TRIUMF

CANADA'S NATIONAL LABORATORY FOR PARTICLE AND NUCLEAR PHYSICS

Owned and operated as a joint venture by a consortium of Canadian universities via a contribution through the National Research Council Canada

World View of Radioisotope Production

Thomas J. Ruth

TRIUMF

Vancouver, Canada

05 August 2008

LABORATOIRE NATIONAL CANADIEN POUR LA RECHERCHE EN PHYSIQUE NUCLÉAIRE ET EN PHYSIQUE DES PARTICULES

Propriété d'un consortium d'universités canadiennes, géré en co-entreprise à partir d'une contribution administrée par le Conseil national de recherches Canada

View from 12,000 M
(or 39,000 feet)

Disclaimer

- Member of a NAS panel on "The Production of Medical Isotopes without HEU"
- The views expressed in this talk are my personal views and should not be construed as representing any conclusions derived from the committee deliberations.

Outline

- A look at the international accelerator facilities for radionuclide production.
- An overlooked source of Mo-99
- View from TRIUMF
- Reflections on radionuclide availability
- Future of Nuclear Imaging
- Distribution of small cyclotrons around the world

What is not in the Talk

- Will not discuss the capacity of the commercial suppliers of radionuclides.
- Will not discuss the DOE labs – leave this for the next talk, reactor capabilities eluded to in Dr. Goldman's talk.

Russia

Isotope Production Facilities Around Moscow

KURCHATOV INSTITUTE OF ATOMIC ENERGY
p - 30 MeV,
Solution nuclear reactor

INSTITUTE OF BIOPHYSICS
Radiopharmaceuticals

DUBNA

JOINT INSTITUTE FOR NUCLEAR RESEARCH
p-680 MeV, Pulse nuclear reactor
α - 36 MeV, Heavy Ions

MOSCOW

TROITSK

INSTITUTE FOR NUCLEAR RESEARCH
p - 160-600 MeV

OBNINSK

INSTITUTE FOR PHYSICS AND POWER ENGINEERING

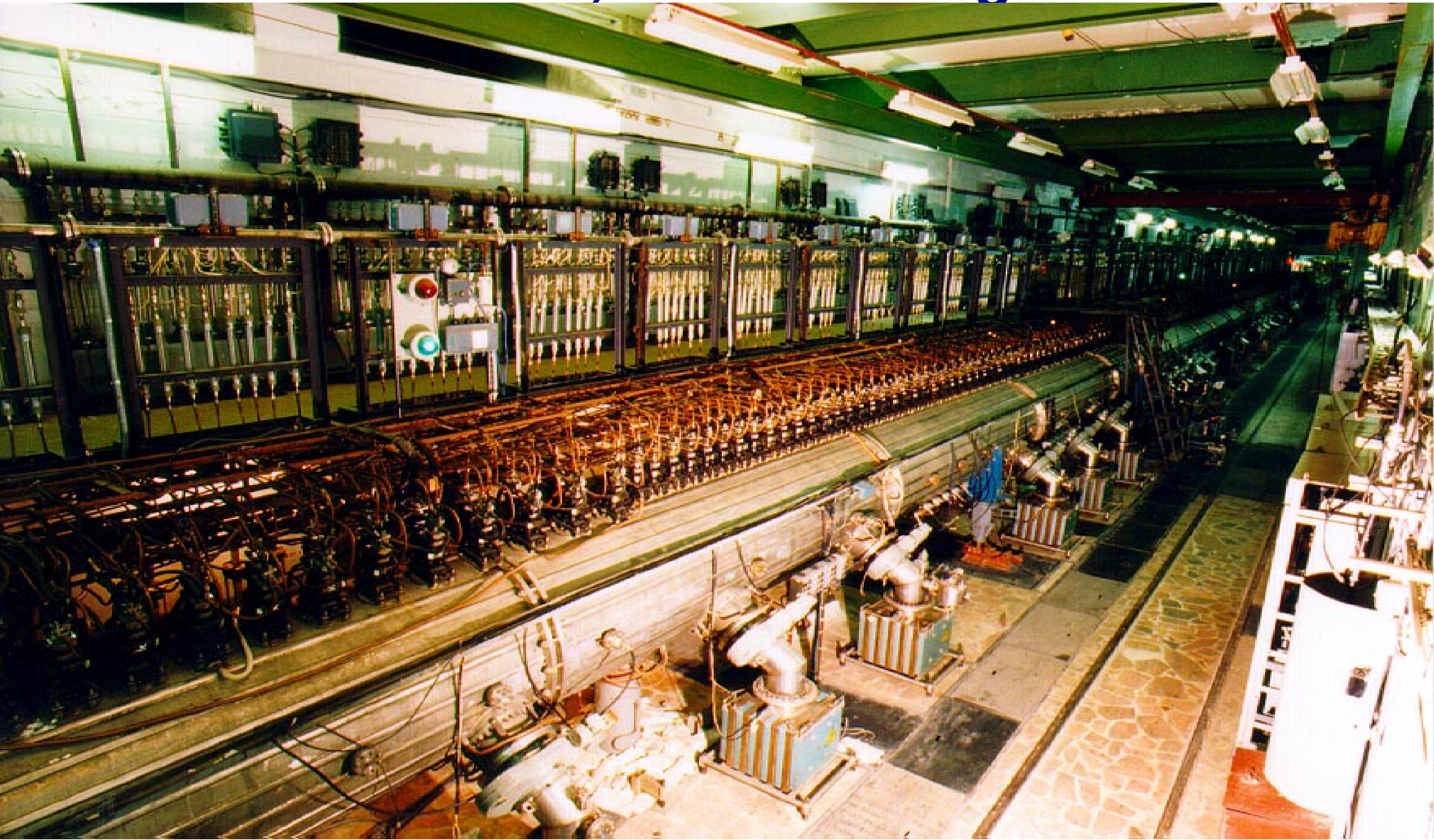
KARPOV INSTITUTE OF PHYSICAL CHEMISTRY
Nuclear reactor, Radiopharmaceuticals

CYCLOTRON Co.
d, p - 22 MeV

PROTVINO

INSTITUTE FOR HIGH ENERGY PHYSICS
p - 100 MeV
p - 70 GeV

INR Linear Proton Accelerator (up to 600 MeV) Troitsk, Moscow Region



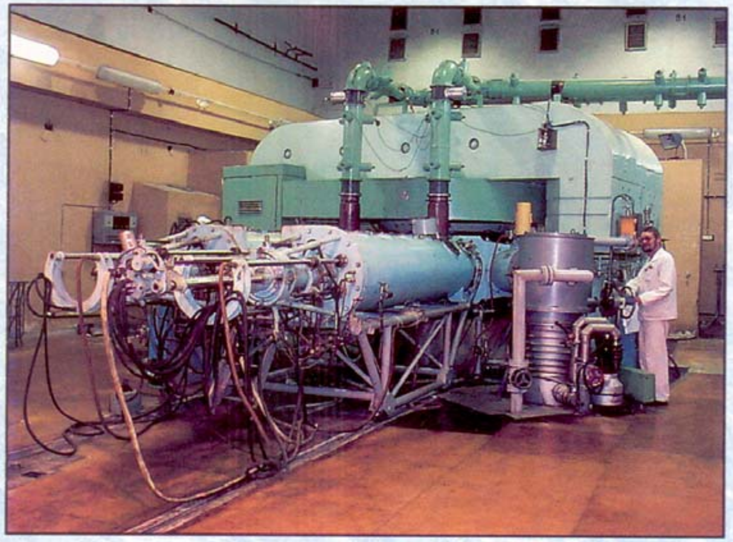
Isotopes Produced in INR and Possible Activity for Generation in One Accelerator Run at 120 μA

Radio-nuclide	Half life period	Target	Energy range, *MeV*	Bombardment period, *hr*	Activity produced in one run at EOB, *Ci*
Sr-82	25.3 d	Rb	100-40	250	5
Na-22	2.6 y	Mg, Al	150-35	250	2
Cd-109	453 d	In	150-80	250	2
Pd-103	17 d	Ag	150-50	250	50
Ge-68	288 d	Ga, GaNi	50-15	250	0.5
Se-72	8.5 d	GaAs	60-45	250	3
Cu-67	62 hr	Zn-68	150-70	100	10
Cu-64	12.7 hr	Zn	150-40	15	15
Sn-117m	14 d	Sb	150-40	250	3
Ac-225	10 d	Th	150-30	250	1
Ra-223	11.4 d	Th	150-30	250	7

Isotope Production at Cyclotron Co., Obninsk

TWO CYCLOTRONS:
23 MeV and 15 MeV protons, deuterons, α-particles (>1000 μA)

PRODUCED ISOTOPES
^{68}Ge/^{68}Ga-generator,
^{67}Ga, ^{68}Ga, ^{85}Sr, ^{103}Pd, ^{111}In, ^{195}Au, ^{57}Co

