kotron-13	H+	40372	100	PIG	77.3	H	20	80	18?
Siemens	Eclipse RD	H-	11	2x40	PIG		H	11	39	35
Siemens	Eclipse HP/ST	H-	11	2x60	PIG	72				35
Sumitomo	HM-7	H-/D-	7.5/3.8				V		30	
Sumitomo	HM-10	H-/D-	9.6/4.8				V		52	
Sumitomo	HM-12/S	H-/D-	12/6	>60/30	PIG	45	V	11	56	45
Sumitomo	HM-18	H-/D-	18/10	>90/50	PIG	45	H	24	86	55

Comparison
$20 \leq E_p \leq 35$ MeV

Company Name	Cyclotron Model	Particles	Energy (MeV)	Beam Current (μA)	Ion Source Type	Peak Field (T)	Hill Valley ratio	RF Freq. (MHz)	Plane Of Accel	Cyc. Weight (t)	Power (kW)
ACSI	TR24	H-	24	>300	Cusp	2.1	4	83.5	H or V	84	80
ACSI	TR30/(15)	H-/(D-)	30/(15)	1500/400	Cusp	1.9			H	56	150
Best	BCSI 35p	H-	15-35	1500	Cusp			70	H	55	280
IBA	Cyclone 30	H-/(D-)	30 /(15)	1500/?	Cusp	1.7	14		H	50	180
KIRAMS	KIRAMS-30	H-	15-30	500	Cusp	1.9	8	64	H		

AAPS Advanced Applied Physics Solutions
ETPP Exploitation des Techniques de Pointe en Physique

