Boris Zhuikov

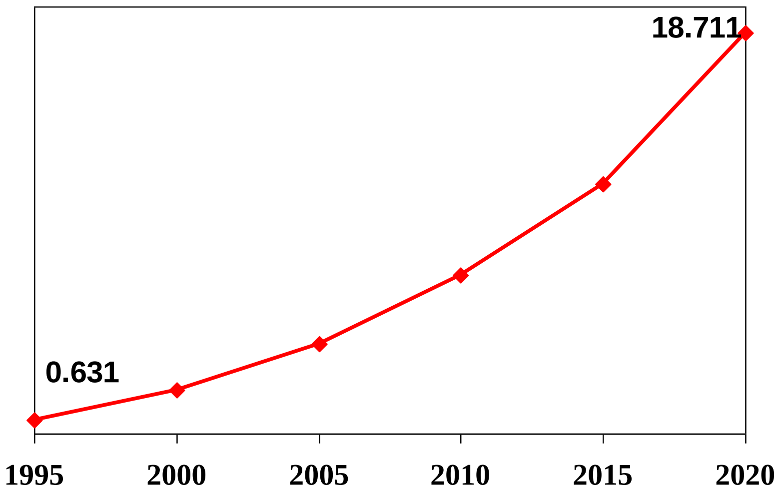
Production of Medical Radionuclides in Russia and Isotope Program in Institute for Nuclear Research, Moscow-Troitsk

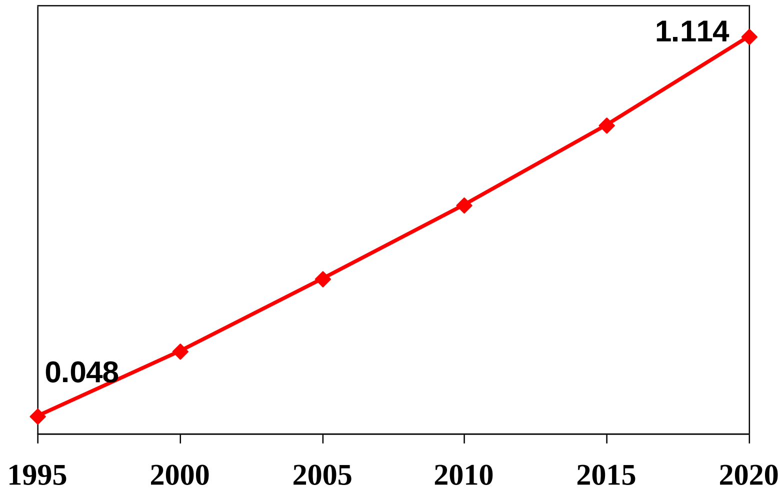
Geneva, Switzerland, June 21, 2018

<u>OLD</u> Prognosis of Sales of Radiopharmaceuticals in World Market for Years 1995-2020

DIAGNOSTICS ***THERAPHY***

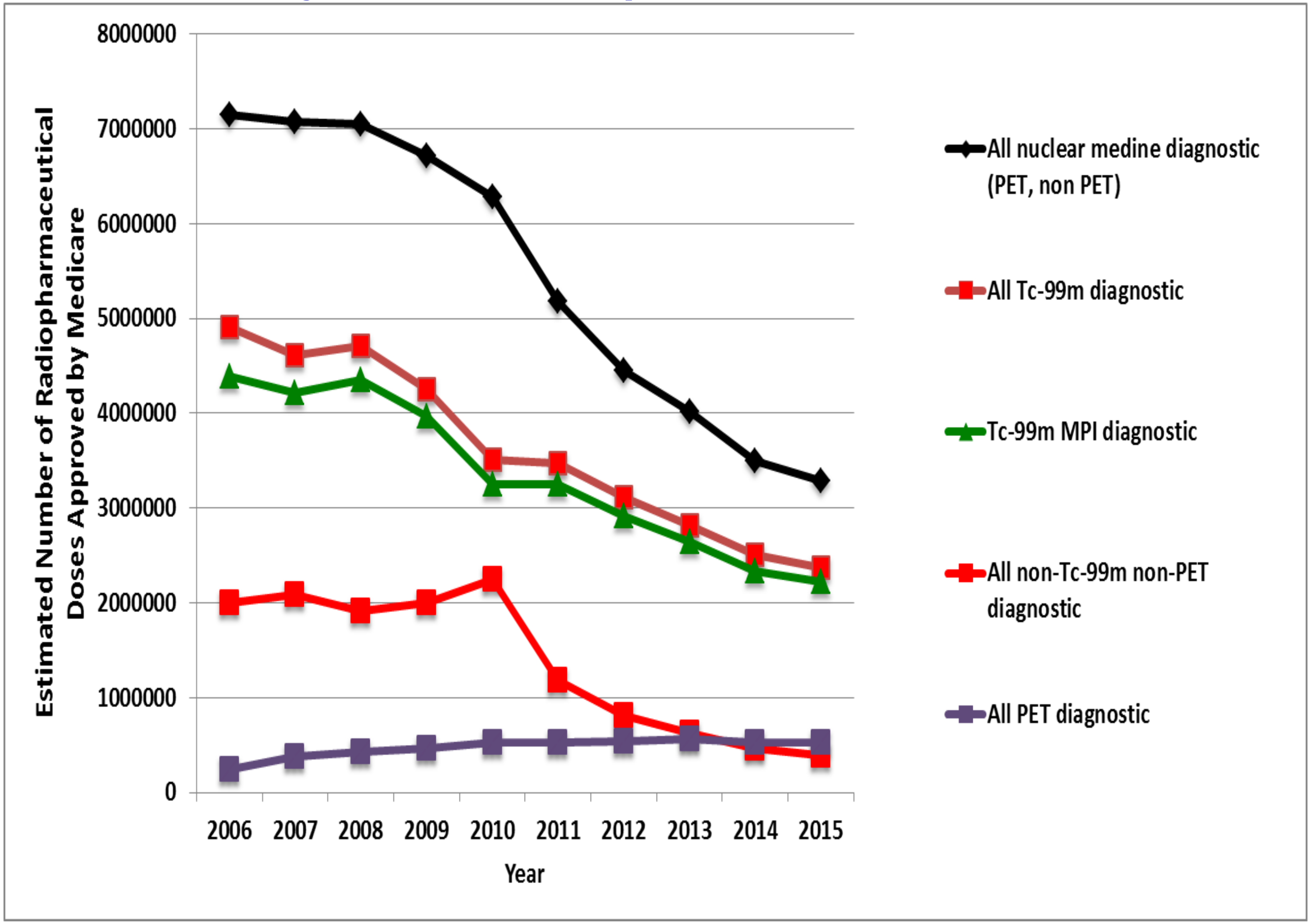
Billion $





USA NASEM-Russian Academy of Sciences Committee, 2017
«Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets»

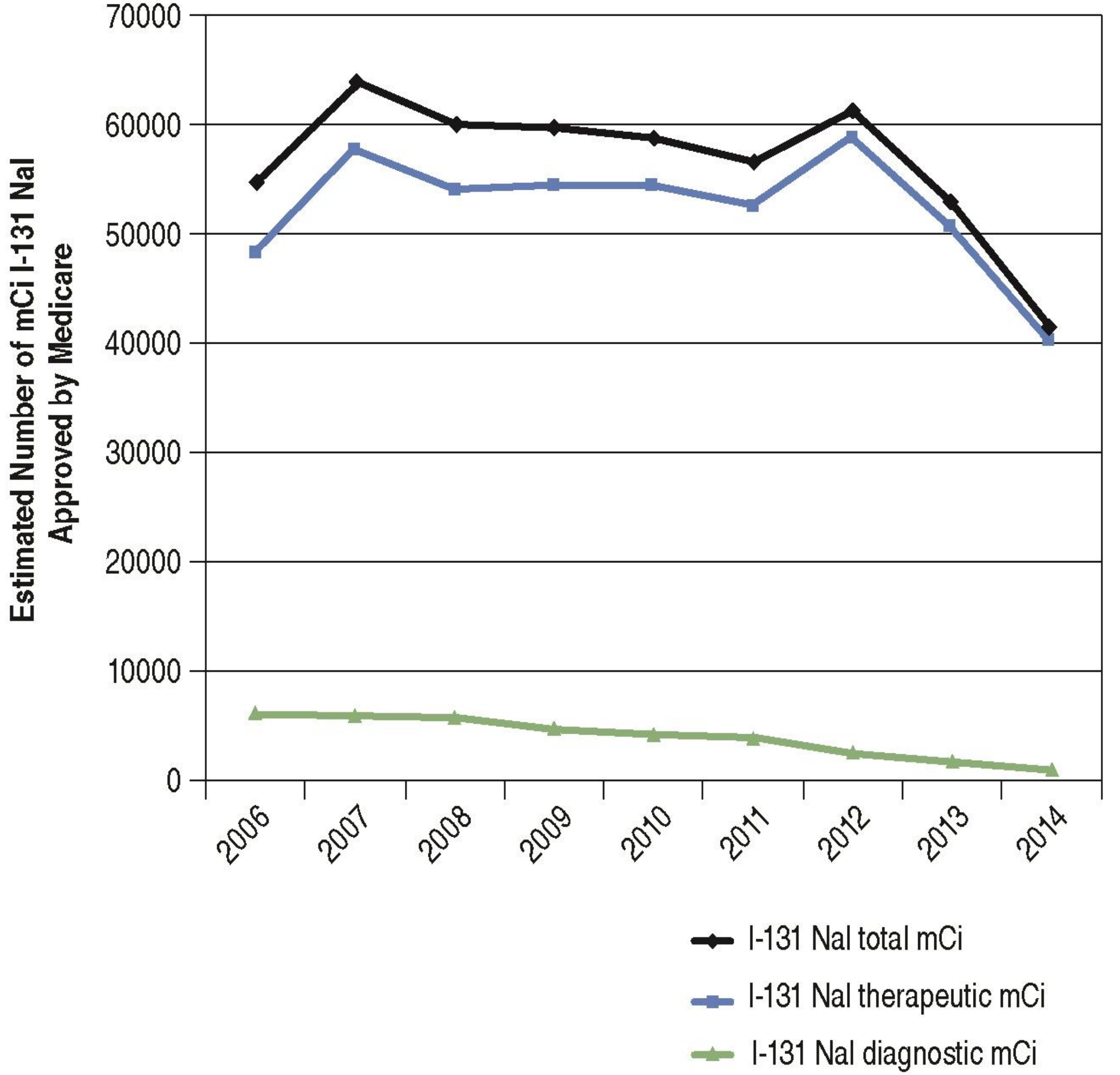
Estimated utilization of nuclear medicine diagnostic radiopharmaceuticals by Medicare beneficiaries: 2006-2015



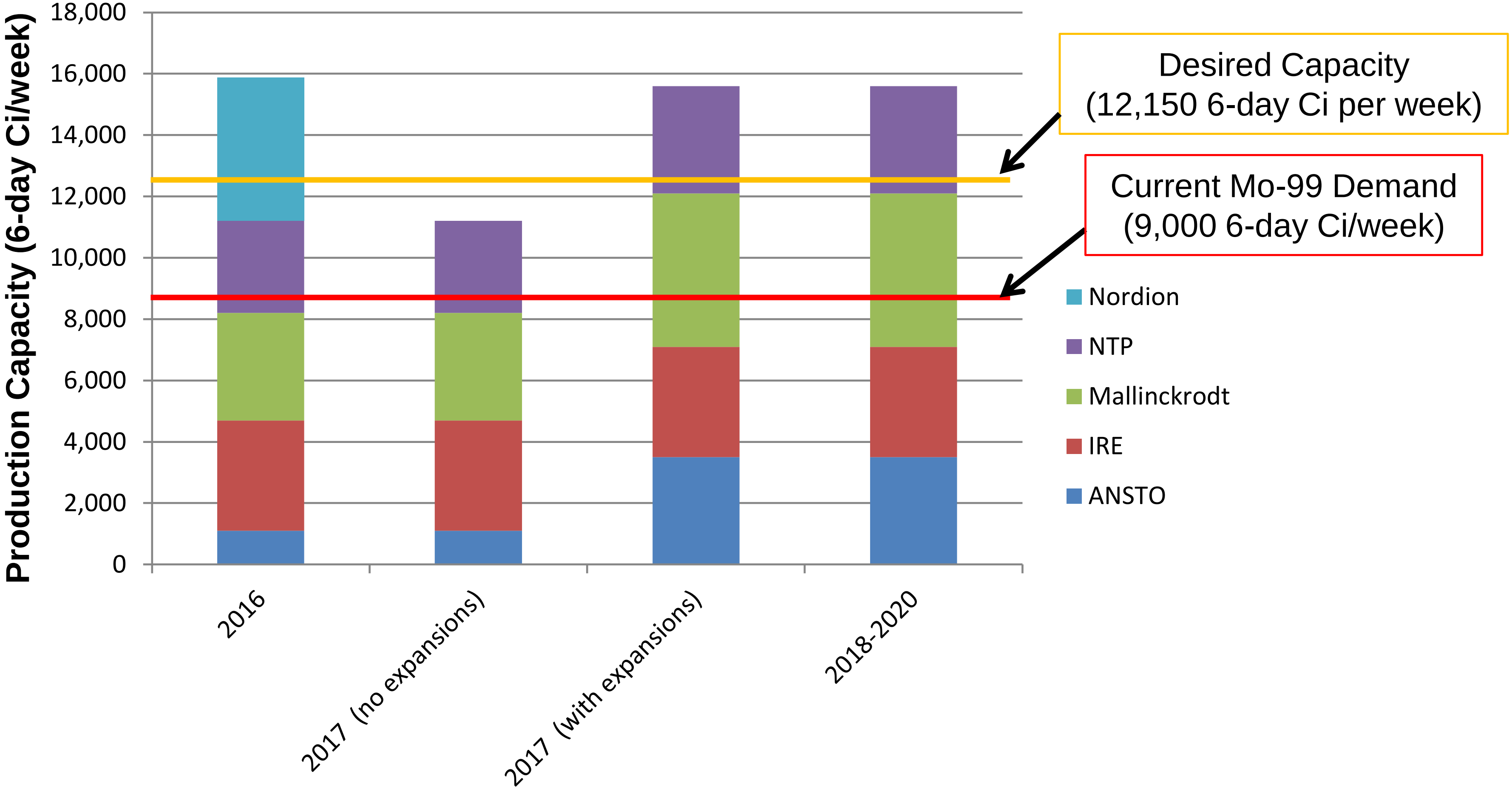
SOURCE: Courtesy of Kathrine Morton, University of Utah

Estimated Utilization of I-131 by Medicare Beneficiaries: 2006-2014

(NASEM-2016)