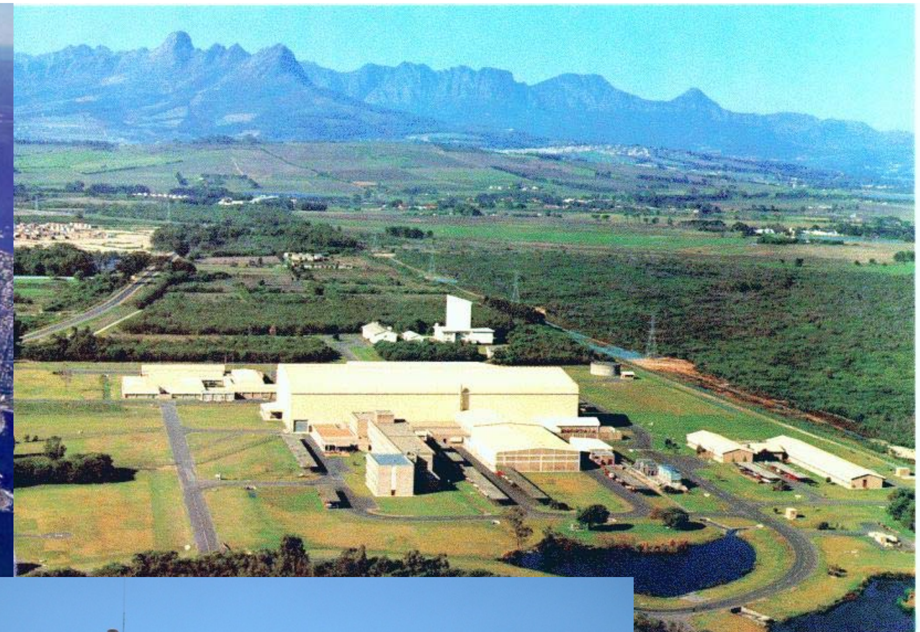


CYCLOTRON U-150

RADIOCHEMICAL SECTION

South Africa

Expansion of Radionuclide Production Facilities at iThemba LABS



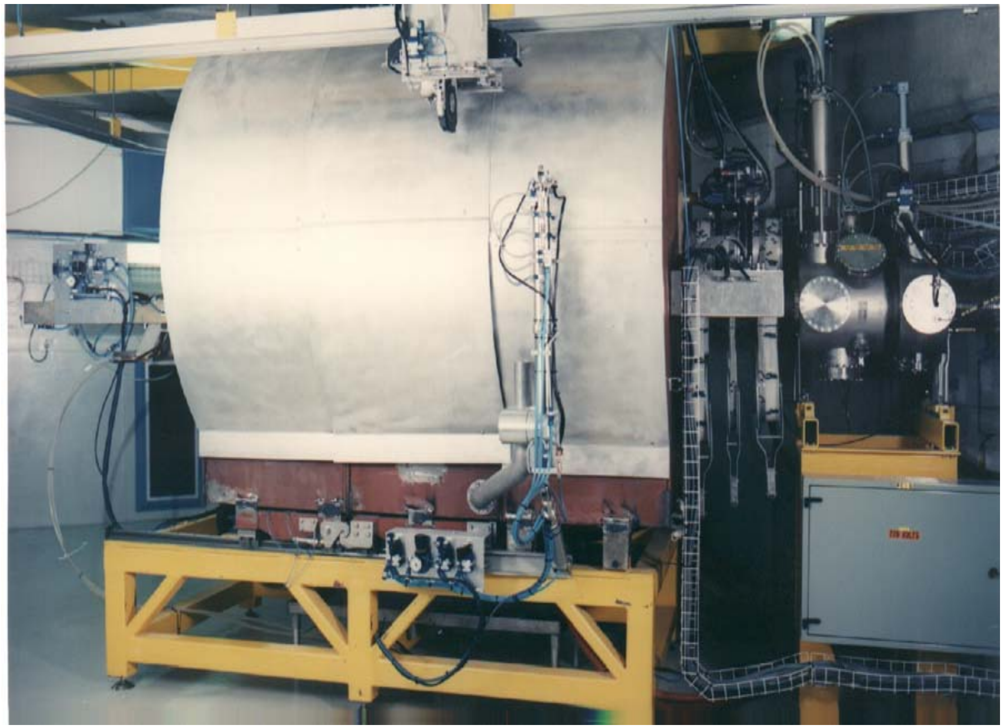
C. Naidoo, PhD (Chemistry)
Head: Radionuclide Production Group
iThemba LABS
P.O. Box 722
Somerset West, 7129
South Africa.

Bombardment Station-HBTS

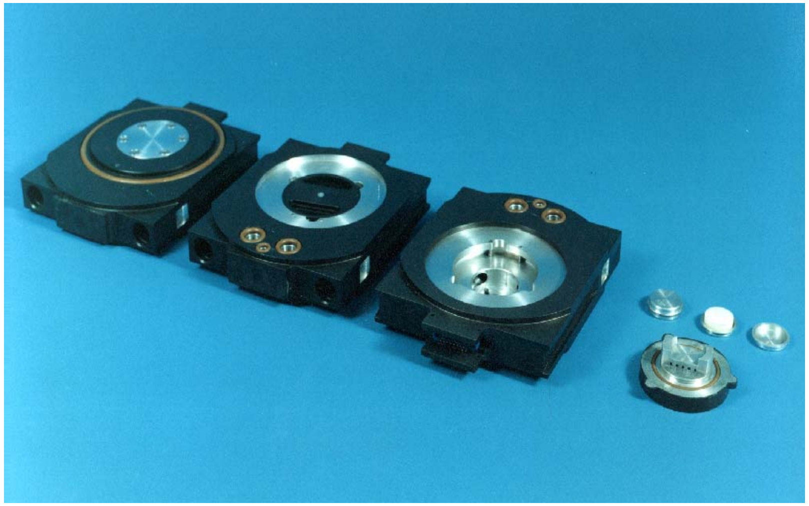
Produce:

^{67}Ga, ^{123}I and ^{81}Rb

^{22}Na, ^{88}Y, ^{57}Co and ^{109}Cd



Horizontal Beam Target Station (HBTS)



HBTS Target and target holders

66 MeV proton beam with an intensity of 80-90 μA

Bombardment Station-VBTS

Produce in Tandem
$^{82}Sr/^{68}Ge$
$^{22}Na/^{68}Ge$

Vertical Beam Target Station (VBTS)
66 MeV proton beam with an intensity of ~250 µA

VBTS Thick Target Holders

VBTS Tandem targets

France

ARRONAX, a high energy and high intensity cyclotron for nuclear medicine.

F. Haddad on behalf of ARRONAX team

ARRONAX

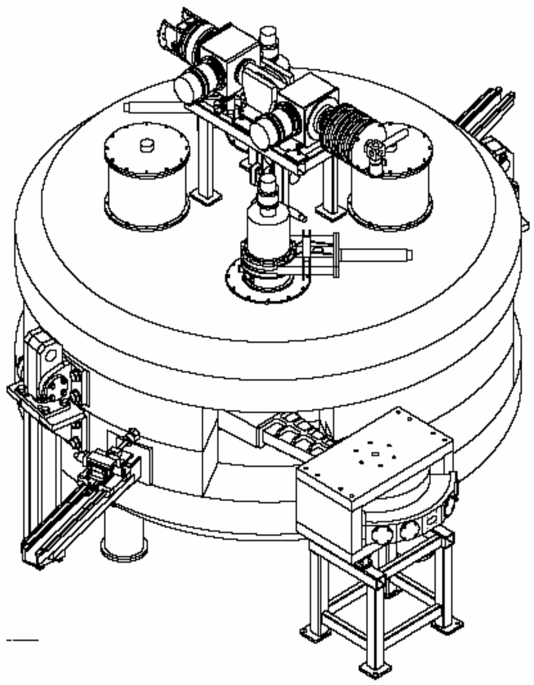
an Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique

3 main fields of investigations

- Radionuclides for nuclear medicine
- Radiolysis and Nuclear Physics
- Teaching & Training

The **ARRONAX** project is supported by:

the **Regional Council of Pays de la Loire**
the **Université de Nantes**
the **French government** (CNRS, INSERM)
the **European Union**.



ARRONAX will deliver beams

At **high energy**: up to **70 MeV**.

At **high current** : up to **700 µA** for protons

ARRONAX will accelerate **different type of particles**

•negative ions → extraction using a stripper foil

Variable energy

2 simultaneous beams with different energy and current

•positive ions → extraction using a electromagnetic septum

Fixed energy

1 beam

Beam Characteristics

Beam	Accelerated particles	Energy range (MeV)	Intensity (µA)	number of beam	number of Hall
Proton	H-	30-70	<350	2	6
	HH+	17.5	<50	1	3
Deuteron	D-	15-35	<50	2	6
Alpha	He++	70	<35	1	3

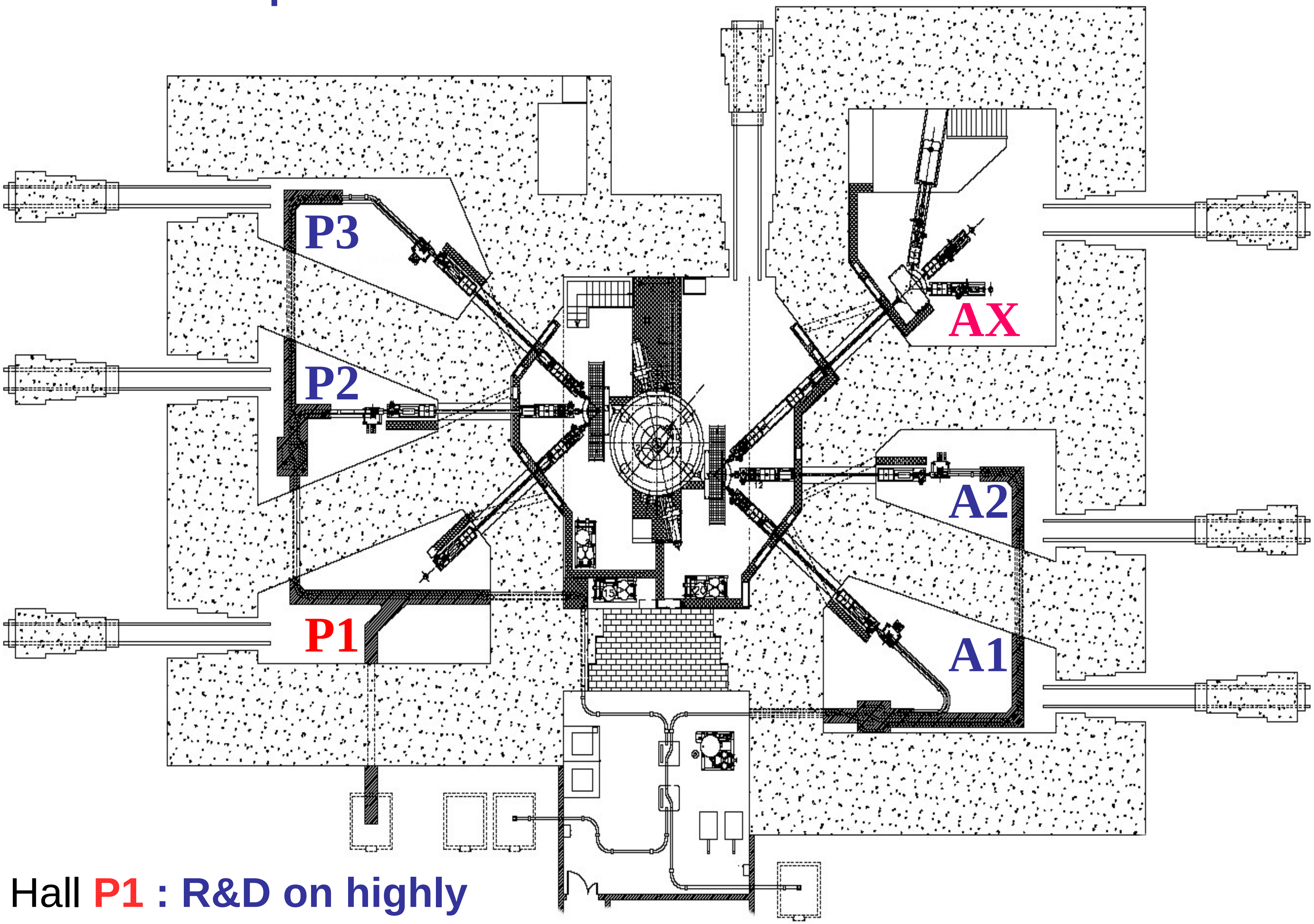
6 experimental **Halls** connected to **hot cells** through a **pneumatic system**