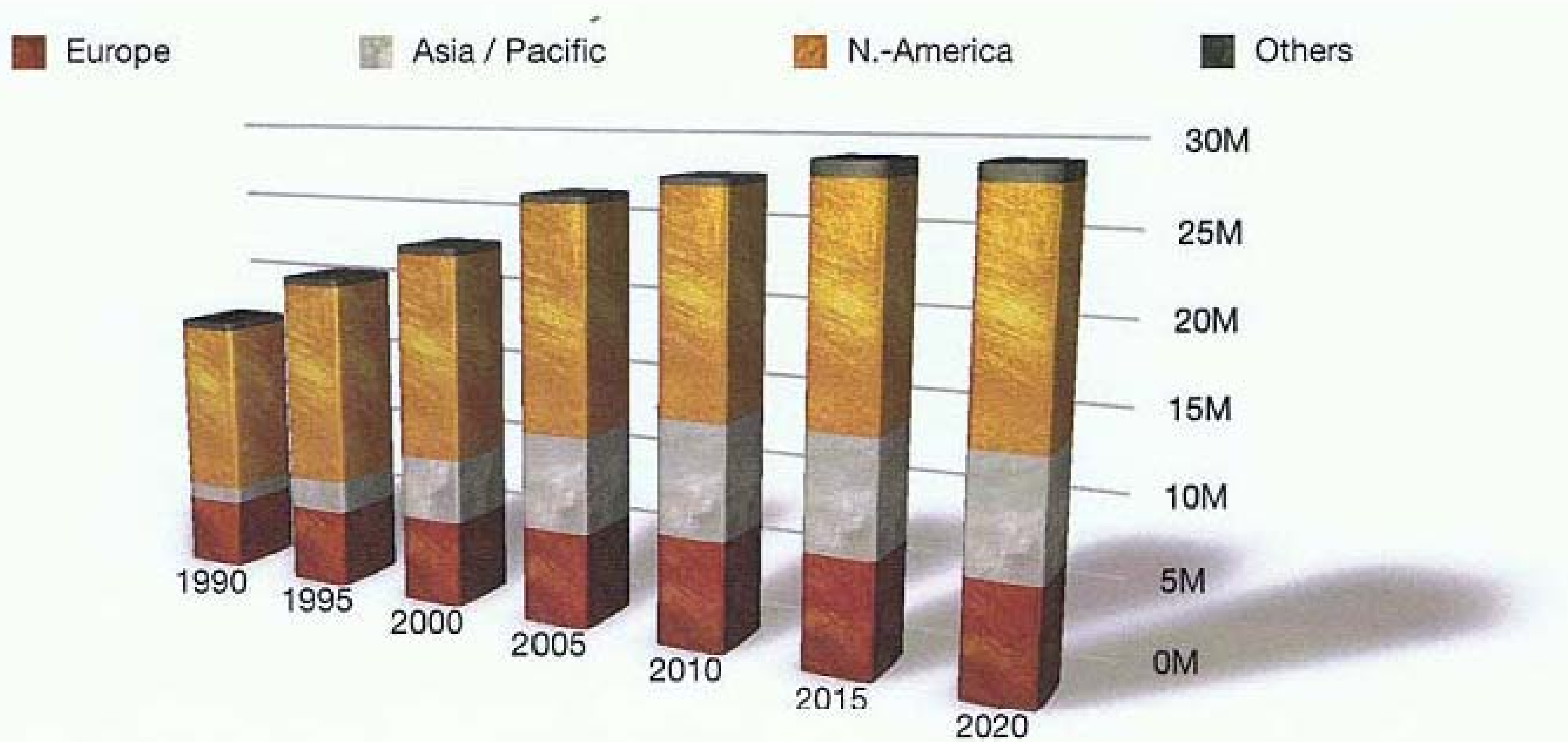
Comparison
$E_p \geq 35$ MeV

Company Name	Cyclotron Model	Particles	Energy (MeV)	Beam Current (μA)	Ion Source Type	Peak Field (T)	Hill Valley ratio	RF Freq. (MHz)	Cyc. Weight (t)	Power (kW)
Best	BSCI 70p	H-	70	800	Cusp	1.6		58	195	400
CIAE	CYCCIAE70	H-	70	750	Cusp					
IBA	Cyclone 70	H-/α								
IBA	Cyclone 70 (Arronax)	H-/D-/H_2+/He^{++}	30-70/15-35 /17.5/70	2x350/50 /50/35		1.7	14	66/30	125	350

Future

Projected 99mTc Use/demand

EC Commission Report SANCO/C/3/HW D(2009) Rev. 8



. - *Estimated* in vivo *nuclear medicine procedures with* $^{99m}Tc/^{99}Mo$*, lab tests excluded, for major world regions 1990-2020 (million procedures per year).*

Direct Production of ^{99m}Tc

- Nuclear Medicine Depends on $^{99}Mo/^{99}mTc$
  - Approximately 80% of Nuclear Medicine Procedures use ^{99m}Tc
- World Shortage
  - Aging Research Reactors
  - Produced by fission of Highly Enriched Uranium
    - Security issue
    - Waste issue

AAPS Advanced Applied Physics Solutions | ETPP Exploitation des Techniques de Pointe en Physique

Direct Production of ^{99m}Tc

- $^{100}Mo(p,2n)^{99m}Tc$ yields 15 mCi/µAh at 20 MeV
- Each medical procedure uses about 20 mCi
- B. Scholten et al. / Applied Radiation and Isotopes 51 (1999) 69-80