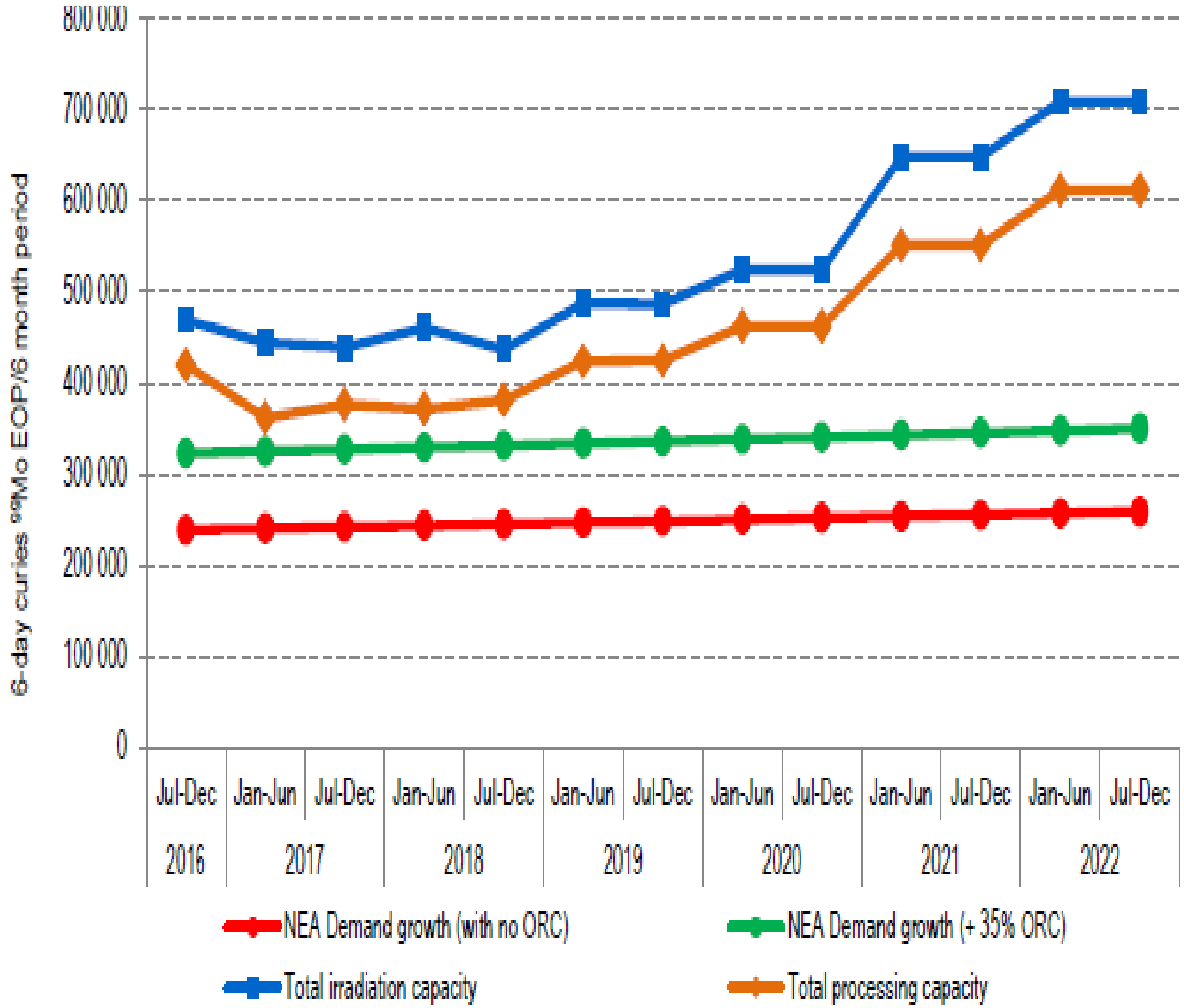


Fractures of the Main Producers of Mo-99



SOURCE: Kevin D. Crowley, Director, Nuclear and Radiation Studies Board

Modeling Scenarios for Demand and Production Capacity of Mo-99



Main Producers of Medical Isotopes in Russia

- **Research Institute of Atomic Reactors (Dimitrovgrad): 4 nuclear reactor, hot cells**
  ^{99}Mo, ^{144}Ce-sources, ^{117m}Sn, ^{153}Sm , ^{153}Gd, ^{192}Ir, ^{177}Lu, ^{117m}Sn, ^{125}I, ^{131}I, ^{188}W, ^{89}Sr, ^{131}Cs
- **Karpov Institute of Physical Chemistry (Obninsk): nuclear reactor, hot cells**
  ^{99}Mo, ^{153}Sm, ^{99m}Tc-generator, ^{131}I-radiopharmaceuticals, ^{188}W/^{188}Re-generator (under development), ^{192}Ir, ^{225}Ac (under development with INR RAS and MSU)
- **Institute for Physicas and Power Engineering (Obninsk): hot cells**
  ^{99m}Tc-generator, ^{188}W/^{188}Re-generator, ^{89}Sr, ^{225}Ac, ^{133}Xe, ^{32}P, ^{90}Sr –source,^{125}I-source, ^{106}Ru-applicator, generator ^{225}Ac/^{213}Bi (under development)
- **Production Association MAYAK (Ozersk, Ural region): nuclear reactor, hot cells**
  ^{89,90}Sr, ^{32}P, ^{35}S, ^{14}C, (^{192}Ir , ^{60}Co)
- **Kurchatov Institute of Atomic Energy (Moscow): cyclotron, liquid fuel reactor**
  ^{201}Tl, ^{123}I, ^{99}Mo-^{89}Sr (in development)
- **Institute of Nuclear Physics of Polytechnic University(Tomsk):reactor, cyclotron**
  ^{99}Mo, ^{99}Mo/^{99}Tc-generator, ^{199}Tl, ^{67}Ga, ^{123}I
- **Khlopin Radio Institute (St-Petersburg): cyclotron, nuclear reactor of LAES,hot cells**
  $^{123, 124,125}$I, ^{67}Ga, ^{106}Ru,^{186}Re, ^{99}Mo/^{99m}Tc-generator
- **Institute of Nuclear Materials (Zarechny, Ural region): reactor, hot cells**
  ^{14}C, ^{33}P, ^{32}P, ^{35}S, ^{90}Y, ^{192}Ir, ^{131}Cs
- **Medical Preparations Plant at A.I. Burnazyan Medical Center (Moscow): hot cells**
  ^{201}Tl, ^{89}Sr, ^{67}Ga-^{131}I-radiopharmaceuticals,^{59}Fe(under development)
- **Cyclotron Co. (Obninsk): two cyclotrons, hot cells**
  ^{68}Ge, ^{68}Ge/^{68}Ga-generator, ^{67}Ga, ^{85}Sr, ^{103}Pd, ^{111}In, ^{195}Au
- **Institute for Nuclear Research of Russian Academy of Sciences (Troitsk): LINAC**
  Targets with ^{82}Sr, ^{117m}Sn, ^{103}Pd, ^{68}Ge; ^{72}Se, ^{64,67}Cu, ^{225}Ac-^{223}Ra (under development)

Research Institute of Atomic Reactors (RIAR), Dimitrovgrad (Volga region)

Produced radionuclides:

^{99}Mo

^{117m}Sn, ^{125}I, ^{131}I, ^{188}W, ^{89}Sr, ^{153}Sm, ^{177}Lu, ^{144}Ce - spring microsources, actinides

Nuclear reactors for isotope production: RBT-10/2, RBT-6

BOR-60 (fast neutrons)

SM-3 $3 \cdot 10^{15}$ n/cm$^2 \cdot$s

Karpov Institute of Physical Chemistry (Obninsk branch)

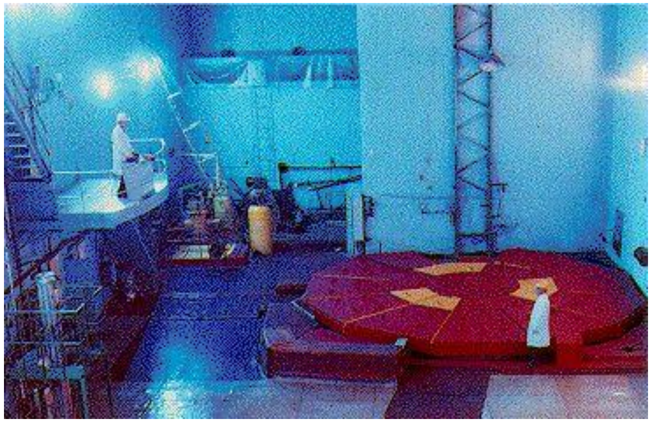
Nuclear reactor
Hot cells

PRODUCED RADIONUCLIDES

^{99}Mo (local supplies and export)
^{99m}Tc-generator
^{131}I-sodium iodide, sodium hippurate, bengal rose, human serum albumin
^{125}I (under development)
^{153}Sm, ^{67}Ga-citrate,
^{188}W/^{188}Re-generator (under development)
^{103}Pd (together with INR)
^{225}Ac (together with INR and MSU)

Institute for Physics and Power Engineering (IPPE), Obninsk, Kaluga region

First world's nuclear power plant



MEDICAL ISOTOPE PRODUCTION

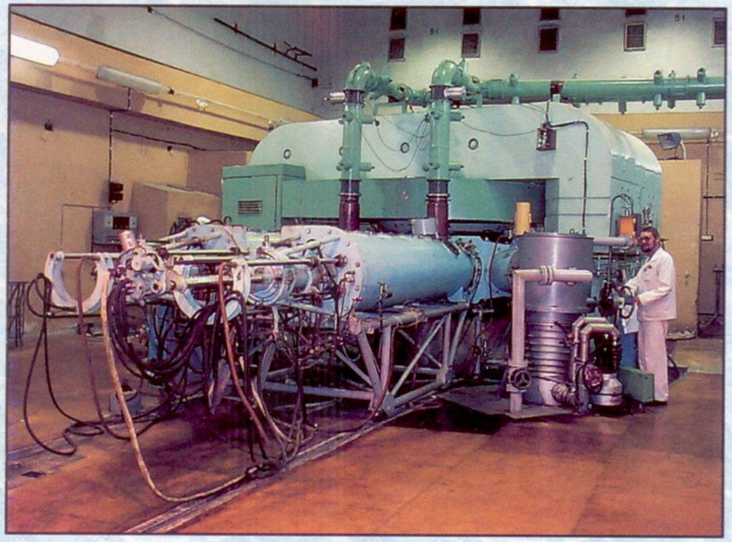
- ^{99m}Tc-generator (GMP in project)
- ^{188}W/^{188}Re-generator
- ^{125}I – microsources for prostate cancer therapy
- ^{90}Sr – microsources for cardio-vascular therapy
- ^{225}Ac, ^{225}Ac/^{213}Bi-generator (under development)
- ^{133}Xe
- ^{32}P

Cyclotron Co., Obninsk (at IPPE site)

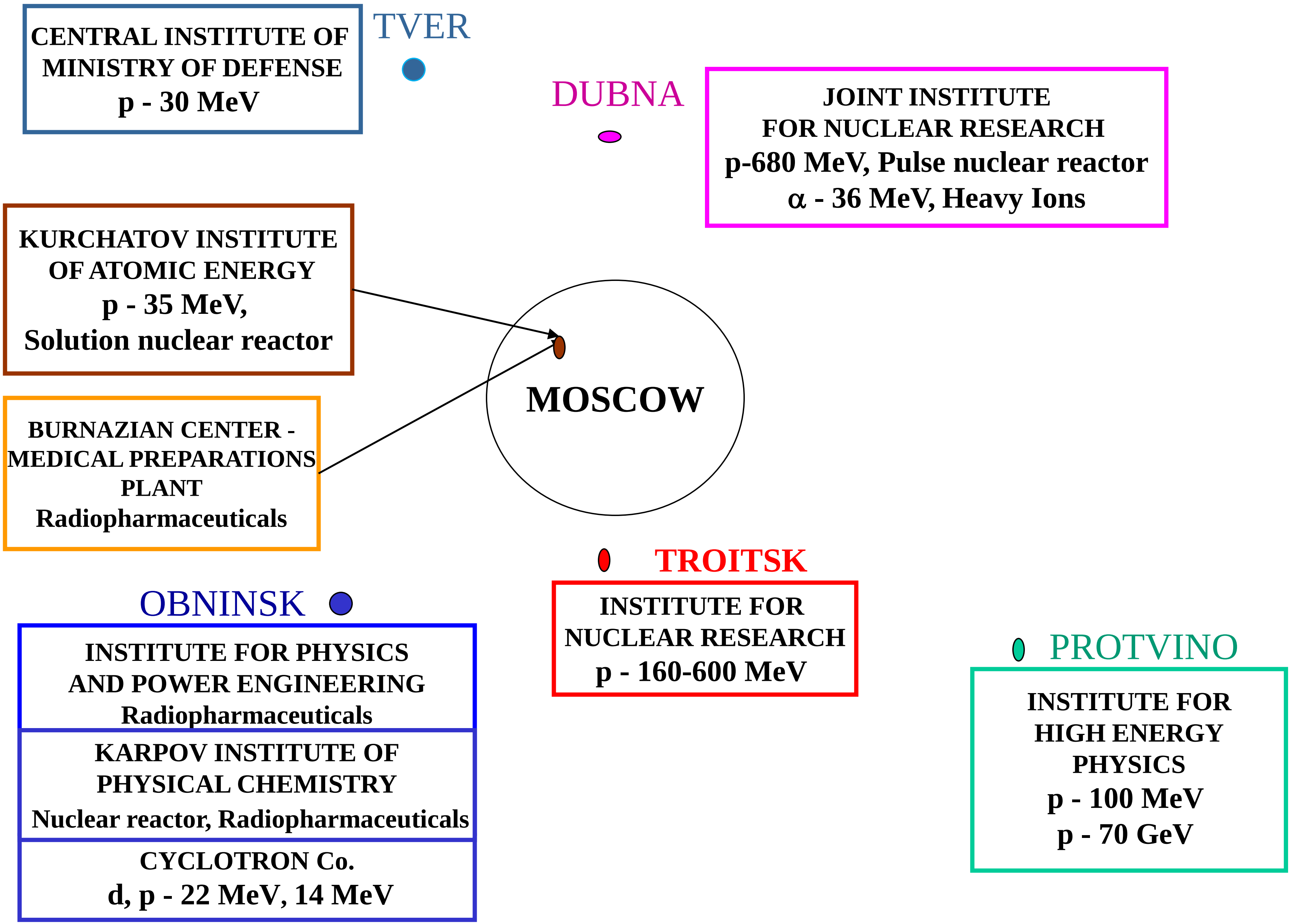
TWO CYCLOTRONS:
23 MeV (1100μA) and 14 MeV (1500μA) protons, deuterons, α-particles

PRODUCED RADIONUCLIDES
^{67}Ga, ^{68}Ge, ^{103}Pd, ^{111}In, ^{85}Sr,
^{68}Ge/^{68}Ga-generator (in collaboration with A.I.Burazyan Medical-Biological center)

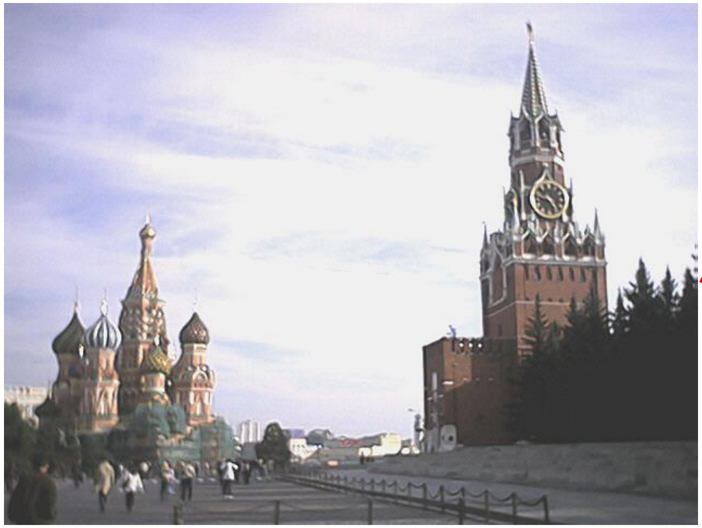
7 HOT CELLS


CYCLOTRON U-150


RADIOCHEMICAL SECTION


CENTRAL INSTITUTE OF MINISTRY OF DEFENSE
p - 30 MeV
TVER
DUBNA
JOINT INSTITUTE FOR NUCLEAR RESEARCH
p-680 MeV, Pulse nuclear reactor
α - 36 MeV, Heavy Ions
KURCHATOV INSTITUTE OF ATOMIC ENERGY
p - 35 MeV,
Solution nuclear reactor
MOSCOW
BURNAZIAN CENTER - MEDICAL PREPARATIONS PLANT
Radiopharmaceuticals
TROITSK
INSTITUTE FOR NUCLEAR RESEARCH
p - 160-600 MeV
OBNINSK
INSTITUTE FOR PHYSICS AND POWER ENGINEERING
Radiopharmaceuticals
KARPOV INSTITUTE OF PHYSICAL CHEMISTRY
Nuclear reactor, Radiopharmaceuticals
CYCLOTRON Co.
d, p - 22 MeV, 14 MeV
PROTVINO
INSTITUTE FOR HIGH ENERGY PHYSICS
p - 100 MeV
p - 70 GeV