GMP facility

Surrounding labs :

radiochemistry , biochemistry, cells radiolabeling, chemical analysis, nuclear metrology

Halls **A1, A2, P2 and P3: radionuclide production.**



Hall **P1 : R&D on highly intense beam**

Radionuclides of interest

Targeted radionuclide therapy:

^{211}At : appropriate for **α-therapy** due to its half-life (7.2 hours).

^{67}Cu and **^{47}Sc** : **β-therapy** (same β energy)

require high proton energy and high current intensity
(small production cross sections (p,2p))

PET imaging:

^{124}I, ^{64}Cu and **^{44}Sc**: pre-therapeutic PET dosimetry before injection of their beta-emitting counterparts ^{131}I, ^{67}Cu and ^{47}Sc

^{82}Sr/^{82}Rb and ^{68}Ge/^{68}Ga generators

^{44}Sc : β^{+} γ emitter (3 γ imaging)

Schedule

Cyclotron:

- March 2008 : Transport to ARRONAX
- May 2008 : Installation of the cyclotron
- July 2008: Delivery of the building

First beam by the end of September 2008

Production:

First irradiations start in april 2009

end of **2009**: Expected production of ^{211}At, ^{64}Cu, ^{82}Rb

end of **2010:** Expected production of ^{67}Cu, ^{68}Ge

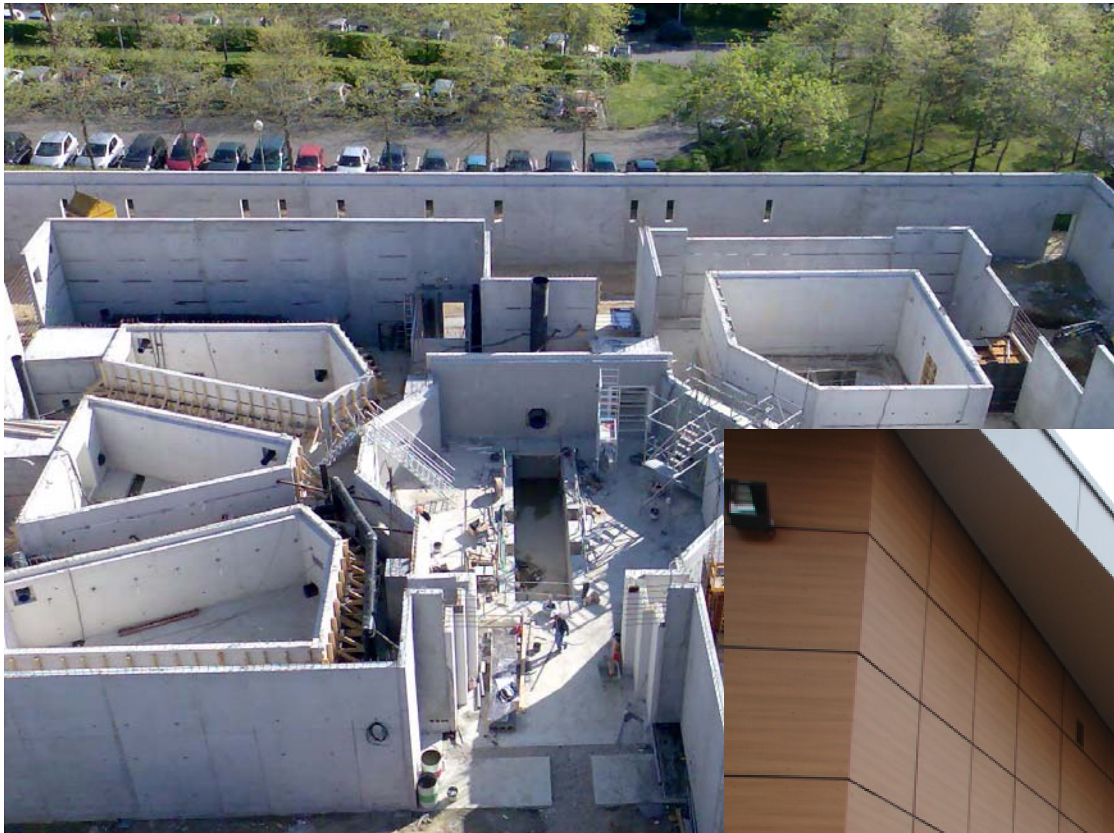
end of **2011**: Expected high intensity production

Running:

5 days a week (2*8h)

Time shared with companies

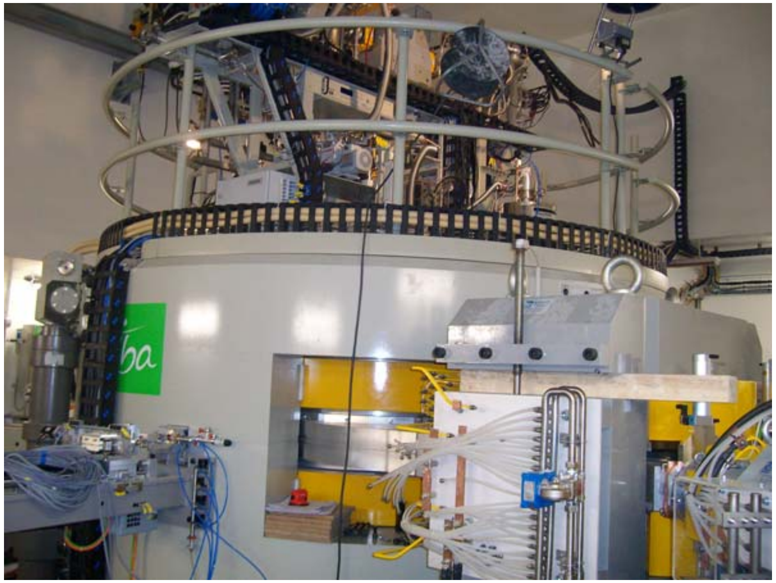
ARRONAX Status



1 year ago

June 08 : the building
is finished

The cyclotron is in place



Beam line are being installed

South Korea

Project Goals of PEFP

■ Project Name : Proton Engineering Frontier Project (PEFP)

21C Frontier Project, Ministry of Science and Technology

■ Project Goals :

1st : Developing & constructing a proton linear accelerator (100MeV, 20mA)

2nd : Developing technologies for the proton beam utilizations & accelerator applications

3rd : Promoting industrial applications with the developed technologies

■ Project Period : 2002.7 – 2012.3 (10 years)

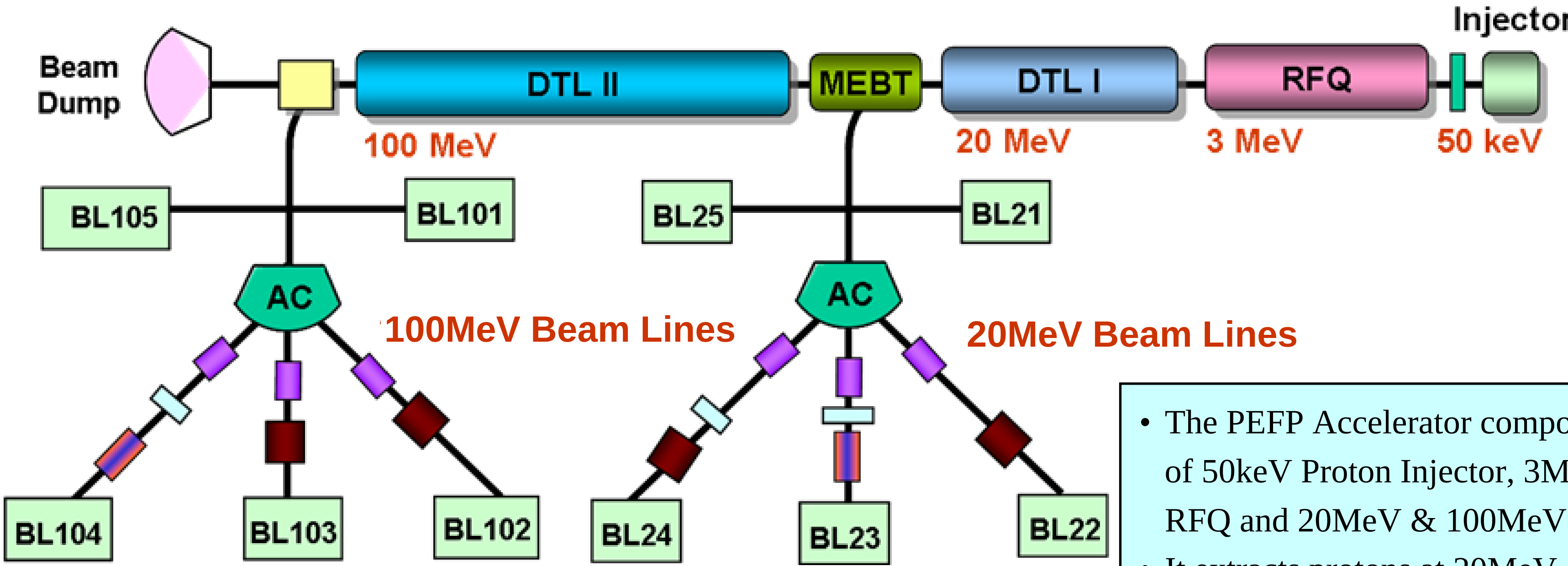
■ Project Cost : 128.6 B Won (Gov. 115.7 B, Private 12.9 B)
(Gyoungju City provides **the land, buildings & supporting facilities)**