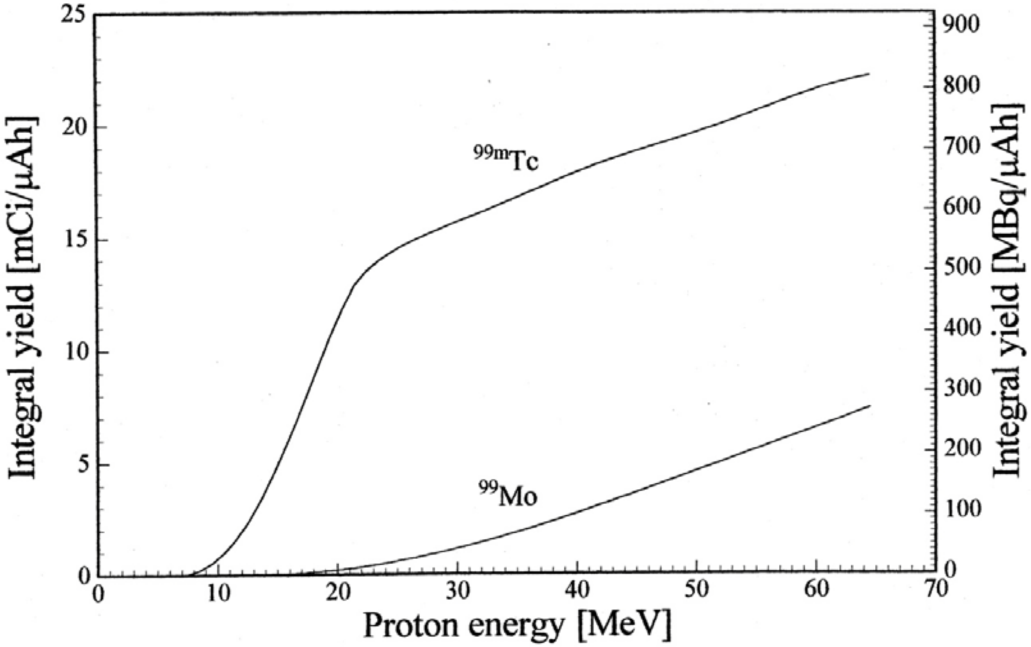
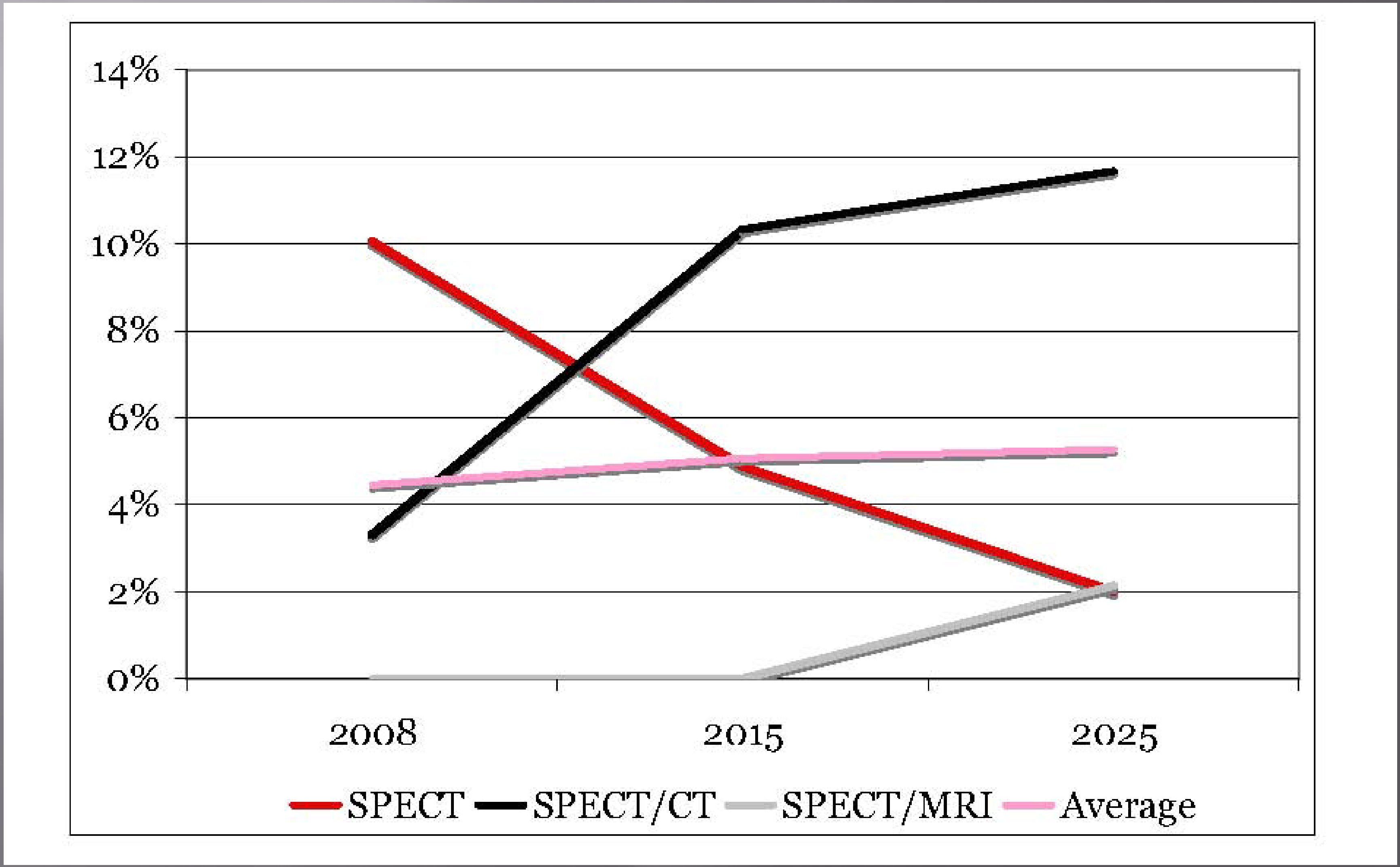