Institute for Nuclear Research of Russian Academy of Sciences



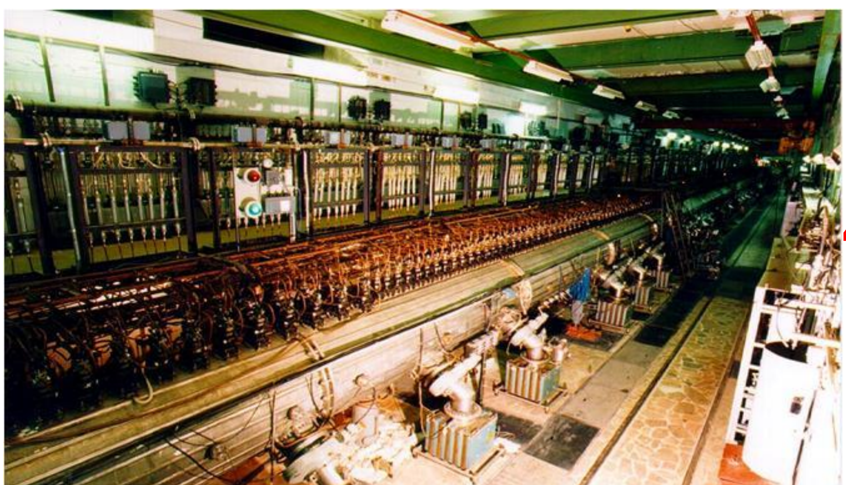
20 km

TROITSK TOWN

Now a part of Moscow

1 km

INR ACCELERATOR

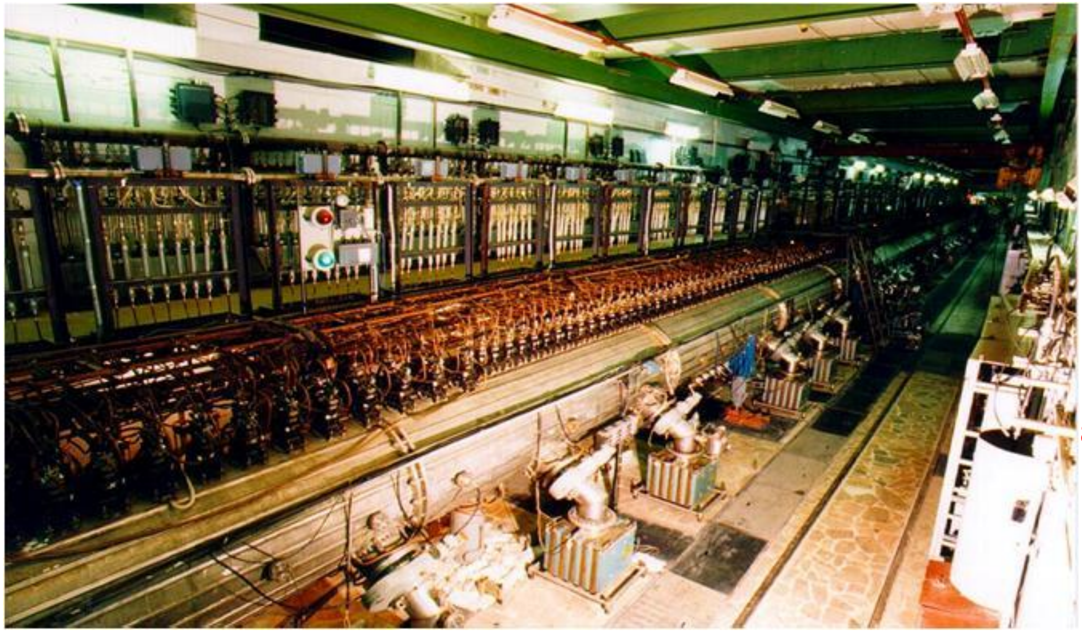


Protons 160 (600) MeV,

Beam current 120 (500) μA

Target Irradiation Facility for Isotope Production at Linear Accelerator of Institute for Nuclear Research, Troitsk

(constructed 1992, several upgrades)



Proton energy: 158 MeV

***(options:* 143,127,113,100,94 MeV)**

Typical beam current: 120 μA

PRODUCED RADIONUCLIDES:

^{82}Sr, ^{117m}Sn, ^{22}Na, ^{109}Cd, ^{103}Pd, ^{68}Ge, ^{83}Rb

Under development:

^{72}Se, ^{64,67}Cu, ^{225}Ac, ^{223}Ra

Existing Accelerator Facilities for Radioisotope Production at High Intensity Proton Beam of Intermediate Energy

- **Los Alamos National Laboratory (NM, USA), 100 MeV, 200 μA**
- **Brookhaven National Laboratory (NY, USA), 200 MeV, 100 μA**
- **Institute for Nuclear Research (Troitsk, Russia), 160 MeV, 120 μA**
- **TRIUMF (Vancouver, Canada), 110 MeV, 500 MeV, 80 μA**
- **iThemba Laboratory (Cape Town, South Africa), 66 MeV, 250 μA**
- **ARRONAX GIP (Nantes, France), 70 MeV, 2 x 150 μA**
- **ZEVACOR (Indianapolis, USA), 70 MeV, 2 x 200 μA**

Proposed Accelerator Facilities for Radioisotope Production at High Intensity Proton Beam of Middle Energy

- **Legnaro National Laboratory, INFN (Padova, Italy)**
  Cyclotron - 70 MeV, 2x400 μA

- **Proton Engineering Frontier Project (Gyoungju, South Korea)**
  LINAC - 100 MeV, >300 μA

- **CDNM, Institute of High Energy Physics of Kurchatov National Center (Protvino, Russia) H^- Cyclotron – 70 MeV: production of ^{82}Sr**

- **Institute for Nuclear Research (Troitsk, Russia)**
  H^- Cyclotron – 70 (120) MeV, 750-1000 μA: production of ^{82}Sr, ^{117m}Sn (^{225}Ac,^{223}Ra)

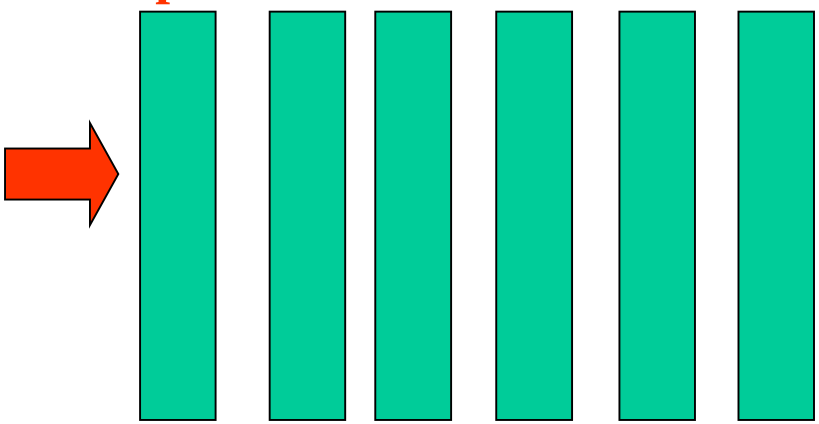
- **Petersburg Nuclear Physics Institute**
  H^- Cyclotron - 80 MeV, 100-200 μA, Isotope separator facility: ^{82}Sr from Y-target

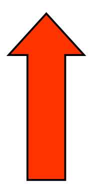
- **Institute for Nuclear Research of National Academy of Sciences of Ukraine (Kiev)**
  H+ Cyclotron, 70 MeV, 100 μA (^{82}Sr production from RbCl-target)

Advantages and disadvantages of targetry at different proton energy

High energy 500-800 MeV (p, xp yn)

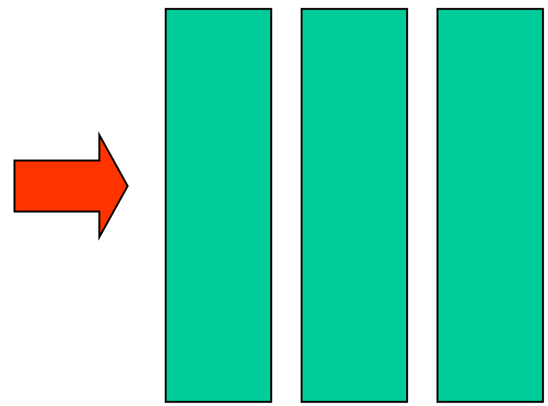
- Low dE/dx (low energy release)
- Wide water gaps (easy cooling)
- Low cross-sections
- Large amount of impurities
- Expensive beam





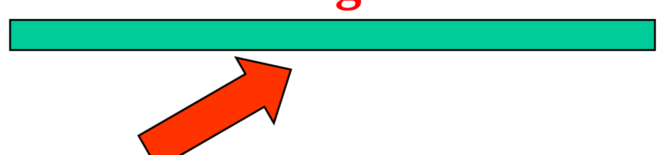
Middle energy 70-200 MeV (p, xp yn)

- High dE/dx (high energy release)
- Narrow water gaps (difficult cooling)
- High cross-sections
- Small amount of impurities

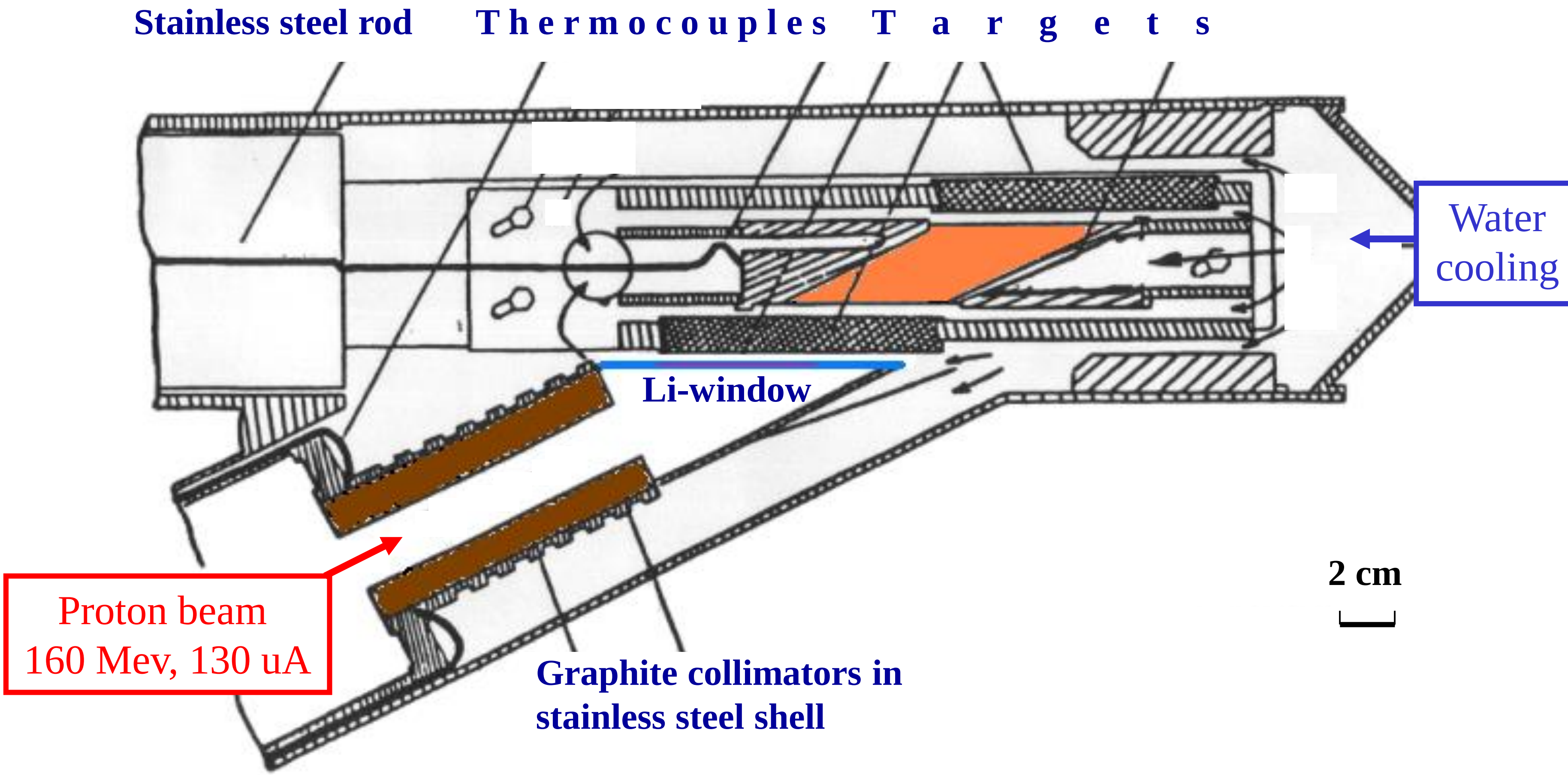


Low energy 15-40 MeV (p, 1-3n)

- Small amount of impurities
- Good cooling
- Restricted spectrum of isotopes
- Enriched target material



Target holder with graphite collimators and lithium beam window at INR facility



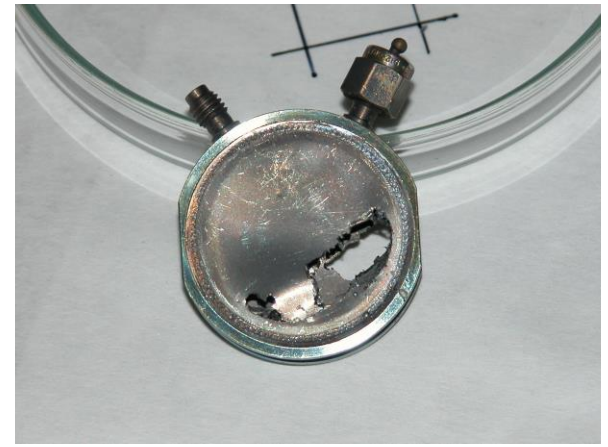
What happens if the target requirements are not fulfilled?

(not only thermal but also radiation impact)

Aluminum

Graphite

Molybdenum



Antimony in stainless steel

Isotopes Produced in INR and Possible Activity Generating 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	25.5 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
Sn-117m	14 d	Sb, TiSb	150-40	250	3
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
Ac-225	10 d	Th	150-40	250	4
Ra-223	11.4 d	Th	150-40	250	13

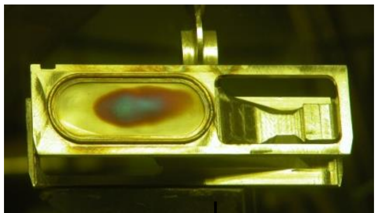
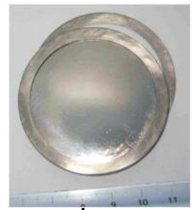
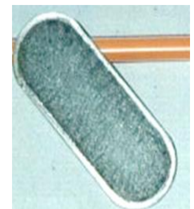
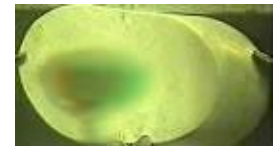
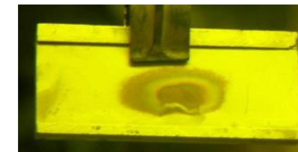
Green – regular mass production

Blue – technology developed, test samples supplied to customers

Red – production method developed, technology under development

Isotopes exported by INR

Targets

Sr-82	Pd-103	Sn-117m	Ge-68	Na-22	Ac-225
Rb	Ag	SbTi	GaNi	Al	Th
					
-Los Alamos, USA -IPPE, Obninsk	-Karpov,Obninsk -Mayak, Ozersk	IPPE, Obninsk Brookhaven, USA	-Los Alamos, USA	-IPPE, Obninsk	- Karpov, Obninsk

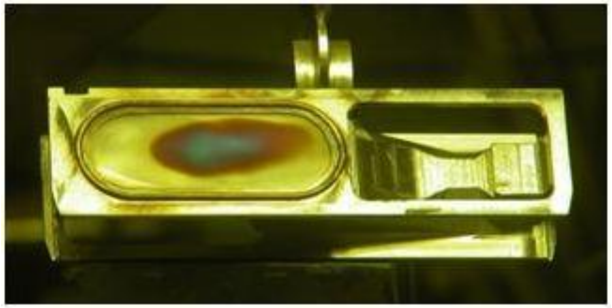
Main INR's Collaborators in Isotope Production

- **Los Alamos National Laboratory, USA**
- **Brookhaven National Laboratory, USA**
- **Canada's National Facility TRIUMF, Canada**
- **1st Milano University, Italy**
- **GIP ARRONAX, France**
- **ZEVACOR Molecular, USA**
- **Institute for Physics and Power Engineering, Obninsk, Russia**
- **Karpov Institute for Physical Chemistry, Obninsk**
- **Russian Research Centre of Roentgenology and Surgery Technologies, St-Petersburg**
- **Lomonosov Moscow State University**
- **Medical Radiological Research Cetre, Obninsk**
- **Production Association "Mayak", Ozersk**
- **Vernadsky Institute of Geochemistry and Analytical Chemistry, Moscow**
- **Institute of Physical Chemistry and Electrochemistry, Moscow**
- **Institute of Atomic Reactors, Dimitrovgrad**

Last International Projects on GIPP (Initiatives for Proliferation Prevention)

- **IPP - ISTC, 116 people, 6 Russian Institutions, LANL, BNL**
  "Co-Production of Palladium-103, Strontium-82, and Germanium-68 for Distribution and Medical Applications"
- **IPP – CRDF, 32 people, 4 Russian institutes, BNL**
  "Development of High-Specific activity and No-Carrier-Added Tin-117m for Radionuclide Therapy"

Processing of INR's irradiated rubidium targets for recovery strontium-82 at Los Alamos



Total amount of irradiated and shipped targets: about 150

More than 300,000 US patients passed diagnostics with isotopes produced at INR

More than 2,000,000 patients – with isotopes produced with mutually developed methods

Choice of target material for ^{82}Sr-production: Rb or RbCl ?