Basic Accelerator Parameters

▪ Particle	:	Proton
▪ Beam Energy	:	100 MeV
▪ Operational Mode	:	Pulsed
▪ Max. Peak Current	:	20 mA
▪ RF Frequency	:	350 MHz
▪ Repetition Rate	:	15Hz / **60Hz***
▪ Pulse Width	:	< 1 ms / **1.33ms***
▪ Max. Beam Duty	:	1.5% / **8%***

***) Modified Parameters (06.2)**

PEFP Accelerator and Beam Lines

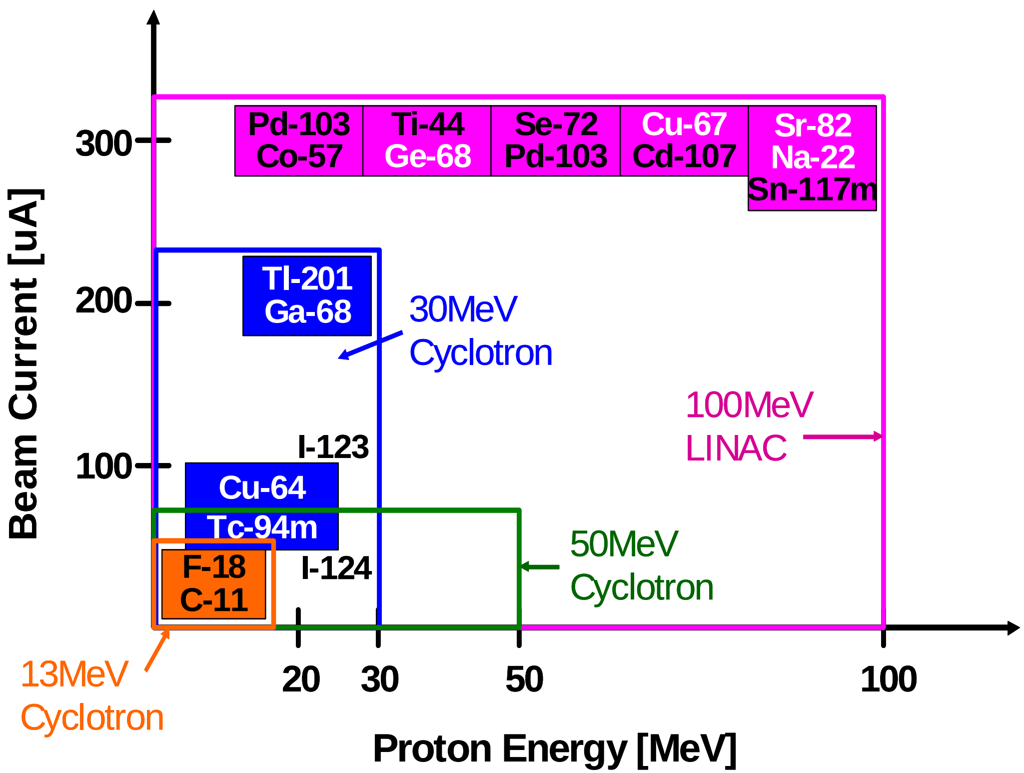


- **102 : ST, BT**
- **104 : LEPT, Medical Application**
- **105 : Neutron Science**
- **101 : RI**
- **103 : Material Science**

- **25 : Material Science, Industrial Application**
- **23 : IT, Semiconductor**
- **22 : BT/ST, Medical Application**
- **24 : Neutron Science**
- **21 : RI**

- The PEFP Accelerator composes of 50keV Proton Injector, 3MeV RFQ and 20MeV & 100MeV DTL's.
- It extracts protons at 20MeV and 100MeV for energy dependent uses.
- Extracted beams are distributed by AC magnets to 5 beam lines at 20MeV and 5 beam lines at 100MeV simultaneously.
- Each beam line has specific beam parameters for appropriate irradiations.

RI Development Plan of PEFP



Status and prospect of RI Production using proton accelerators of various energy range in Korea

- **Several proton accelerators of 11~50MeV are now operating for radioisotope production in Korea.**
- **PEFP will focused on the production of radioisotopes difficult to produce using existing RI production facilities.**
- **Sr-82, Na-22, Cu-67, Ge-68 are the main radioisotopes we are interested in now.**
- **PEFP are going to construct target irradiation facility for RI production at the one end of the beam lines for 100MeV proton beam.**
- **R&D Issues;**
  - **- Target development :100MeV, >300μA**
  - **- Irradiation System : Scanning Magnet etc.**
  - **- New RI development**

RI Development Plan of PEFP

- Benchmarking foreign institutes and facilities
  - TRIUMF (Canada)
  - IPF (LANL, USA)

KIRAMS
Cyclotron Development
MC-50, Cyclone30 Cyclotron
Medical RI Production
New RI Development
Feasibility Study
Basic Demand Survey

- Collaboration with R&D groups of other domestic institute

PEFP
100MeV Proton Linac Development
Irradiation Facility for RI Production
(100MeV, >300μA)
Target Development

Target Irradiation

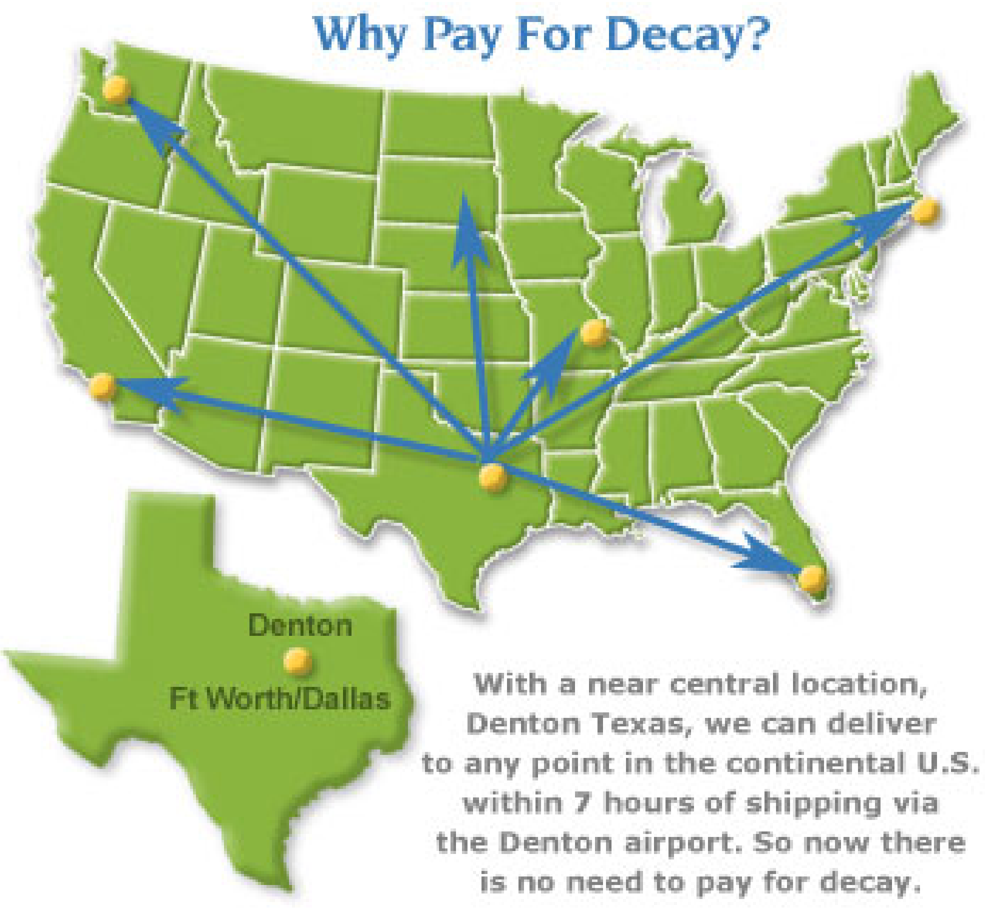
ARTI
30MeV Cyclotron
RI Production Facility
R&D of RI Utilization
New RI Development

- Model : RFT-30
- Particles : Proton
- Current : 350μA
- Energy : 15~30MeV

HANARO
Research Reactor
RI Production Facility
R&D of RI Utilization
New RI Development

- Collaboration with hospital, R&D Institutes, RI society, RI distributor or manufacturers

United States



^{64}Cu
^{67}Cu
^{111}In
^{123}I
^{201}Tl

TRACE LIFE SCIENCES
... Enriching Lives.

Trace Life Sciences is involved in the manufacture and distribution of radioactive pharmaceuticals for use in diagnostic and therapeutic medicine

- **Trace's manufactures medical radioisotopes for three markets:**
  - As active pharmaceutical ingredients for companies to turn into finished goods
  - As finished, approved generic drugs
  - As finished branded drugs sold by specialty pharmaceutical companies (contact mfg.)

Competitive Advantages

- The Linear Accelerator (Linac) allows for the production of radioisotopes more cost effective than the competition; it also has the capacity to generate up to six different radioisotopes simultaneously.
- Trace's facility is centrally located in the U.S., which should provide a cost advantage in shipping radioisotopes around the country.

Current Products

Thallium-201 (Tl-201): Radiochemical and Radiopharmaceutical

- **Iodine-123 (I-123):Radiochemical**; Trace is expected to receive ANDA in mid 2009 for I-123 capsules
- **Indium-111 (In-111):** Radiochemical and Sterile Solution
- **Copper-67 (Cu-67)**
- **Copper-64 (Cu-64)**
- **Other Radioisotopes**: Trace has the capability to produce a wide variety of other isotopes via its linear accelerator and cyclotrons.
- **Contract Manufacturing**: Trace currently has multiple labs and clean rooms available for contract manufacturing.