Fig. 4. Integral yields of ^{99m}Tc and ^{99}Mo calculated from our excitation function curves given in Figs. 1 and 2.

Projected Future for SPECT

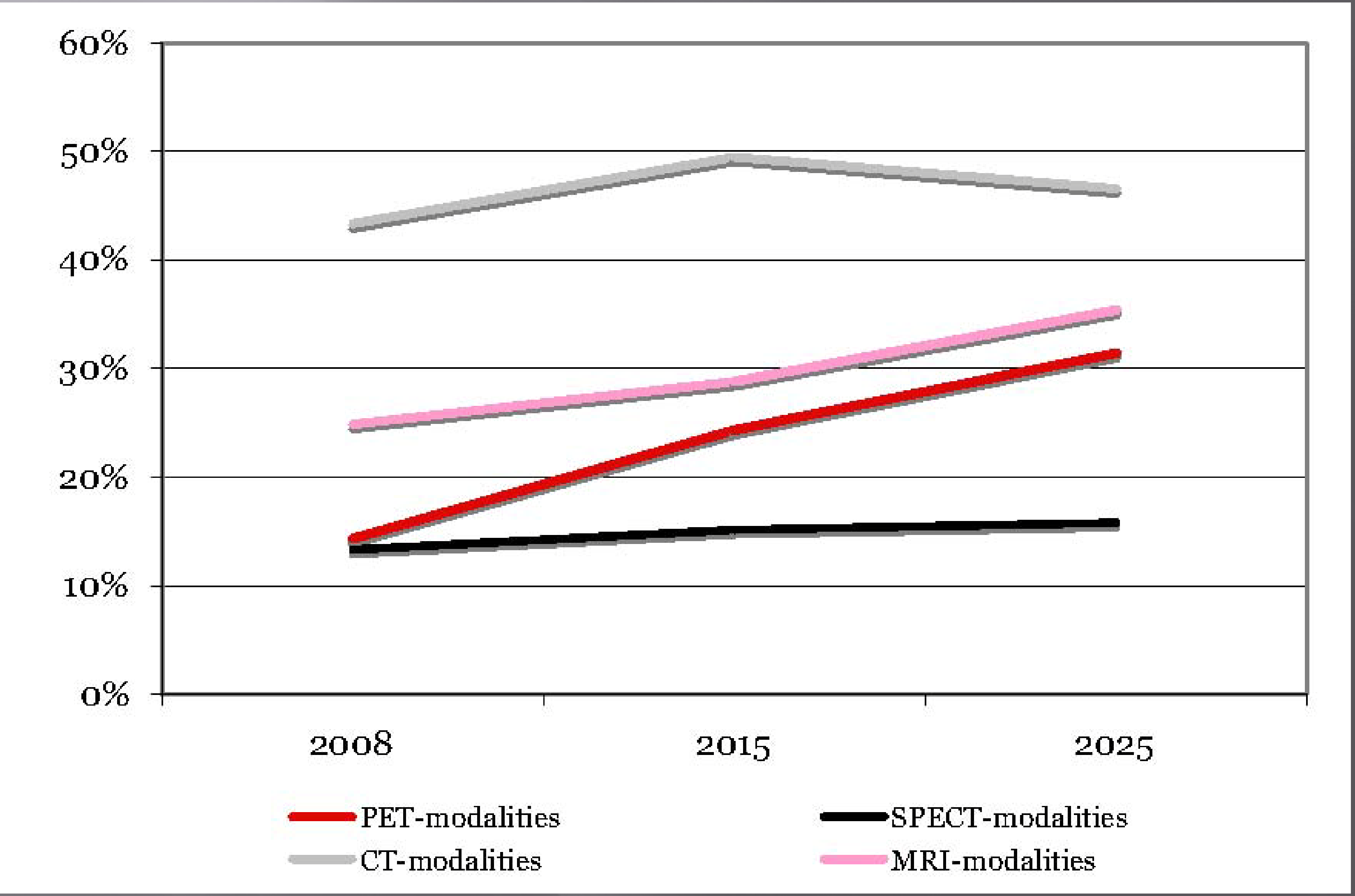
EC Commission Report SANCO/C/3/HW D(2009) Rev. 8