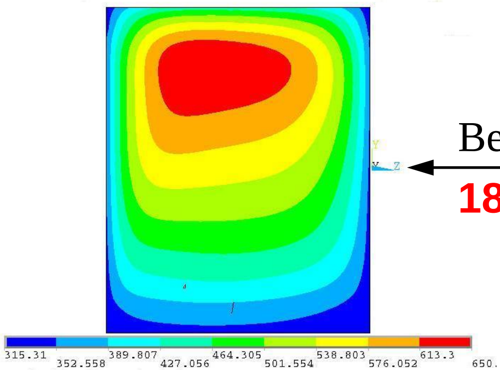
(Energy Range 65 – 35 MeV)

Metallic Rubidium *(liquid)* | **Rubidium Chloride** *(solid)*

Equal Maximal Temperature (~ 380 °C)

Metallic Rubidium

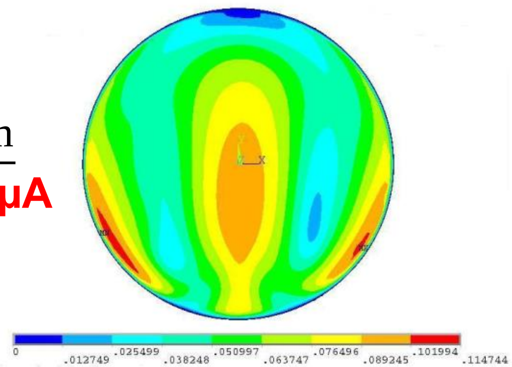
Temperature Distribution



Beam

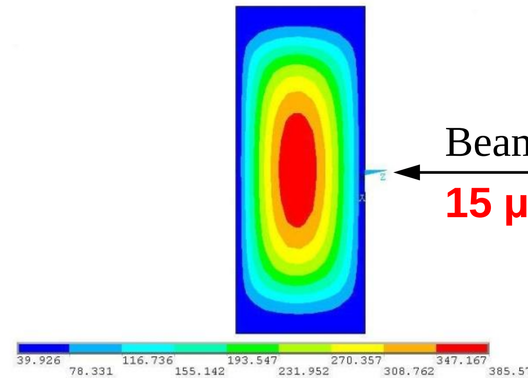
180 μA

Velocity Distribution



Rubidium Chloride

Temperature Distribution

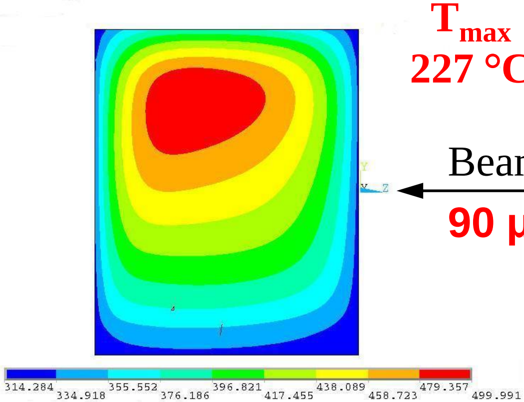


Beam

15 μA

Equal Vapor Pressure (0.1 torr)

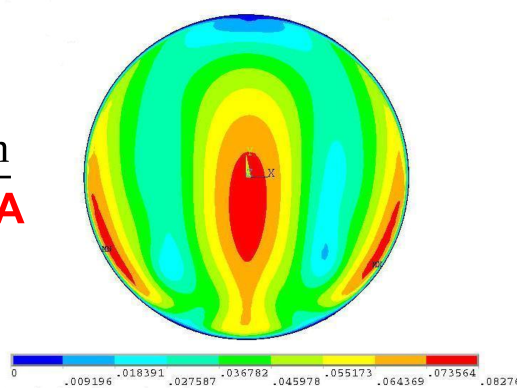
Metallic Rubidium



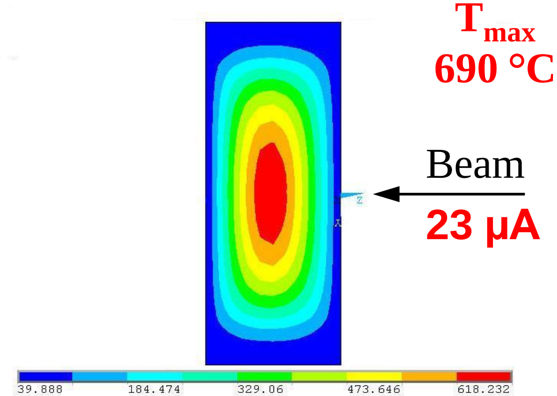
T_{max} 227 °C

Beam

90 μA



Rubidium Chloride

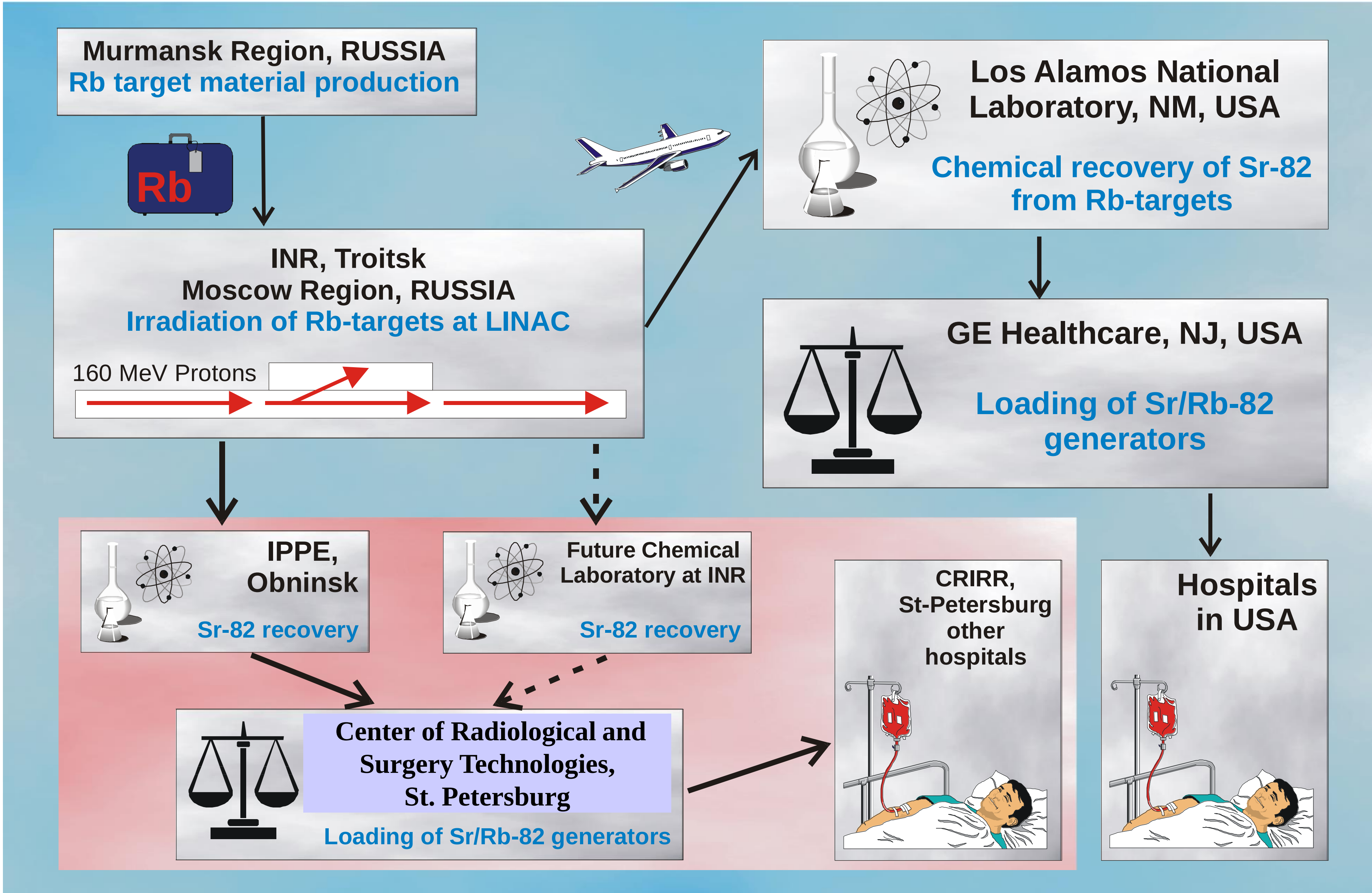


T_{max} 690 °C

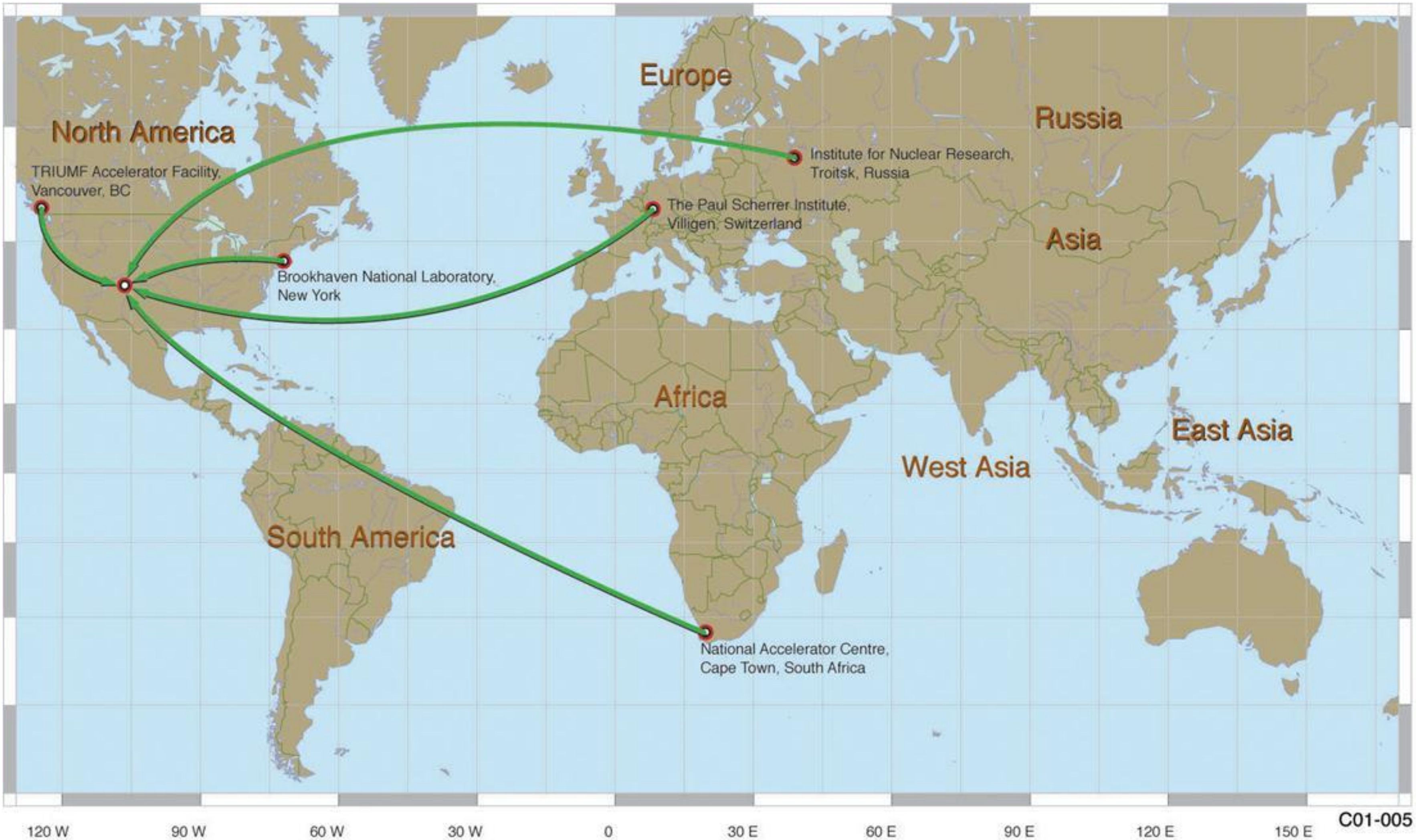
Beam

23 μA

Production and Transportation Scheme of Strontium-82



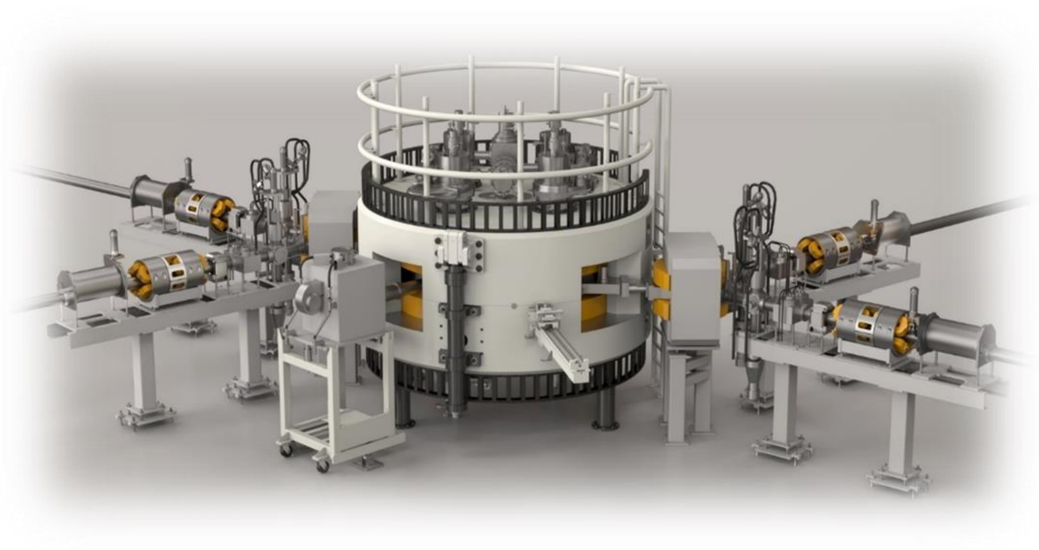
Virtual Isotope Center- supplementing and extending existing availability (organized by DOE)



ARRONAX CYCLOTRON (Nantes, France)

Designed and constructed by IBA

New ZEVACOR Facility (Indiana, USA)



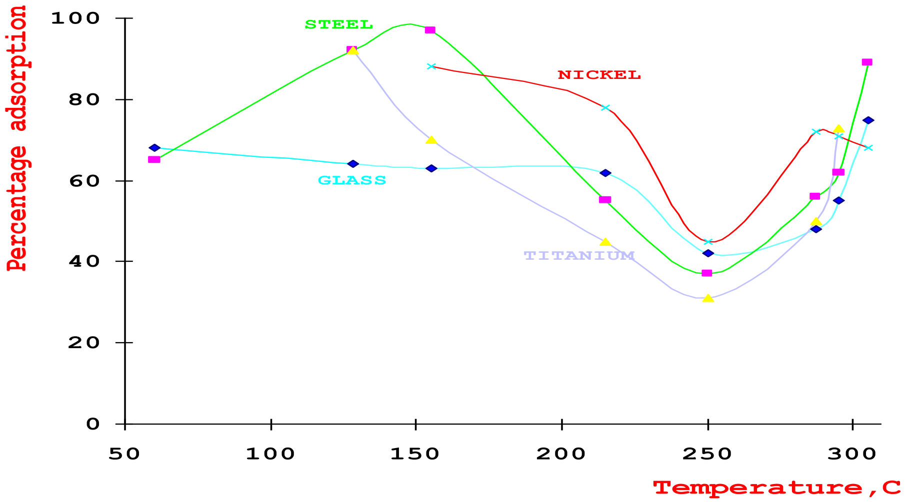
- **70 MeV**
- **H-, proton only**
- **Dual beam 350+350 uA**
- **6 target lines**
- **Weight: 140 metric tons**
- **Vault: 25,000 sq. ft., 11,000 cu yrd of concrete**

- **Beam on target σ=3 mm AC Rastering r=5 mm (60 hz, one circle)**
- **Beamlines: 2 pairs of quadrupoles, Faraday cup, one gate valve**
- **Dedicated diff. pumps on beam lines, 6 cryo pumps on main tank**
- **Vacuum at extractor ~10^{-7} mbar, at target ~10^{-6} mbar**
- **Dual beam at 350 uA on each side demonstrated**
- **1 year of operation without any delayed shipments**