TRACE LIFE SCIENCES
… Enriching Lives.

Manufacturing Facilities

– Our central location provides significant cost advantages over our main competitor located in Vancouver, Canada
  - Our products have an extremely short shelf life (i.e., I-123 < 14 hours) and proximity to clients provides significant cost savings
– Our linear accelerator for radioisotope production, the only facility of its kind in private use, has been configured to manufacture up to six different radioisotopes simultaneously

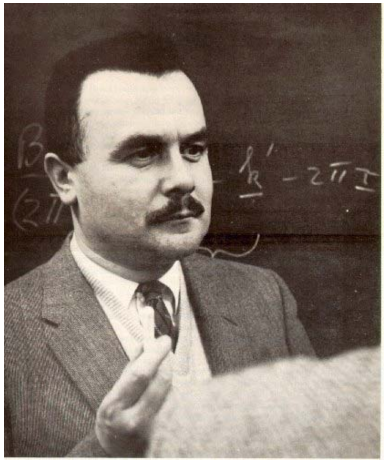
– Our facility is located in Denton, Texas (35 mi from DFW airport) – a key driver of our cost advantage

– The assets (approximately 25 acres) consist of 85,000 sq ft of manufacturing space as well as two cyclotrons and the only non-governmental linear accelerator

– By the third quarter of 2008, our linear accelerator and two cyclotrons will provide us with the largest production base for the manufacturing of radioisotopes in the global nuclear medicine industry

– Trace is currently in discussion to take the linear accelerator to 70Mev.

The Hidden Gem
(in Canada)



Nuclear Science at McMaster University

1957

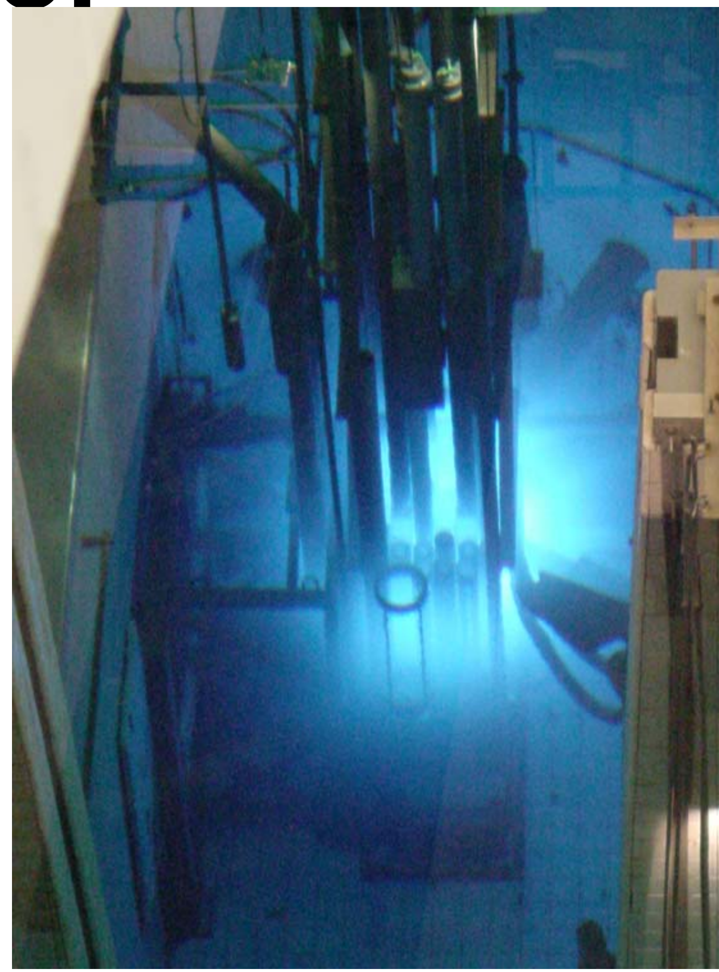
- 1940’s and 50’s: Strong presence in basic nuclear sciences
- 1959: McMaster Nuclear Reactor opened
- 1970’s: Molybdenum-99 production moved from NRU and NRX to McMaster University
- 1990’s: Expansion of the isotope production program (now McMaster is a major Aupplier of I-125)
- 1999: CFI/OIT grant received to renovate nuclear facilities
- 2008: Major grant funding received to establish a centre to translate and commercialize new technologies around medical isotopes and molecular imaging probes

McMaster Nuclear Reactor

- Full Concrete Containment Structure
- Operated under negative pressure
- Adjacent to the Nuclear Research Building (Labs, Researchers, Staff)

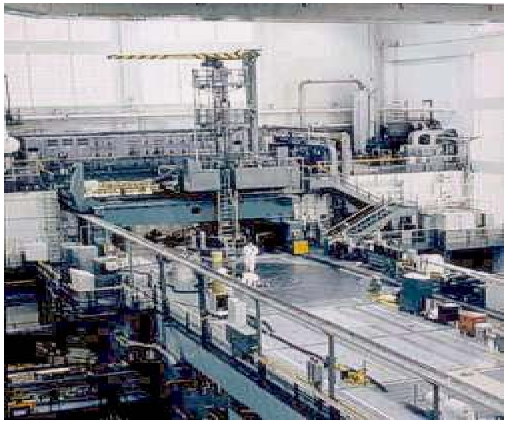
McMaster Nuclear Reactor

- 3 MW Current Power
- 5 d / wk, 16 h / d
- Full Containment Structure (safety and security)
- In-core Irradiations
- Neutron Beams
- Neutron Activation Analysis
- Medical and Commercial Isotopes
- Neutron Radiography
- Hot Cell



Comparing NRU and MNR

NRU



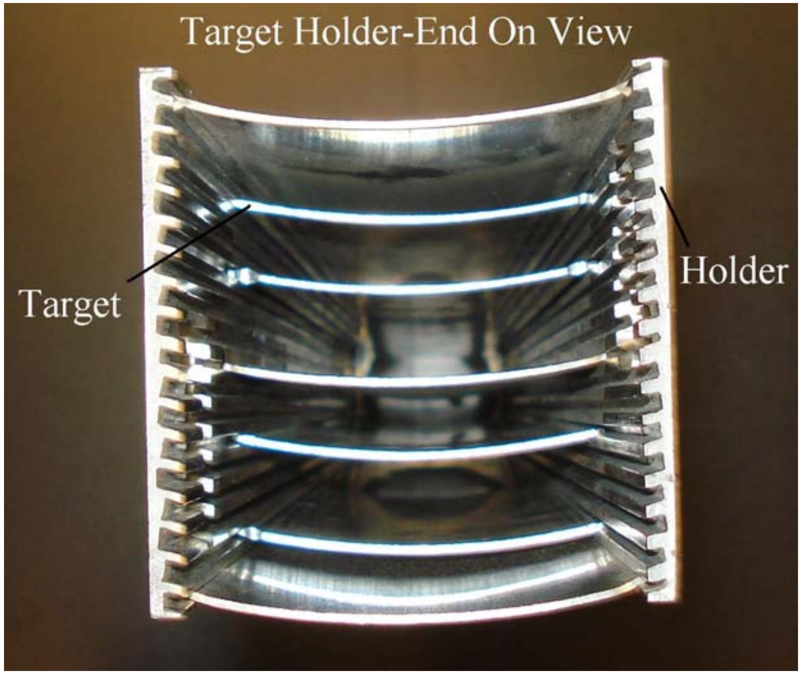
- Flux - 1 x 10^{14}
- Target Enrichment – 93%
- Weight/ target = 2.4 g
- Weight/ assembly = 38.4 g
- 10 assemblies
- Total amount of target = 384 g

MNR

- Flux - 1.75 x 10^{13}
- Target Enrichment – 93%
- Weight/ target = 12.25 g
- Weight/ assembly = 196 g
- 2 - 4 assemblies
- Total amount of target = 392 – 784 g

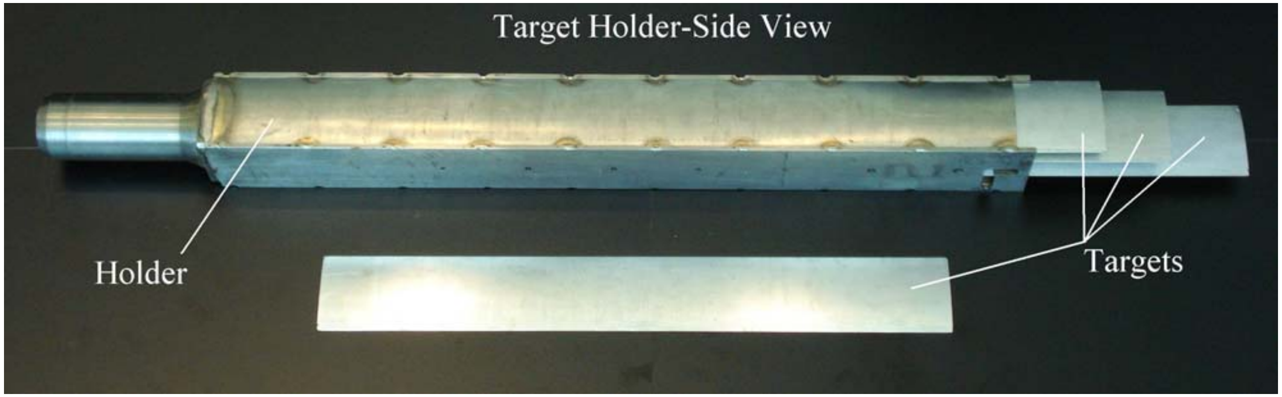
Mo-99 Production at McMaster in the 1970's

- Targets procured from France
- Targets loaded into Zr holder
- Targets irradiated for ~2 weeks
- Irradiated targets shipped to CRL
- Mo-99 recovered at B-225
- Recovered Mo-99 shipped to Kanata