AAPS Advanced Applied Physics Solutions
ETPP Exploitation des Techniques de Pointe en Physique

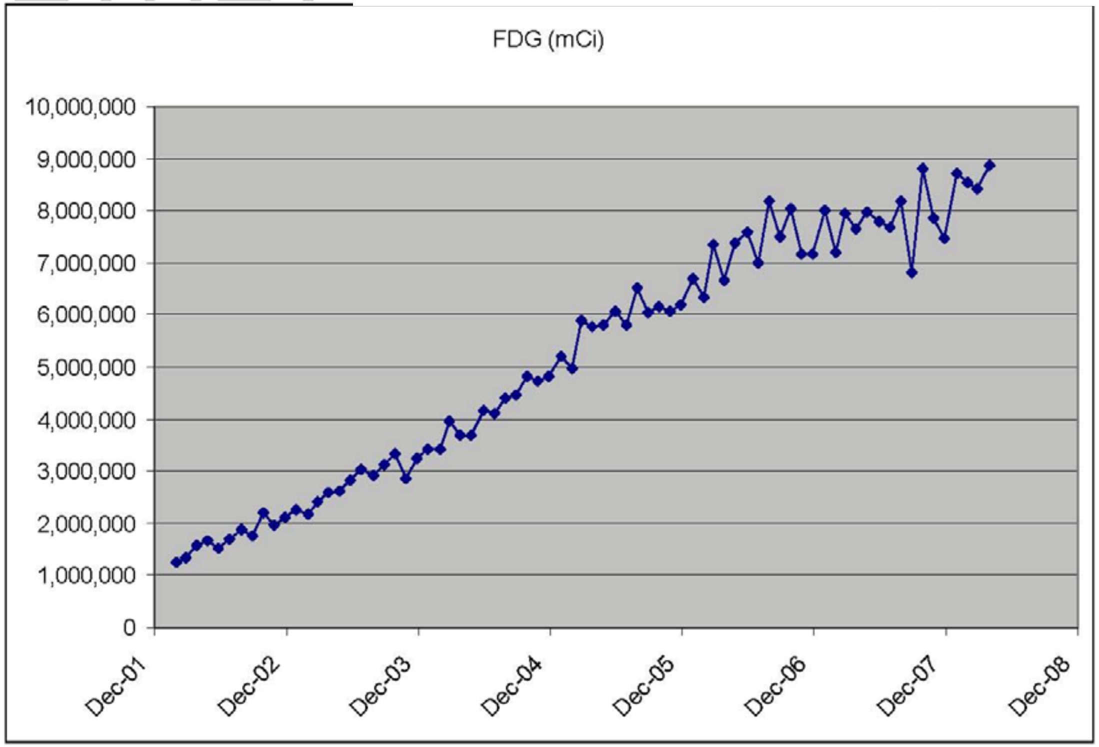
Projected Future for PET

EC Commission Report SANCO/C/3/HW D(2009) Rev. 8



Continued Growth of Nuclear Medicine

Growth of FDG produced by PETNET

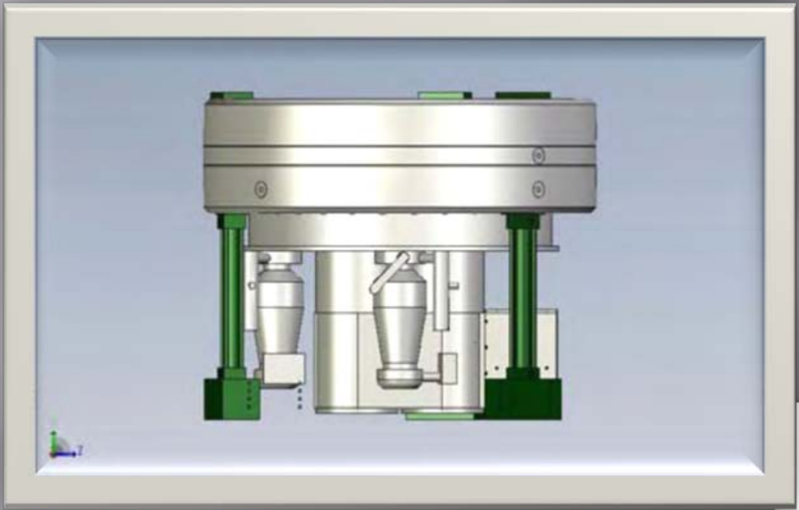


Ci per month of FDG produced – PETNET production records Dec 2001 to present

How will cyclotrons address PET demands?