Major producer of Sr-82 in 2018

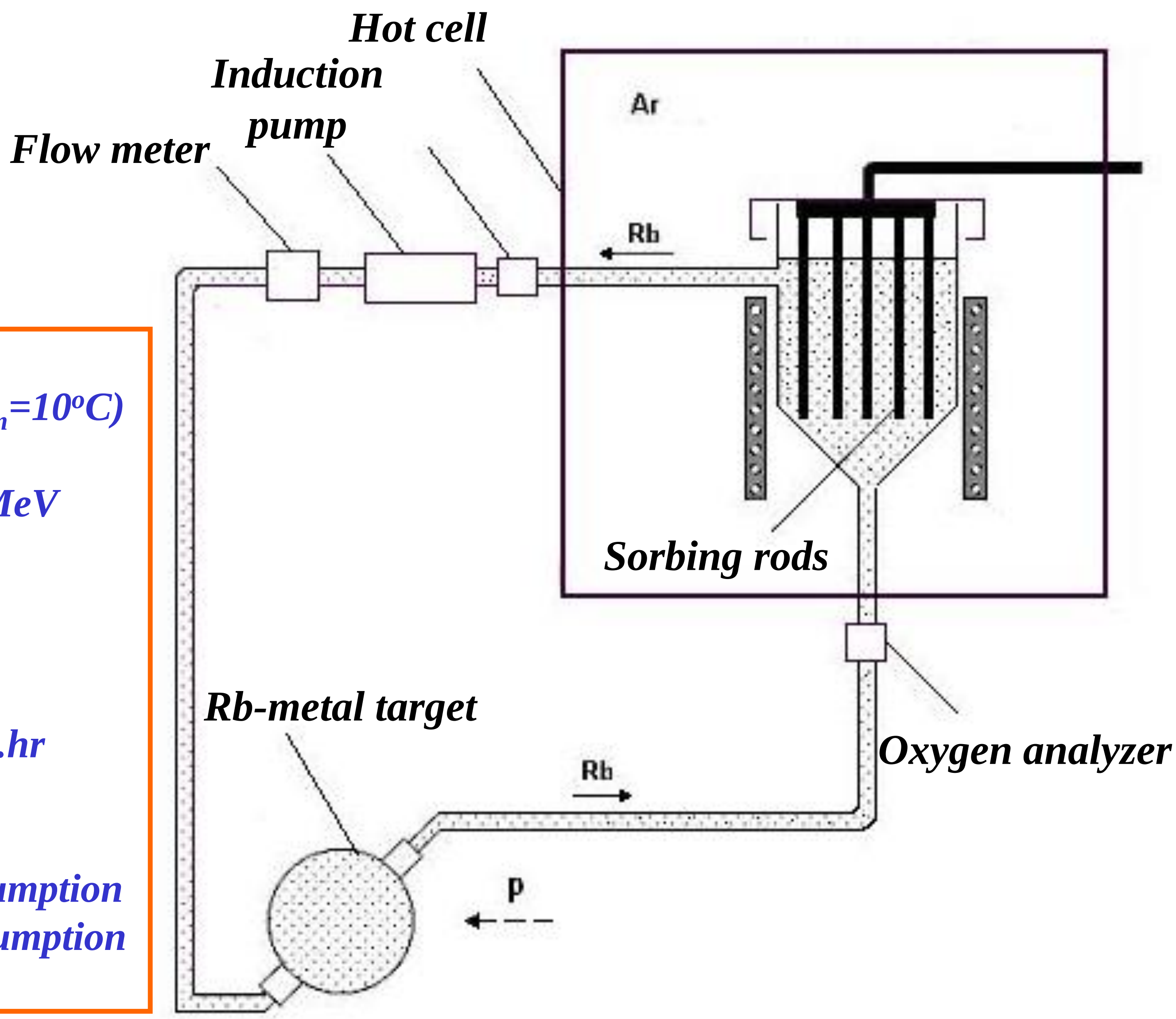
Radiochemical facility based on new technology of Sr-82 sorption directly from liquid metallic rubidium

Temperature dependence of Sr-82 adsorption from liquid metallic irradiated rubidium



A hot cell at IPPE, Obninsk, Russia

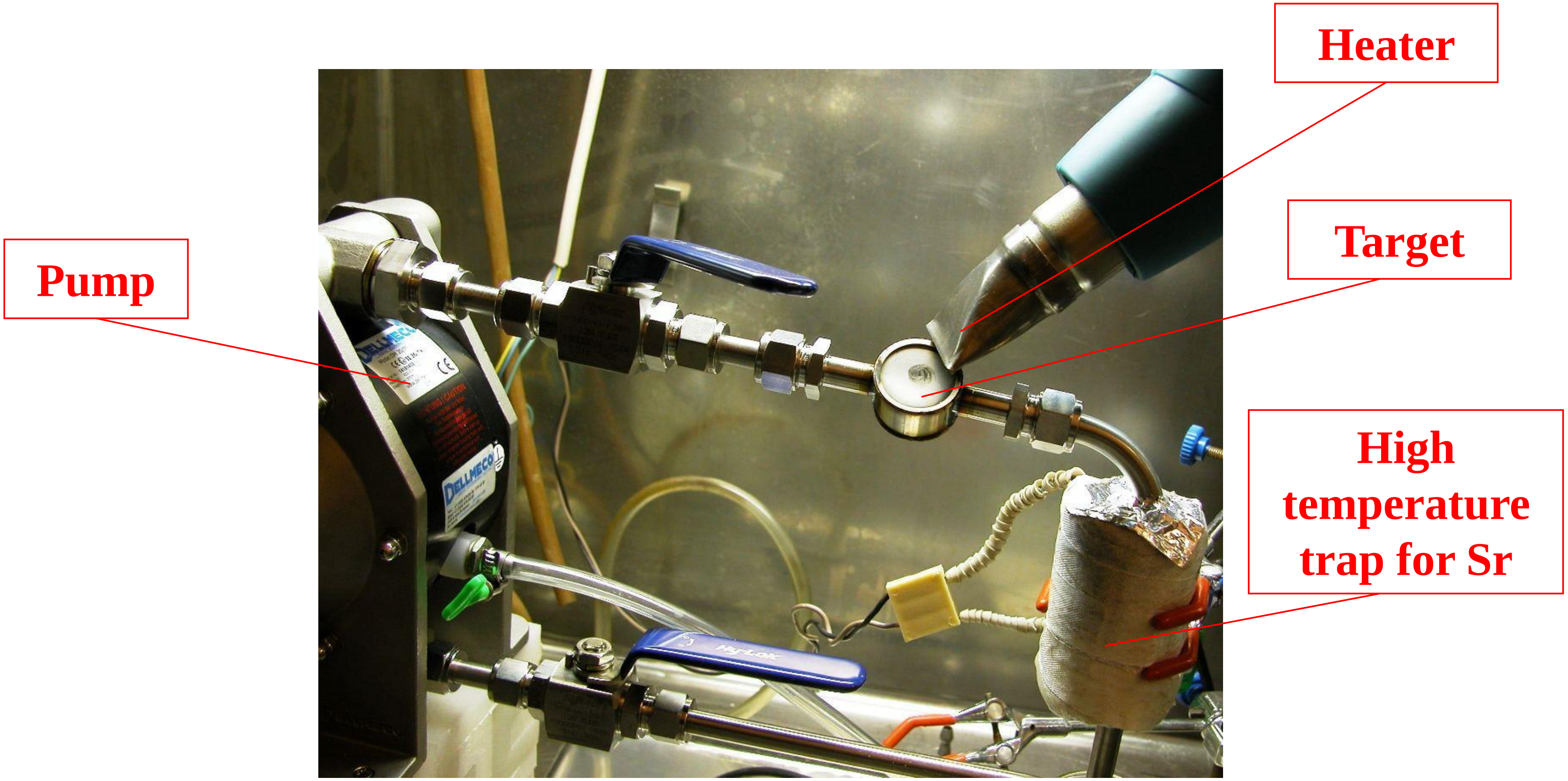
Future Facility for On-Line Sr-82 Production



Main Parameters:

Target material: Rb+3%O (T_m=10^{o}C)
Beam current: 500 μA
Proton energy range: 63-36 MeV
Energy release: 13 kW
Rb volume: ~1.5 L
Rb flow: ~5-10 L/min
Target diameter: ~8 cm
Production yield: 0.4 mCi/μA.hr
Production capacity ^{82}Sr:
4.5 Ci/day at EOB
2.5 Ci/day at consumption
500 Ci/year at consumption

Experimental Setup for Investigation of Sr-Sorption from the Loop of Metallic Rubidium



Sr-82/Rb-82 generators for PET

CardioGen-82®
GEHeathcare/BRACCO, USA

GR-1
RRCRST / INR, Russia

Ruby-Fill
DRAXIMAGE, Canada

RubiJet
INR/LEMER/
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РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ИЗОБРЕТЕНИЕ

№ 2546731

ГЕНЕРАТОР РУБИДИЯ-82 И СПОСОБ ЕГО ПРИГОТОВЛЕНИЯ

Патентообладатель(ли): *Федеральное государственное бюджетное учреждение науки Институт ядерных исследований РАН (ИЯИ РАН) (RU)*

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Врио руководителя Федеральной службы по интеллектуальной собственности

Л.Л. Кирий

ФЕДЕРАЛЬНАЯ СЛУЖБА ПО НАДЗОРУ В СФЕРЕ ЗДРАВООХРАНЕНИЯ (РОСЗДРАВНАДЗОР)

РЕГИСТРАЦИОННОЕ УДОСТОВЕРЕНИЕ НА МЕДИЦИНСКОЕ ИЗДЕЛИЕ

от 01 июля 2014 года № РЗН 2014/1669

На медицинское изделие
Генератор рубидия-82 ГР-01 (ГР-02) по ТУ 9452-025-05627150-2012

Настоящее регистрационное удостоверение выдано
Федеральное государственное бюджетное учреждение "Российский научный центр радиологии и хирургических технологий" Министерства здравоохранения Российской Федерации (ФГБУ "РНЦРХТ" Минздрава России), Россия, 197758, Санкт-Петербург, п. Песочный, ул. Ленинградская, д. 70

Производитель
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Место производства медицинского изделия
Россия, 197758, Санкт-Петербург, п. Песочный, ул. Ленинградская, д. 70

Номер регистрационного досье **№ РД-929/15347 от 14.05.2013**

Вид медицинского изделия **-**

Класс потенциального риска применения медицинского изделия **3**

Код Общероссийского классификатора продукции для медицинского изделия **94 5230**

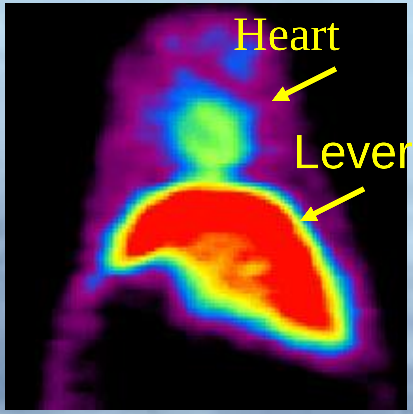
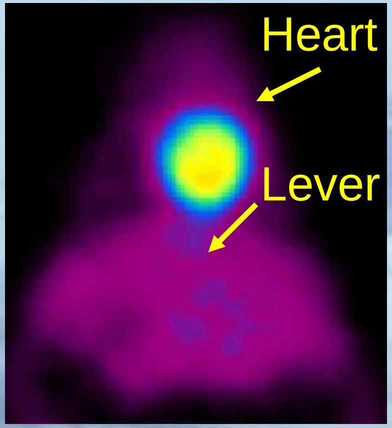
приказом Росздравнадзора от 01 июля 2014 года № 4645
допущено к обращению на территории Российской Федерации.

Врио руководителя Федеральной службы по надзору в сфере здравоохранения

М.А. Мурашко

0008907

Comparison ^{13}N-ammonium and ^{82}Rb-chloride
(RRC RST, St. Petersburg)

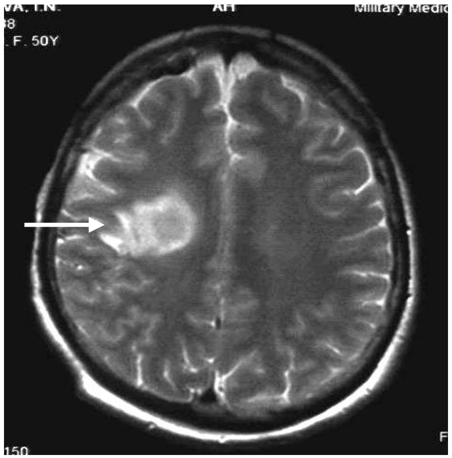
Parameter	*^{13}N-ammonium*	*^{82}Rb-chloride*
Half-life	9.8 min.	1.3 min.
Production method	Cyclotron	Generator
Pharmodynamics	Passive diffusion	Mechanism K^{+}-Na^{+} -ATPhase
Biodistribution		

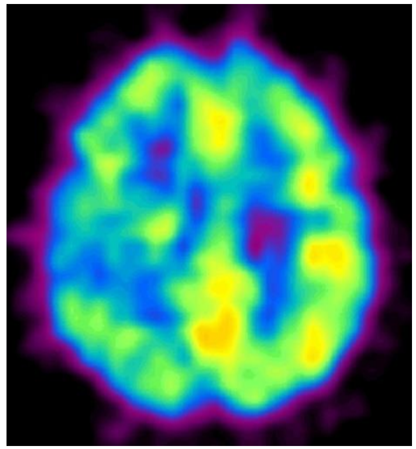
^{82}Rb-chloride-PET of patients with brain space-occupying lesions

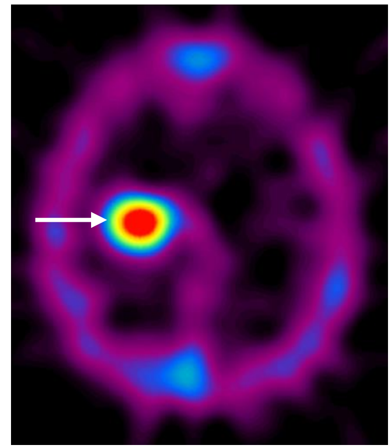
Glioblastoma multiforme Gr IV of Malign. Brain tumors - hot spots

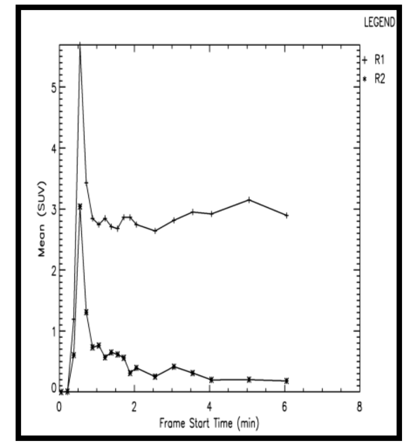
(RRC Radiology and Surgery Technologies, St. Petersburg)

MRI | *^{18}F-FDG-PET* | *^{82}Rb-Chloride-PET*

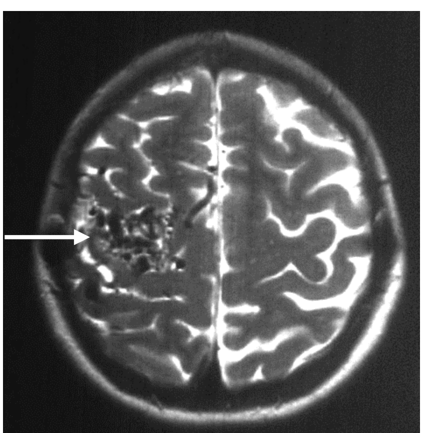


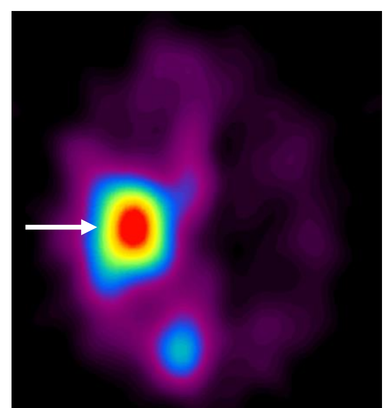


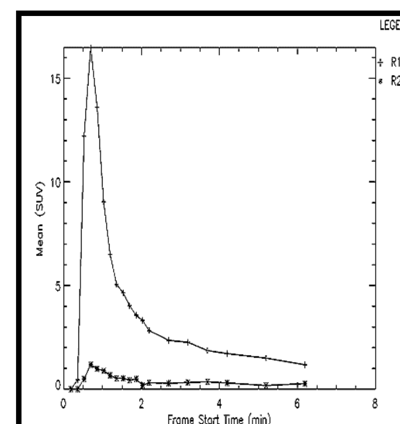




Arteriovenous malformation (AVM)







Production No-carrier-added ^{117m}Sn from antimony targets

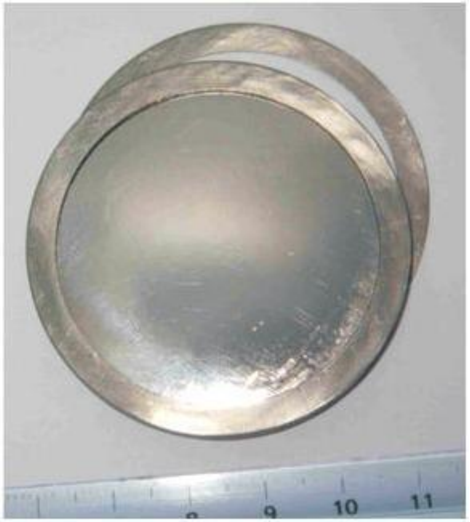
^{121,123}Sb (p; 2p, 3n or 5n) ^{117m}Sn

$T_{1/2}$=14.0 d
Low energy conversial Auger-electrons 127 and 152 keV
Range in water: 0.22 и 0.29 mm

Mutual development of INR and BNL, USA (S. Srivastava et al.)