Capacity: 1 assembly = ~1.5 M Doses

MNR has capacity for up to 4 assemblies



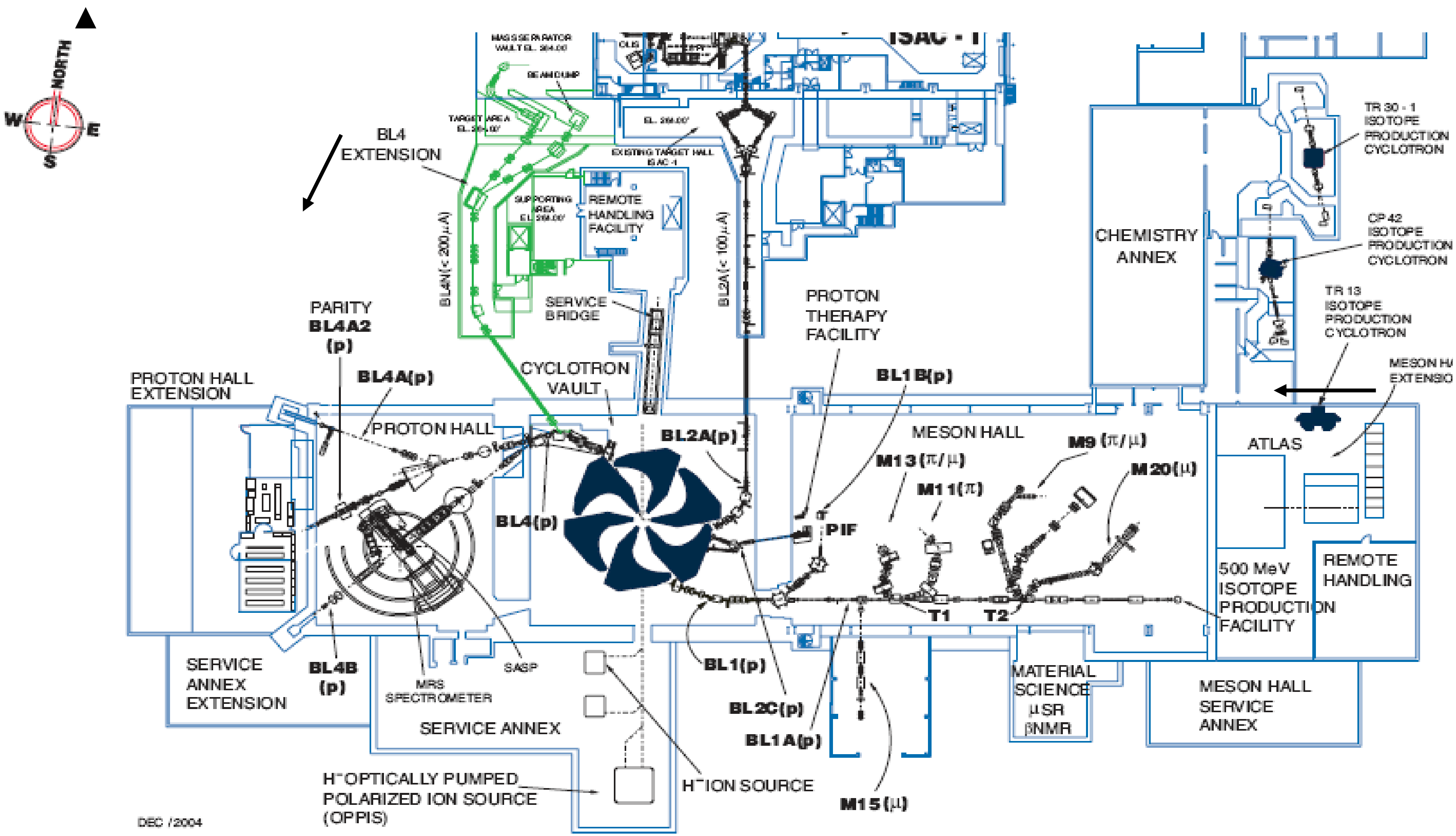
PROPOSED PRODUCTION CYCLES

Number of Target Holders	Frequency of Shipments	Curies per Shipment (EOI)	Curies/ Month (EOI)
One	Every 200h	7,360	26,500
Two	Every 100h	7,360	53,000
Three	Every 67h	7,360	79,500
Four	Every 50h	7,360	106,000

Accelerators at TRIUMF

- 500 MeV Cyclotron (classic H^- design)
- TR13 (13 MeV)
- CP42 (MDS Nordion)
- TR30-1 (MDS Nordion)
- TR30-2 (MDS Nordion)
- Center Region Model (1 MeV)
- RFQ-linac ISAC-I
- Superconducting Linac ISAC-II (contribution agreement milestone met)
- Superconducting E-linac (proposed)

TRIUMF Site



NORTH
W
E
S
BL4 EXTENSION
PARITY BL4A2 (p)
PROTON HALL EXTENSION
BL4A(p)
PROTON HALL
CYCLOTRON VAULT
SERVICE BRIDGE
REMOTE HANDLING FACILITY
BL2A(p)
PROTON THERAPY FACILITY
BL1B(p)
CHEMISTRY ANNEX
MESON HALL
M9 (π/μ)
M13 (π/μ)
M20(μ)
M11(π)
ATLAS
PIF
BL4(p)
T1
T2
500 MeV ISOTOPE PRODUCTION FACILITY
REMOTE HANDLING
TR 30 - 1 ISOTOPE PRODUCTION CYCLOTRON
CP 42 ISOTOPE PRODUCTION CYCLOTRON
TR 13 ISOTOPE PRODUCTION CYCLOTRON
SERVICE ANNEX EXTENSION
BL4B (p)
MRS SPECTROMETER
SASP
SERVICE ANNEX
BL1(p)
BL2C(p)
BL1A(p)
MATERIAL SCIENCE μSR βNMR
MESON HALL SERVICE ANNEX
H⁻ OPTICALLY PUMPED POLARIZED ION SOURCE (OPPIS)
H⁻ ION SOURCE
M15(μ)
DEC /2004

Challenge for TRIUMF

- No chemistry processing cells for the longer lived, non-commercial radionuclides.

e-linac

- Electron linear accelerator or e-linac is a major part of the 5-year funding proposal submitted to NRC in February 2009 (2010-2015 funding cycle for TRIUMF
  - 50 MeV electrons and converter to make gammas that photo-fission U-238
- Present design current 10mA (0.5 MW)
  - 20mA achieved and 100mA viewed as feasible (5 MW)
- Technical limitation is power dissipation in converter
- First phase operation 2013 (> 100 kW)
  - Achieving higher power is funding limited
  - Civil construction of tunnel sets t=0 (assume 2009 is beginning of design work)
- Presently seeking immediate support for civil construction to meet 2013 goal

Role of TRIUMF: Thrust in photo-fission

Machine has significant capabilities for benchmarking Mo-99 production through photo-fission of U-238 (non-weapons grade but “same” high specific activity)

Other Cyclotron Based Efforts

I S T C

М Н Т Ц

International Science and Technology Cooperation

Philosophical Reflections

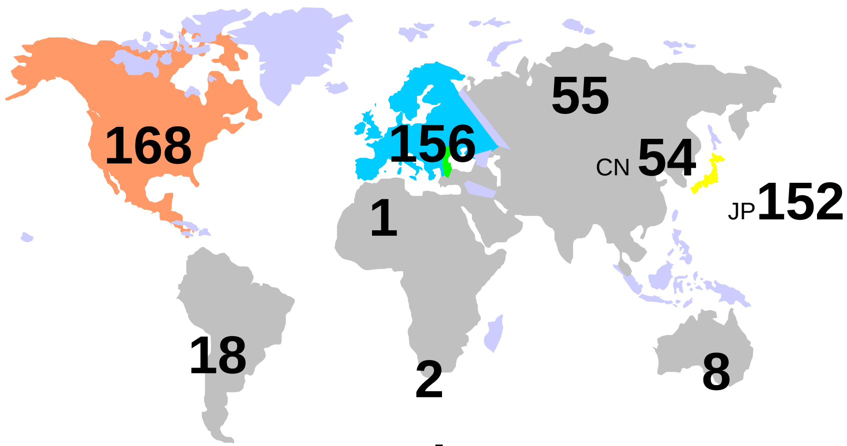
- Private enterprise vs Public Good
- What obligation does government have in securing a stable supply of medical radioisotopes?
- Nearly all radioisotope producers around the world are subsidized by their governments.
- However, DOE radioisotope production labs are not known for their efficiency in supplying the radioisotope community.

PET vs SPECT

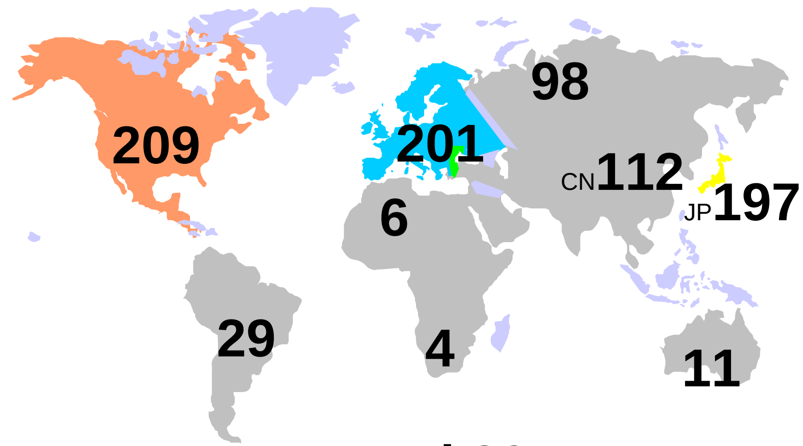
- With the supply of Mo-99 in danger* in the near term will the use of the $^{99}Mo/^{99m}Tc$ generator loose ground to PET imaging for diagnostic medicine?