- PET Cyclotrons need to reduce footprint
  - Shielding Dominates Weight with Current Technology
- If they switch to a Single Dose Modality
  - Reduces Cyclotron Current
  - ReduceCyclotron Energy
    - Reduces Shielding Required
- Simplify Operation
  - Single Button Operation

‘Table top’ Cyclotrons, Microfluidics, & Chemistry on a Chip

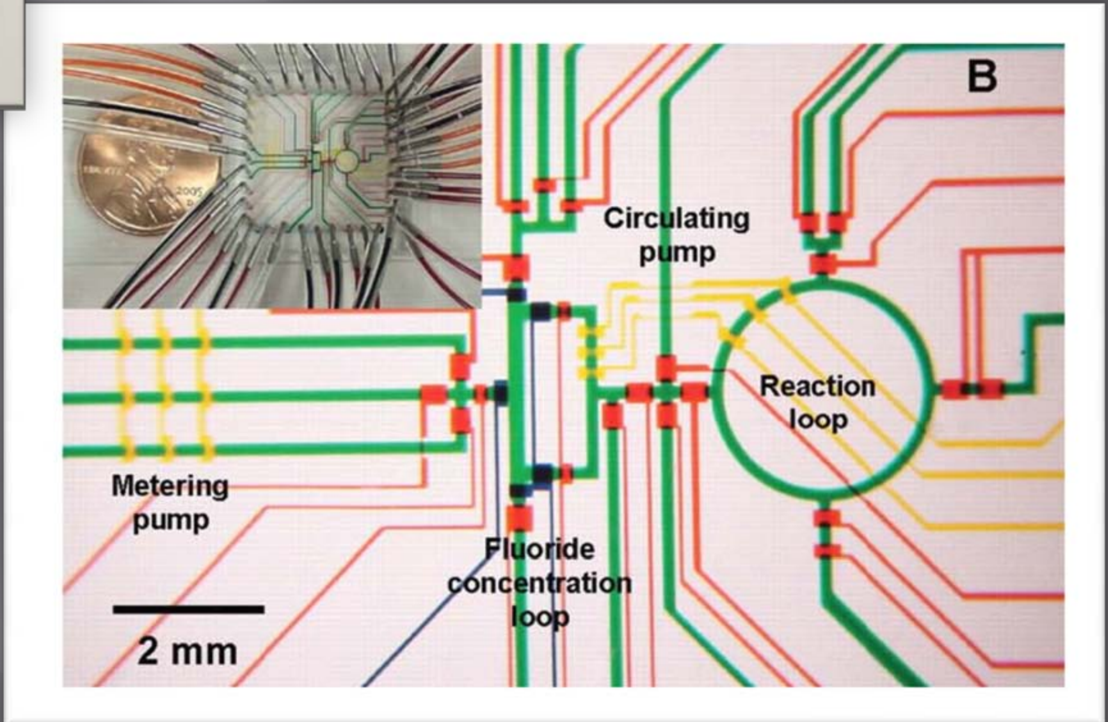


+

SINGLE DOSE TARGET VOLUME

+

Chemistry on a Chip under development



THANK YOU FOR YOUR ATTENTION