Metallic Sb-target in graphite shell covered with nickel

Target from intermetallic compound TiSb



CURRENT STATUS:

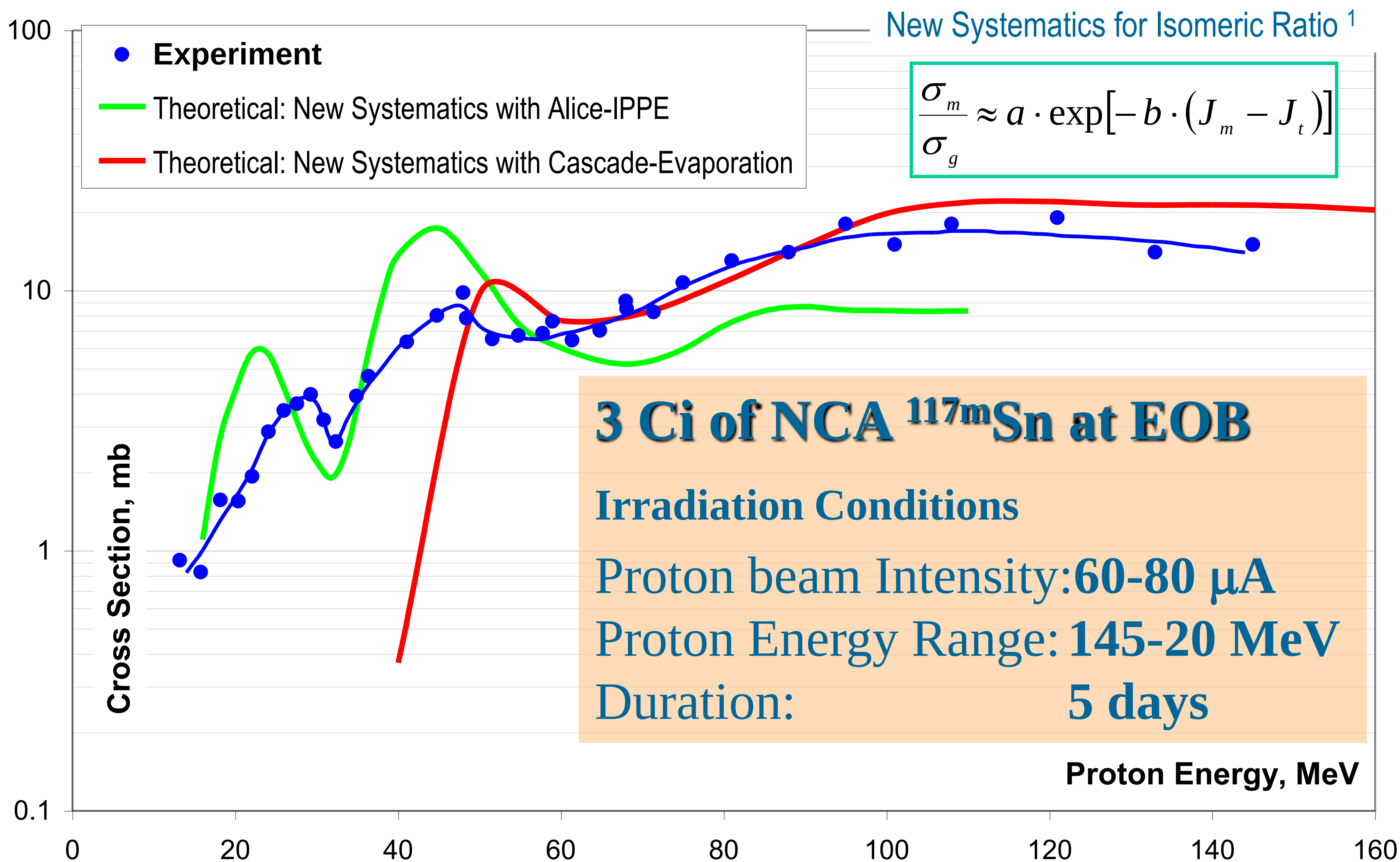
- *^{117m}Sn PRODUCTION TECHNOLOGY COMPLETED*
- *PASSING CLINICAL TRIALS (Clear Vascular Inc.)*

Advantages of Sn-117m

- **Emits low energy conversion electrons 127, 129 and 152 keV that deposits energy with a short discrete ranges 0.22 and 0.29 mm: to destroy the tumors and not damage normal tissues**
- **Suitable half-life 14 days**
- **Gamma-photon 159 keV is ideal for imaging**
- **May be produced in NCA-form, i.e. with high specific activity**
- **DTPA compound is easy to prepare and very stable**
- **Ideal for pain relief in bone cancer: long lasting and may be repeated**
- **Promising for cardiovascular diseases: occluded coronary and vulnerable plaques (via stents or specific labeled molecules)**

Mutual development, supported by GIPP, with participation:
- Brookhaven National Laboratory, USA – S. Srivastava et al.
- Chemical department of Moscow State University
- Institute of Physics and Power Engineering (Obninsk)

Cross-sections of Sn-117m from natural Sb: experimental and calculated by different methods



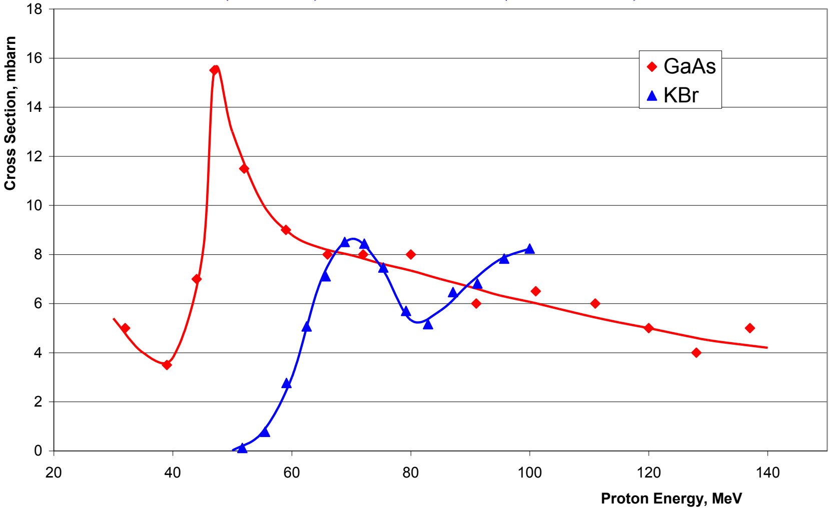
$$\frac{\sigma_m}{\sigma_g} \approx a \cdot \exp\left[-b \cdot \left(J_m - J_t\right)\right]$$

[1] B.L. Zhuikov, A.S. Iljinov, *Physics of Atomic Nuclei*, 2006, **69**, p.739.

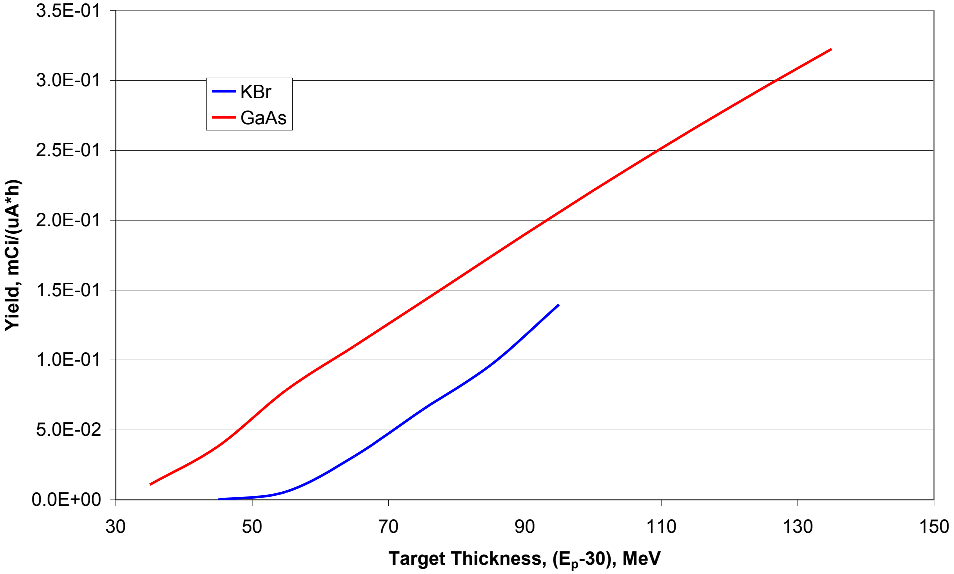
Production of ^{72}Se as Parent Nuclide of ^{72}As Prospective at 70 MeV Cyclotron

^{72}Se (8.5 d) → ^{72}As (26 hr)

Cross-sections of ^{72}Se at As (INR) and Br (LANL)



Integrated yield from AsGa and KBr-targets



<u>GaAs - target</u>

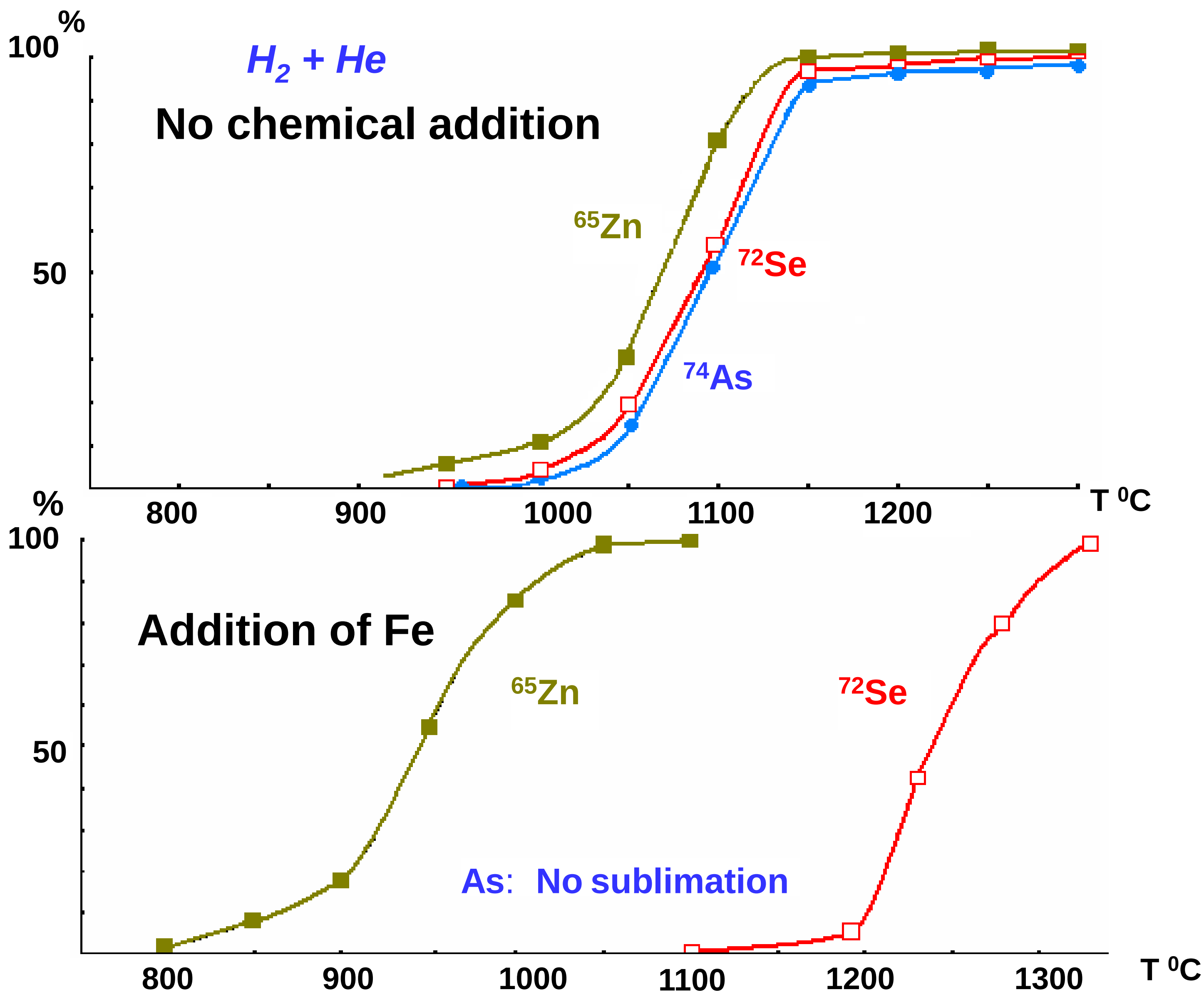
-Proton energy: 65 MeV
-Beam current: 150 μA
-Irradiation period: 10 d
-Decay/processing time: 10 d
-Chemical yield: 90%
-Produced amount: <u>1 Ci</u>

<u>KBr - target</u>

-Proton energy: 65 MeV
-Beam current: 100 μA
-Irradiation period: 10 d
-Decay/processing time: 10 d
-Chemical yield: 90%
-Produced amount: <u>0.2 Ci</u>

Alternative method of ^{72}Se production from enriched Ge: ^{70,72}Ge (α, xn)

Gas Chemical Recovery of ^{72}Se from GaAs -Target Irradiated with 60-145 MeV Protons



Production of ^{67}Cu and ^{64}Cu from Zn-Target

^{67}*Cu:* ($T_{1/2}$=62 hr)
β^- energy 577 (20%), 484 (23%), 395 (56%) keV. Maximum range in water: 2.0 mm
^{64}*Cu:* ($T_{1/2}$=12.7 hr). β^- and β+ emitter (PET diagnostics)
Maximum β^- energy 578 (39%) keV. Maximum range in water: 2.0 mm

INR (Troitsk)

Proton energy: 145 MeV, beam current: 100 μA

^{67}Cu from nat. Zn-target
- **Irradiation period: 3 d**
- **Decay/processing time: 3 d**
- **Chemical yield: 90%**
- **Produced amount: 1.5 Ci**

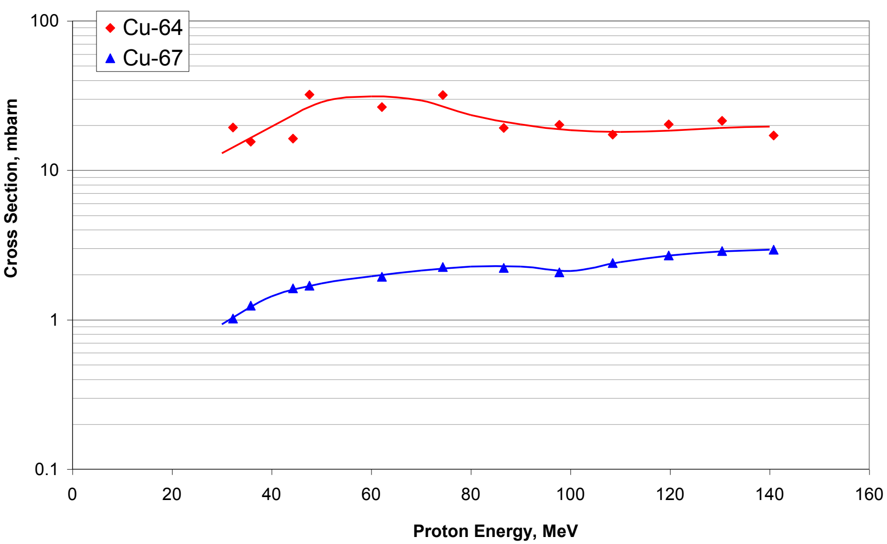
^{64}Cu from nat. Zn-target
- **Irradiation period: 12 hr**
- **Decay/processing time: 2 d**
- **Chemical yield: 90%**
- **Produced amount: 2 Ci**