** Cancellation of Maple project, NRU license expires in 2011 with renewal expected to go to 2015*

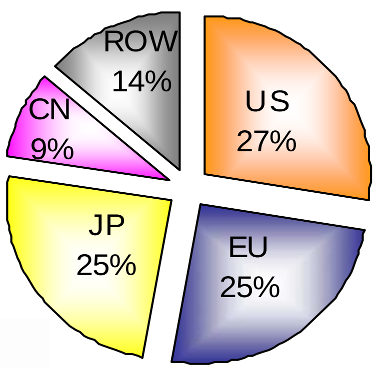
Total PET cyclotrons worldwide 2006-2011



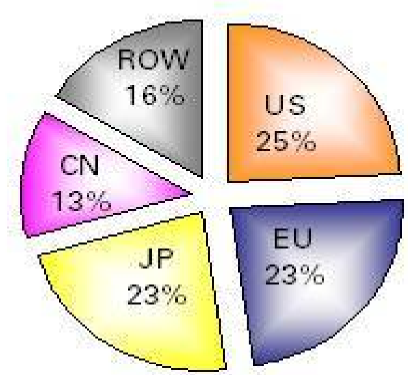
End 2006
613 cyclotrons



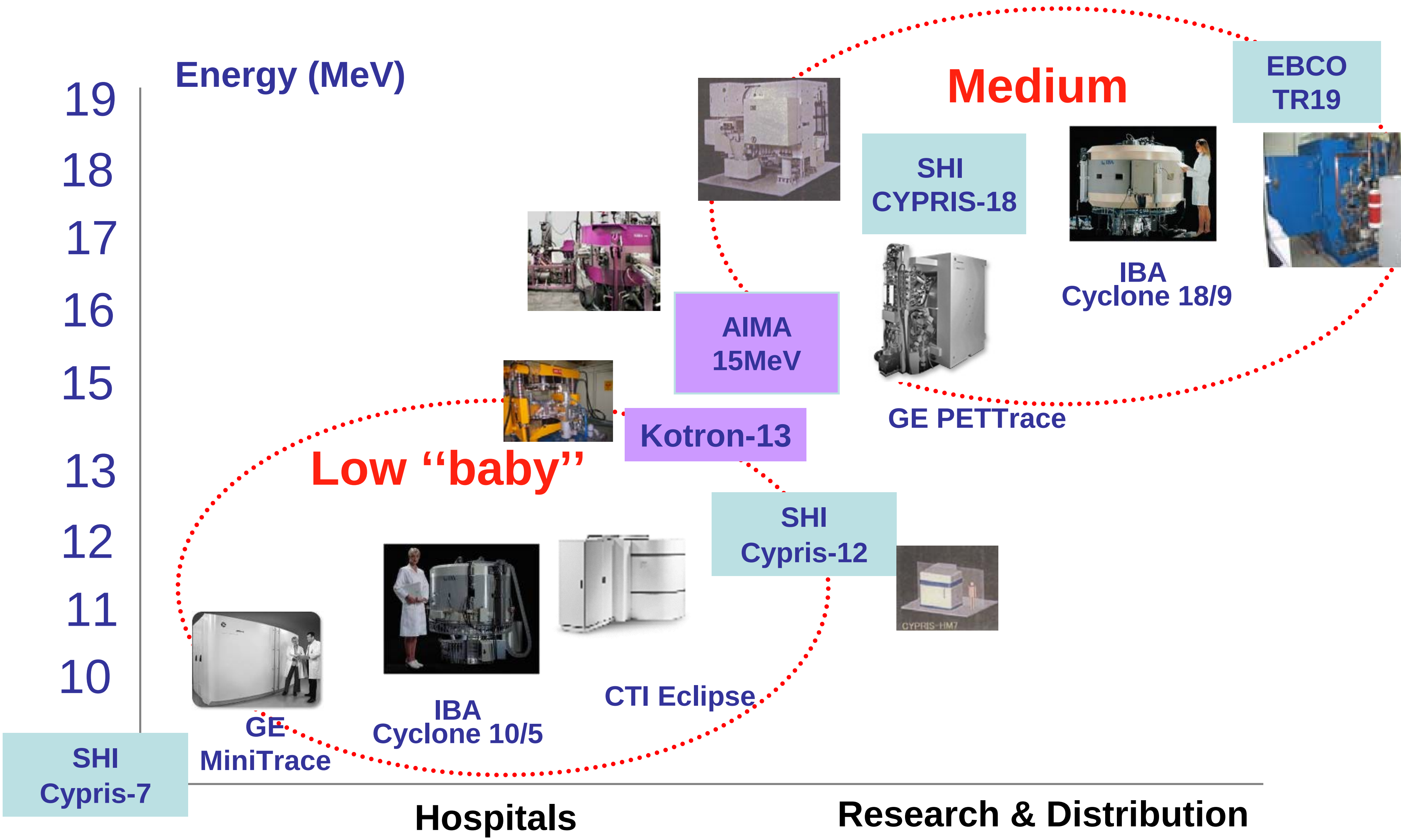
End 2011
863 cyclotrons



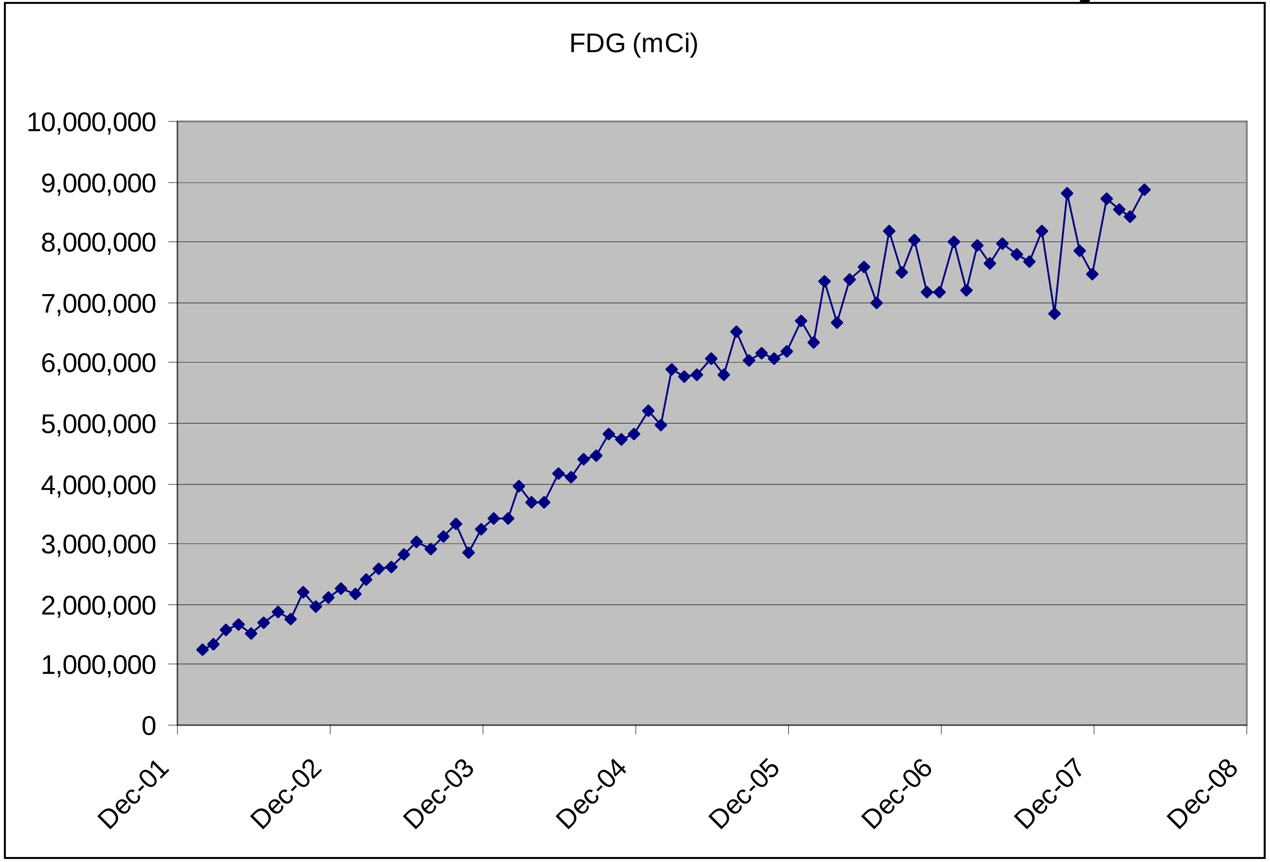
Period 2007-2011 average of 50 cyclos sold/year



PET Cyclotron Market



Growth of FDG produced by PETNET in the last 7 years

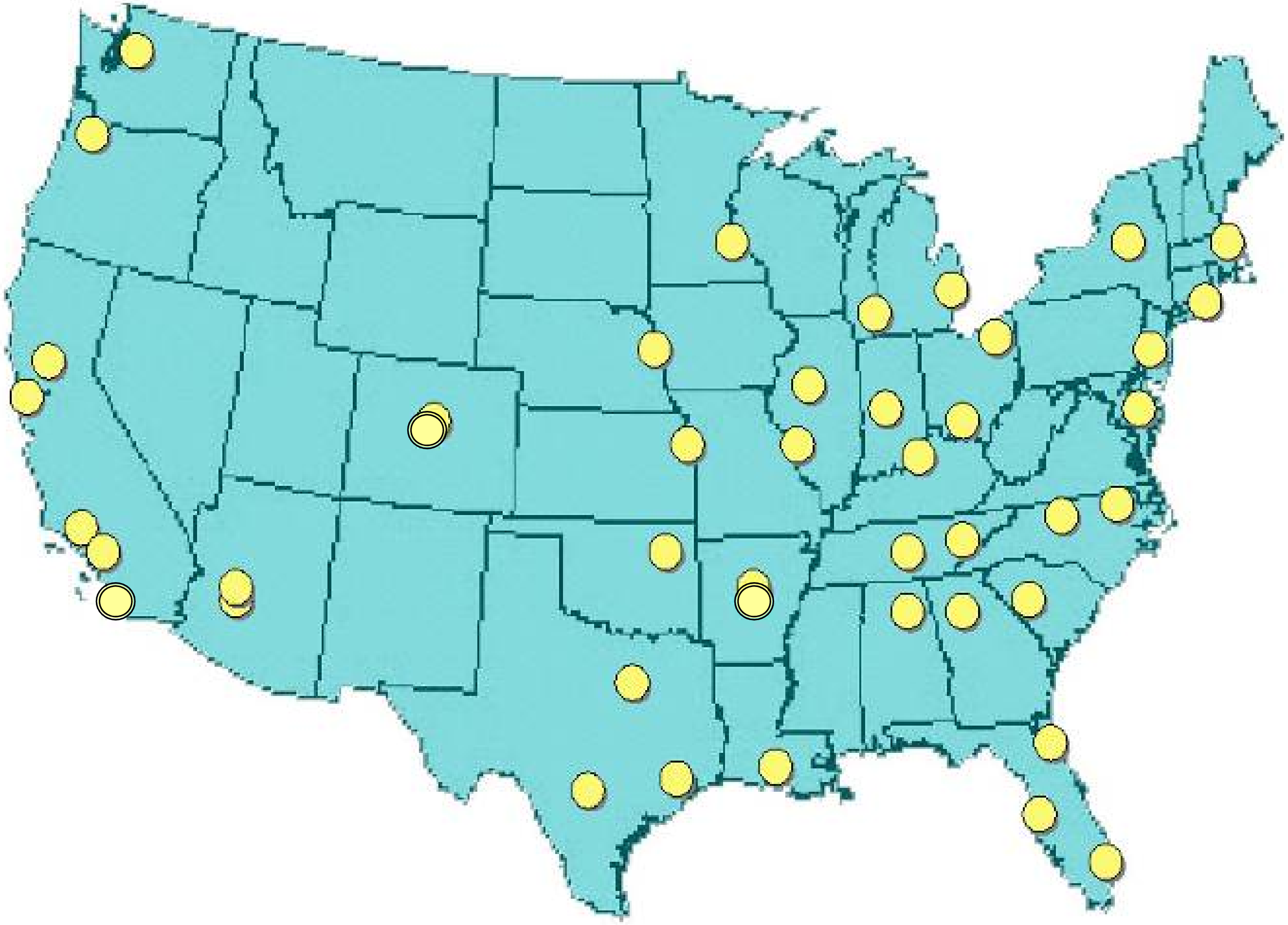


Ci per month of FDG produced – PETNET production records Dec 2001 to present

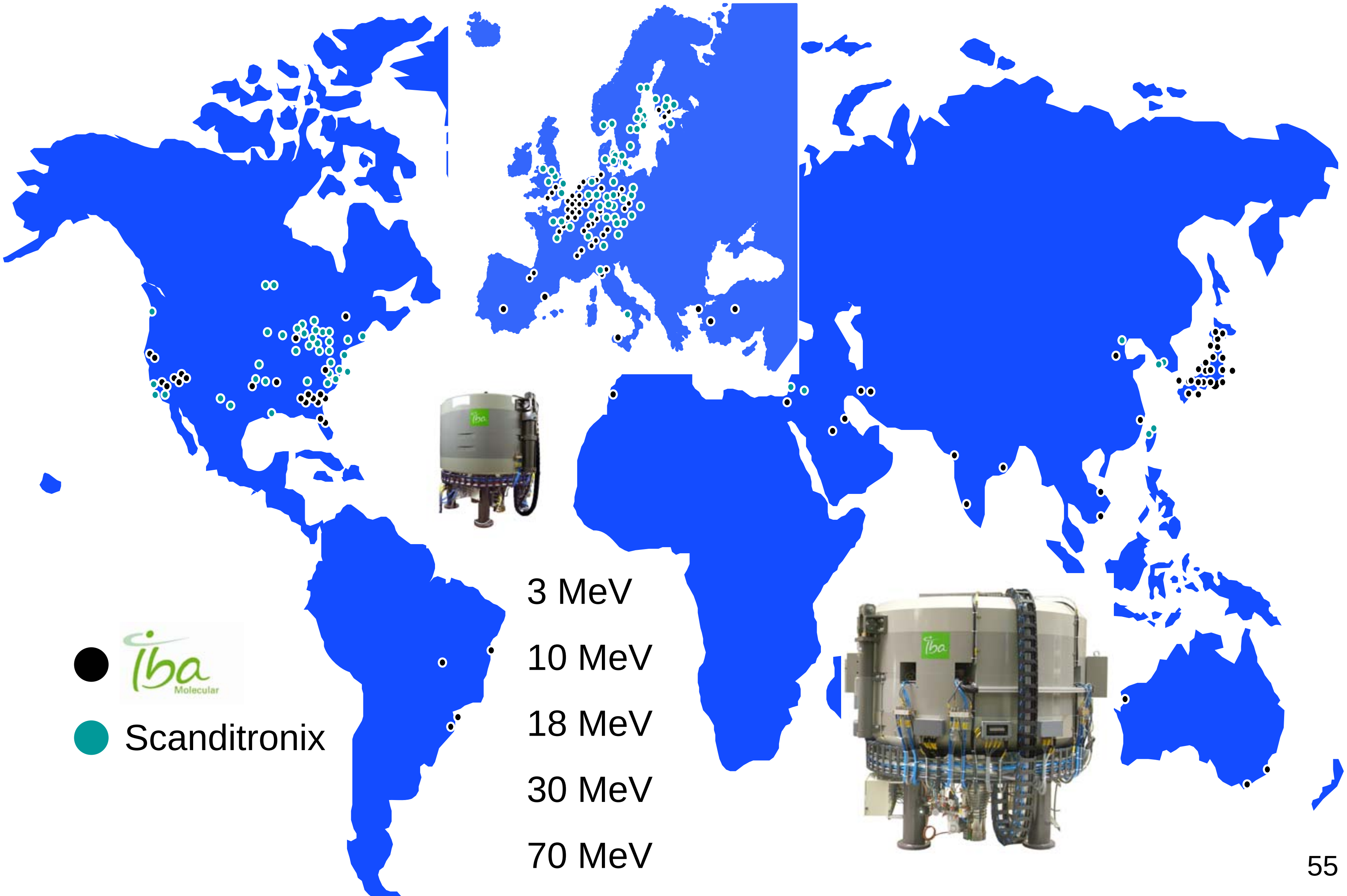
The Gold Standard - Eclipse

- Pioneered the self-shield, fully automated, fully integrated system
- >150 Eclipse cyclotrons systems installed worldwide
- Reliable system with very high uptime
- Proven in research, clinical, and distribution facilities
- Most widely used system for research and distribution
- High production yields of all PET Isotopes

PETNET World-Wide Today



IBA Molecular References



- ● iba Molecular
- ● Scanditronix

3 MeV

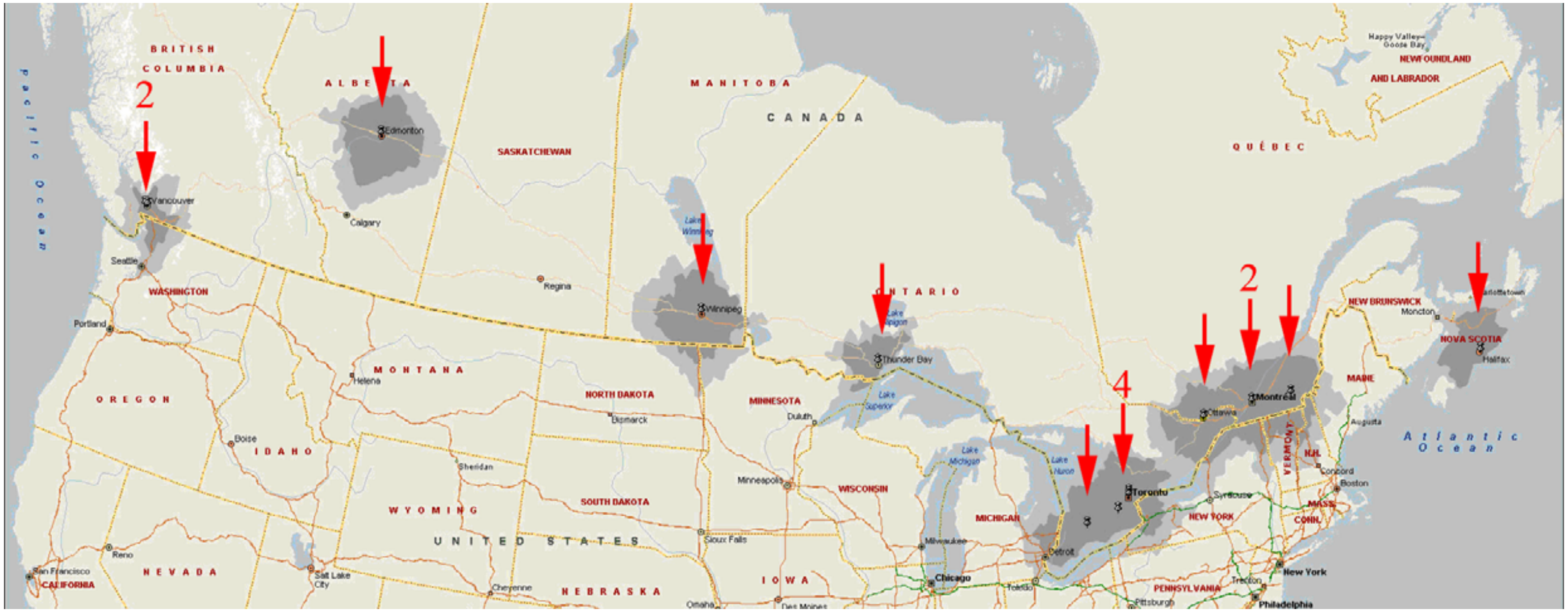
10 MeV

18 MeV

30 MeV

70 MeV

Networking Canada's Cyclotrons



Red arrows indicate operational or nearly operational medical cyclotron facilities. Some arrows indicate more that one facility. Dark and light gray shading represent 120 and 180 minute land transportation regions.

Courtesy, Frank Prato

Errors of Omission/Fact!

- Totally my fault and my humble apologies for leaving out your favor topic or if I have misrepresented some aspect of the resources available around the world or your neighborhood.

Acknowledgements

- I wish to thank the following individuals and the institutions they represent for sharing the slides and information about their facilities:
- Boris Zhuikov – INR, Russia
- Clive Naidoo – iThemba, South Africa
- Ferid Haddad –Arronax, France
- Bill Alvord, Siemens Medical
- Dan Conatser – IBA, Belgium
- Tracey Lane – Trace Life Sciences, Denton, TX
- Kye-Ryung Kim - Proton Engineering Frontier Project, Korea
- John Valliant – McMaster University, Canada
- Frank Prato – St. Joseph Hospital, London, ON

Acknowledgements

- I wish to thank the organizers for inviting me to participate in this workshop.

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