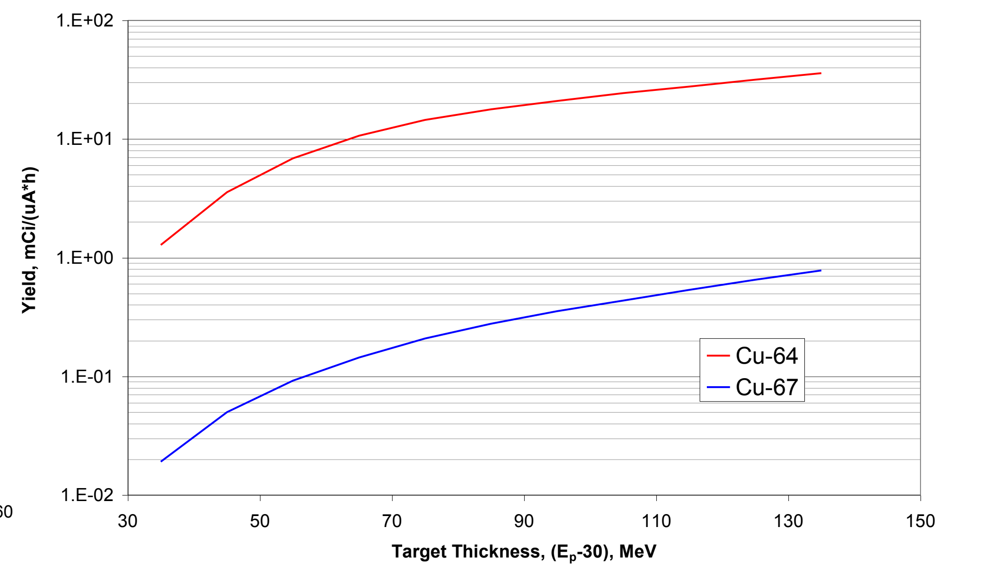
70 MeV Cyclotron

Proton energy: 70 MeV, beam current: 200 μA

^{67}Cu from nat. Zn-target
- **Irradiation period: 3 d**
- **Decay/processing time: 3 d**
- **Chemical yield: 90%**
- **Produced amount: 0.7 Ci**

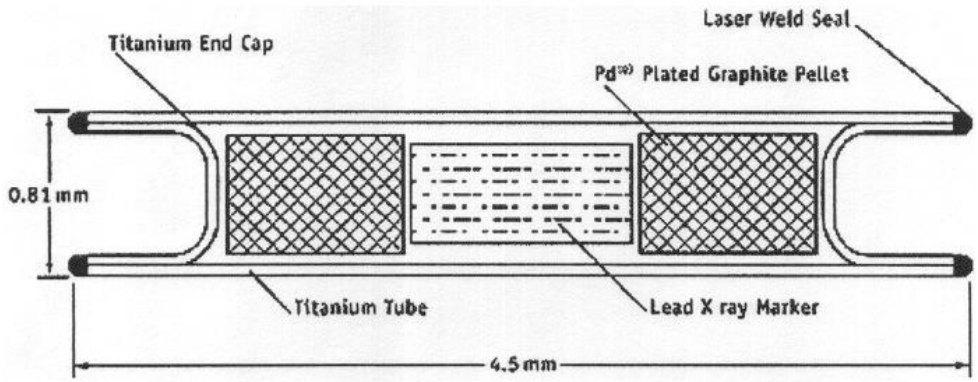
^{64}Cu from nat. Zn-target
- **Irradiation period: 12 hr**
- **Decay/processing time: 2 d**
- **Chemical yield: 90%**
- **Produced amount: 1.5 Ci**



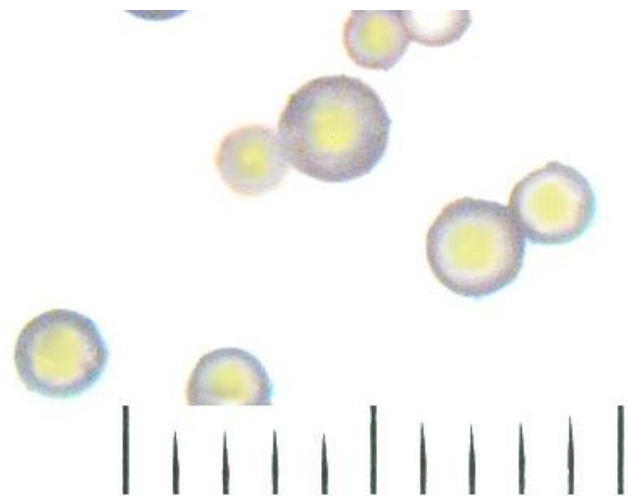


A New Medical Preparation on the Basis of Palladium-103

“Seeds”– Sources for Prostate Therapy (Theraginics Co.)

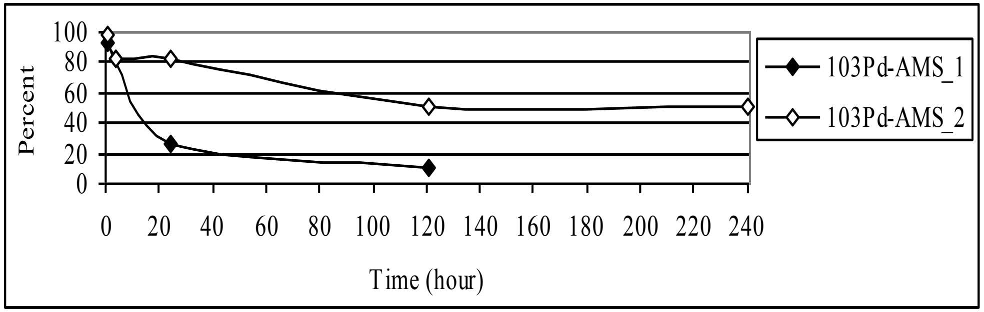


Albumin microspheres (20-40 μm)



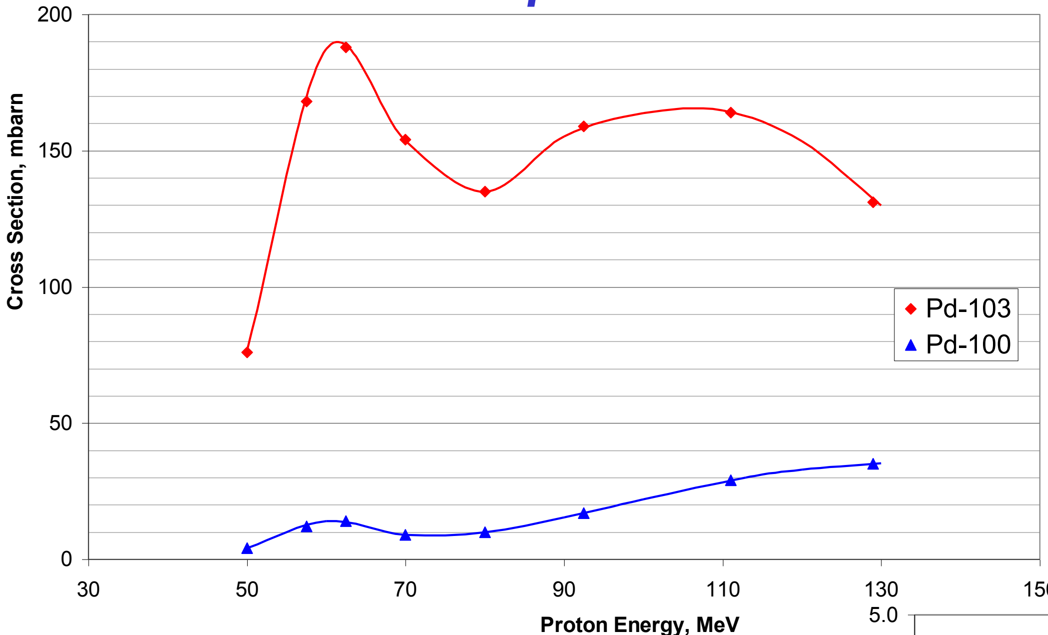
Excretion of Pd-AMS from femoral muscle of intact mice after intramuscular injections of the preparation

(Medical Radiological Centre, Obninsk)



^{103}Pd and ^{100}Pd (3.7 d) Production from Ag-Targets

Cross-sections of ^{103}Pd and ^{100}Pd



^{103}Pd ($T_{1/2}$=17 d)+^{103}Rh ($T_{1/2}$=56 min)
X: 20 keV (64%), 23 keV(23%),
γ: 358 keV (0.02%)

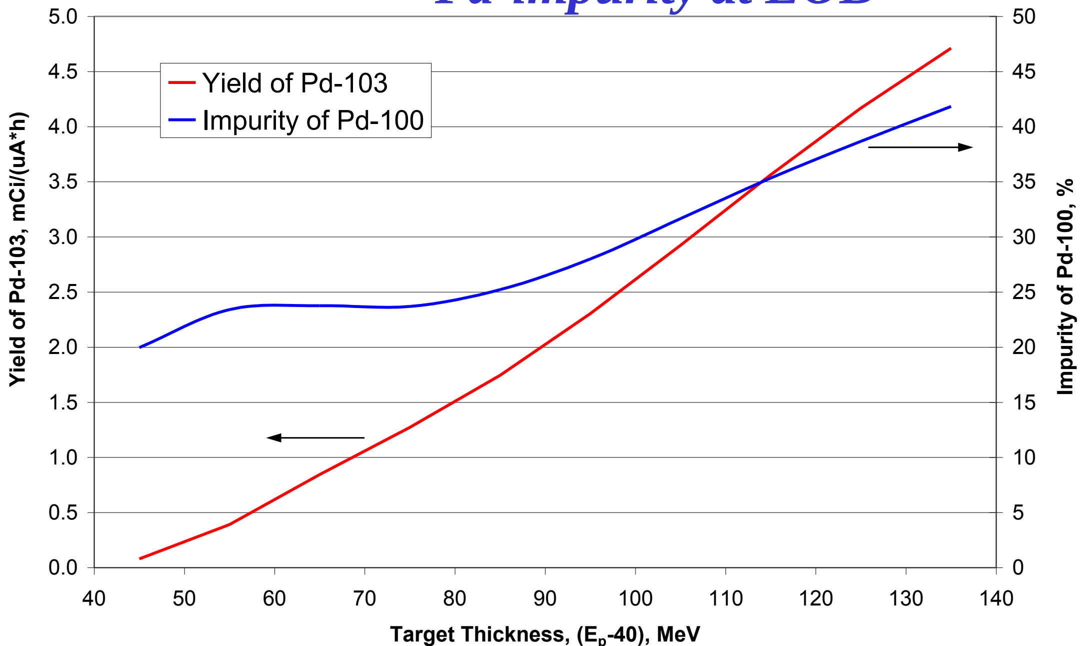
^{100}Pd ($T_{1/2}$=3.63 d)+^{100}Rh ($T_{1/2}$=21 min)
γ: 84 (100%), 539 (100%),2376 keV (46%),..

- Proton energy: 70 MeV
- Beam current: 250 μA
- Irradiation period: 20 d

- Decay/processing time: 10 d
- Produced amount: 50 Ci
- ^{100}Pd-impurity: 1.3%

- Decay/processing time: 30 d
- Produced amount: 23 Ci
- ^{100}Pd-impurity: 0.06%

Integrated yield ^{103}Pd and ^{100}Pd-impurity at EOB



Radioactive decay ^{225}Ac and ^{223}Ra

^{225}Ac (10 d)

↓ α *5.8 MeV*

^{221}Fr(4.9 min)

↓ α 6.*3 MeV*

^{217}At (32 ms)

↓ α 7.*1 MeV*

^{213}Bi (46 min)

↓ β^-

^{213}Po (4.2 μs)

↓ α *8.4 MeV*

^{209}Pb (3.3 h)

↓ 98% β^-

^{209}Bi (stable)

^{227}Ac (28 y)

↓ β^-

^{227}Th (18.7 d)

↓ α *5.6 MeV*

^{223}Ra (11.4 d)

↓ α *5.7 MeV*

^{219}Rn (3.9 s)

↓ α *6.8 MeV*

^{215}Po (1.8 ms)

↓ α *7.4 MeV*

^{211}Pb (36 min)

↓ β^-

^{211}Bi (2.2 min)

↓ α *6.6 МэВ*

^{207}Tl (1,8 ms)

↓ β^-

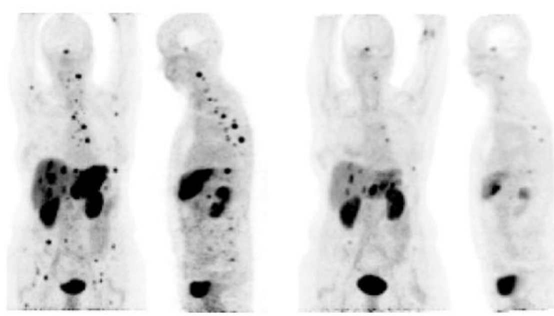
^{207}Pb (stable)

Application of α-active actinium-225 for therapy of oncology diseases: directly or via short-lived bismuth-213

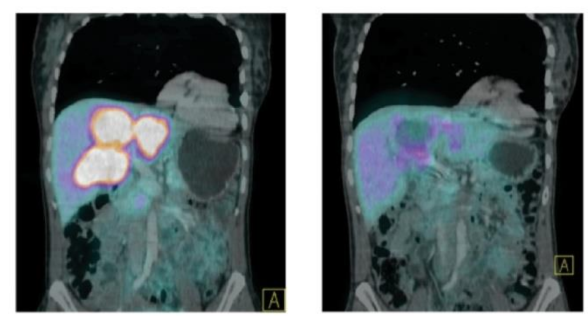
^{225}Ac ($T_{1/2}$=10 d) → ^{213}Bi ($T_{1/2}$=46 min)

- **Prostate cancer, mammary gland, brain, bone, stomach, pancreas, ovaries cancer**
- **Melanoma**
- **Celothelioma**
- **Leukemia**

Remarkable responses to Bi-213-DOTATOC observed in tumors resistant to previous therapy with Y-90/Lu-177-DOTATOC



Case I: Shrinkage of liver lesions and bone metastases after i.a. therapy with 11 GBq Bi-213-DOTATOC



Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

(http://interactive.snm.org/index.cfm?PageID=11752)

The main methods of producing ^{225}Ac

- ^{232}Th (n, γ) → ^{233}U *(1.6 ·10^{5} yr)* → ^{229}Th *(7340 yr)* → ^{225}Ra *(14.8 d)* → ^{225}Ac
  Slow neutron reactors

- ^{226}Ra (p, 2n) → ^{225}Ac
  Proton accelerators of low energy

- ^{226}Ra (n, 2n) → ^{225}Ra *(14.8 d)* → ^{225}Ac
  Fast neutron reactors

- ^{226}Ra (n, γ) →….. → ^{229}Th *(7340 yr)* → ^{225}Ra *(14.8 d)* → ^{225}Ac
  High flux neutron reactors

- ^{226}Ra (γ, n) → ^{225}Ra *(14.8 d)* → ^{225}Ac
  Electron accelerators

- ^{232}Th (p; *x*p, *y*n) → ….. → ^{225}Ac
  Middle and high energy proton accelerators

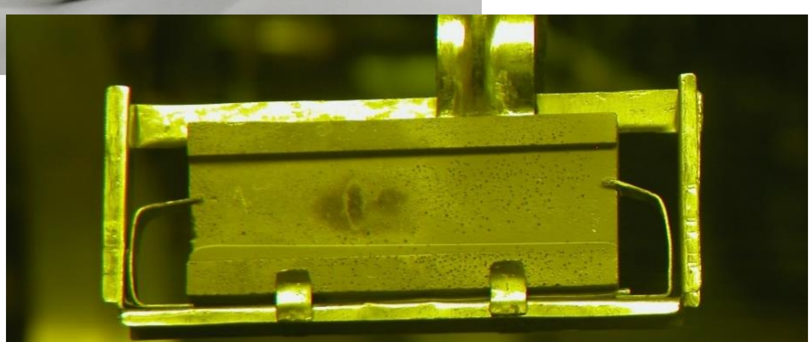
$^{232}Th\ (p;\ xp,\ yn) \rightarrow \ldots.. \rightarrow {}^{225}Ac$

Protons of 160 MeV

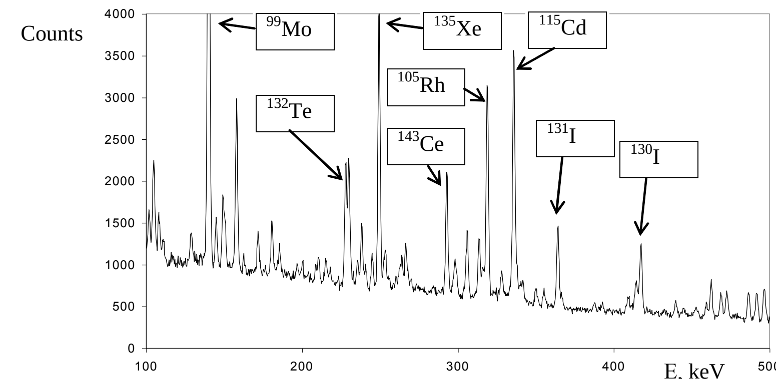
NUCLEAR REACTION ROUTES (calculated)

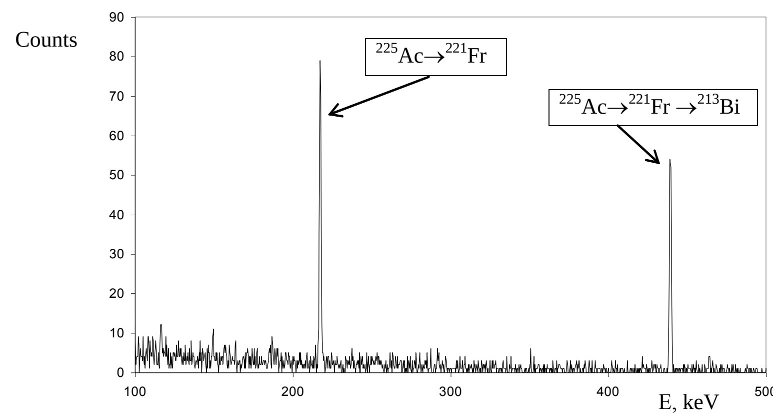
- Direct formation of ^{225}Ac — 20% of total yield
- ^{225}Th (β^{+}-decay, $T_{1/2}$= 8 min) → ^{225}Ac — 70%
- ^{225}Ra (β^{-}-decay, $T_{1/2}$= 14.8 d) → ^{225}Ac — 8%
- ^{229}Pa (α-decay, $T_{1/2}$= 1.4 d) → ^{225}Ac — 2%

Metallic Th-target in niobium and graphite shells

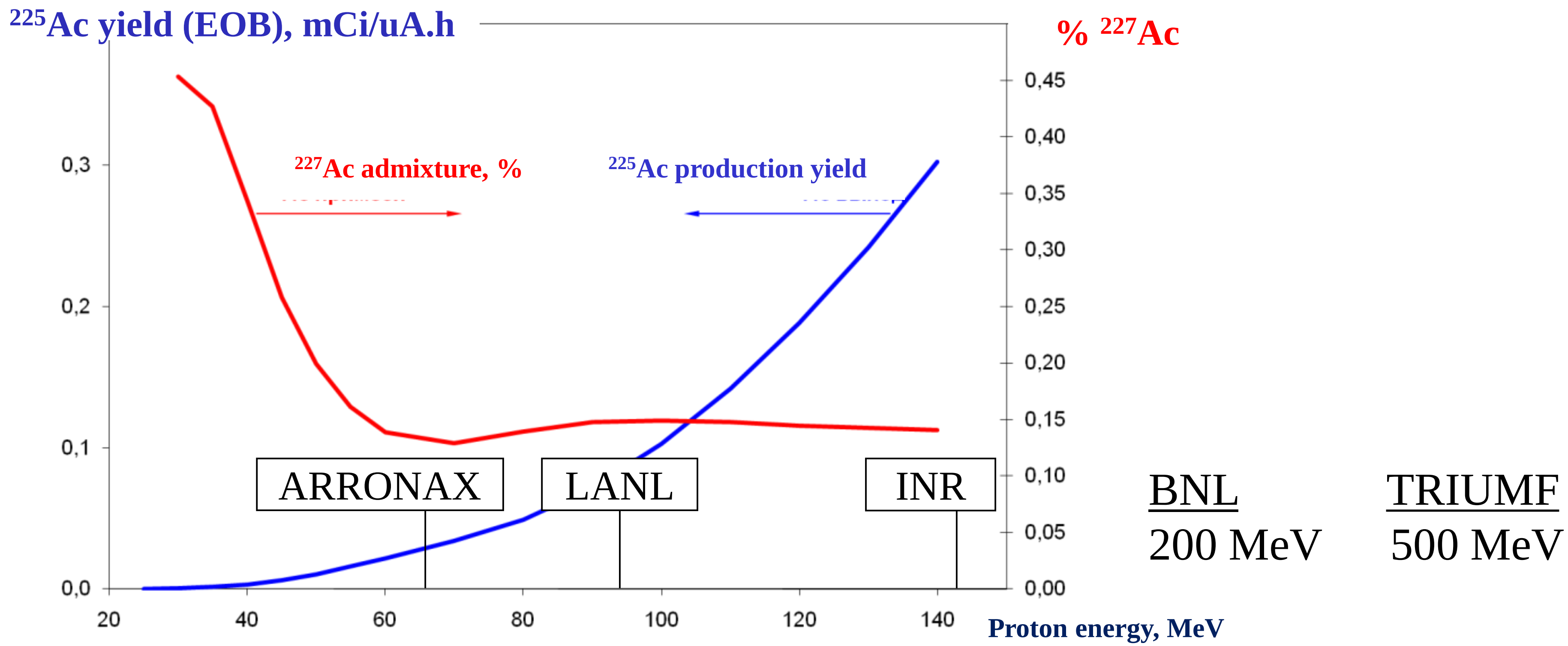


Gamma-spectra of irradiated Th-target and chemically recovered fraction of Ac





Production of ^{225}Ac from natural Th irradiated with middle energy protons



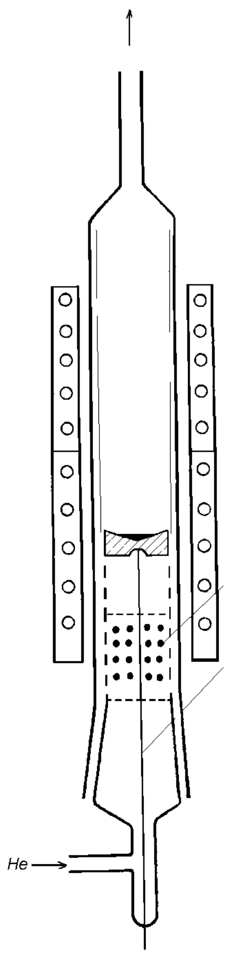
Potential production at 160 MeV (at customer's calibration time):
1 Ci per week ^{225}Ac after 10-day decay

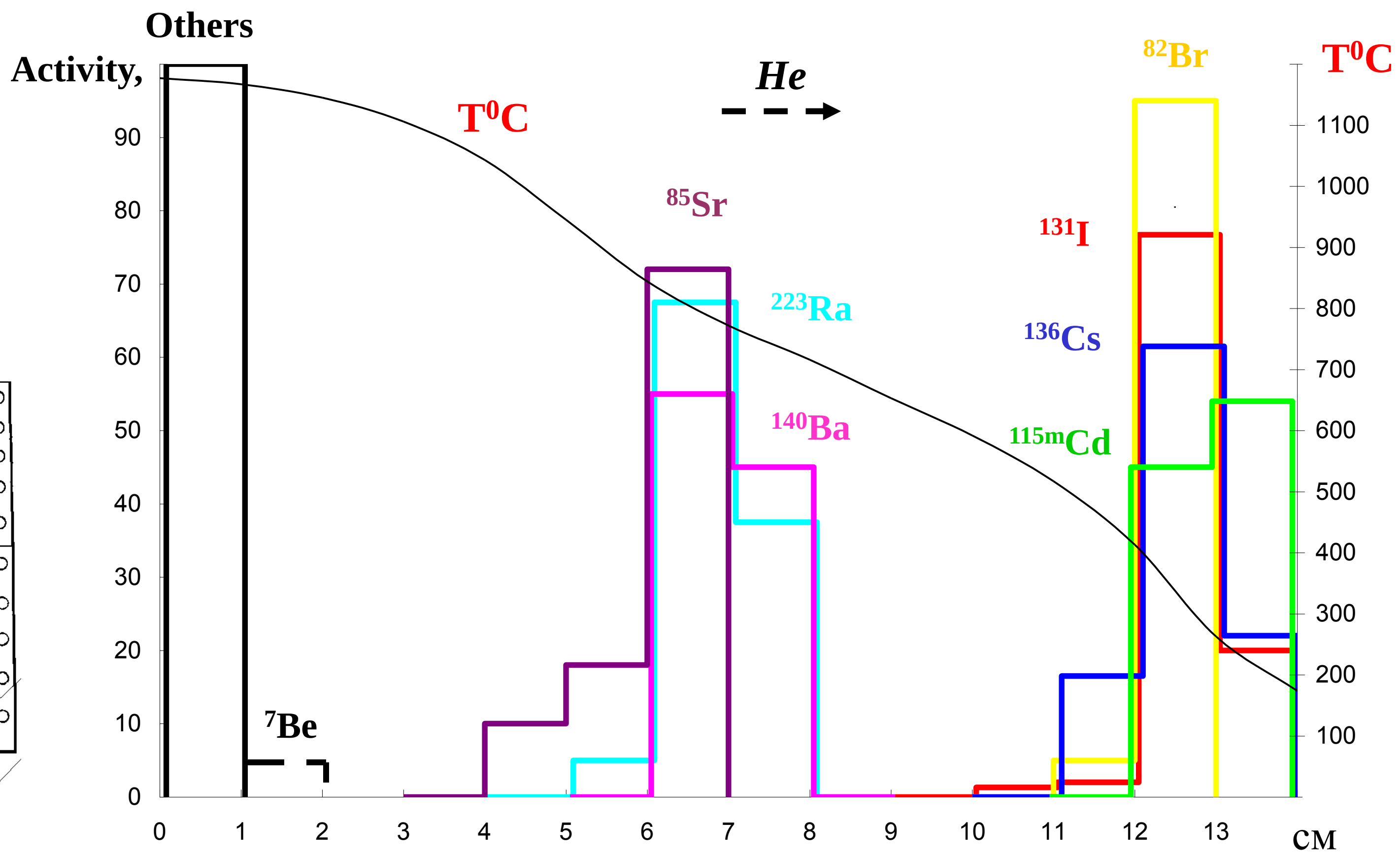
Current world production: 1.7 Ci per year

Demand (DOE's prognosis): 50 Ci per year

Theromochromatographic separation of elements sublimed from metallic Th with La-addition

(He-gas in metallic Ti - column)





Others: Th, Ac, Pa, La, Pm, Ce, Nd, Cr, Zr, Mo, Tc, Nb, Te, Sn, Sb, Ag, Ru, Rh

Nuclear Science Advisory Committee

Ani Aprahamian, Donald Geesaman

A Strategic Plan for the Isotope Development and Production for Research and Applications

5 November 2009

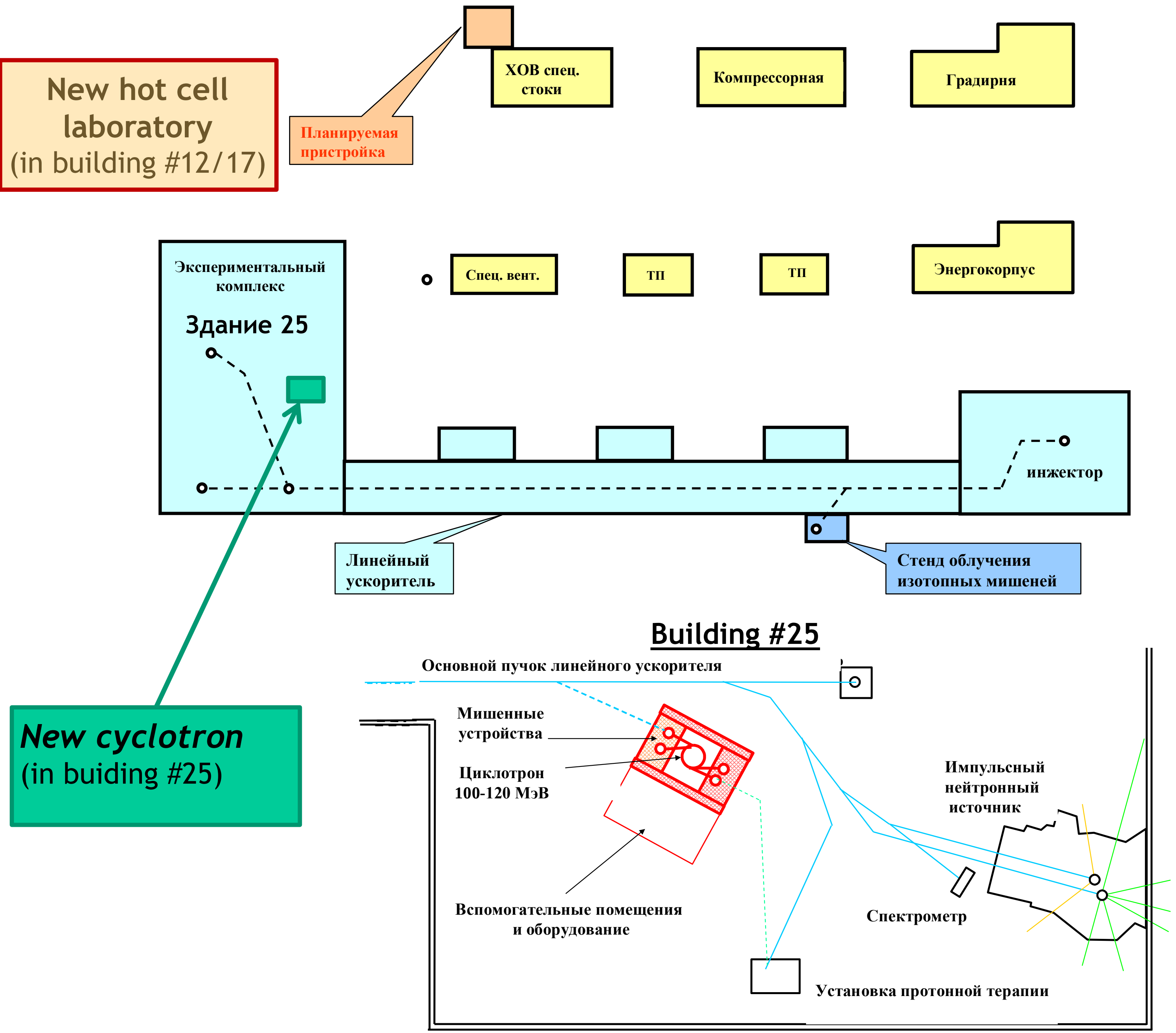
Example of Potential Increases in Demand for Ac-225/Bi-213 and the Risk of Successful Trails

Current source is ^{229}Th milked at ORNL providing 100 mCi every two months. We also get our ^{225}Ra from the same place. This treats five patients for Acute Myeloid Leukemia and could treat 30 patients per year. ^{225}Ac/^{213}Bi are under investigation for other cancers and for HIV treatment.

Estimated annual usage of ^{225}Ac and/or ^{213}Bi based on known needs. Estimates can vary by $\pm$50% depending on whether the approved treatment is with ^{225}Ac or ^{213}Bi.

Year	Amount(mCi)	Program
2009	1600	Clinical trails (1 multi-center)/R&D support
2010	3100	Clinical trails (2 multi-center)/R&D support
2011	4600	Clinical trails (2 multi-center)/R&D support
2012	7400	Clinical trails (3 multi-center)/R&D support
2013	15000	One approval; Clinical trials (2 multi- center)/R&D support
2014	50000+	Two approvals; Clinical trials/R&D support

Existing and future installations for isotope production at INR



Possibility of Medical Isotope Production at INR

RADIO-NUCLIDE	APPLICATION	HALF-LIFE	ANNUAL PRODUCTION, *Ci*		PATIENT AMOUNT (per year)
			Linear accelerator	New cyclotron 70 (120) MeV	
^{82}Sr	PET- diagnostics (cardiology)	25 d	30	500	1 000 000
^{117m}Sn	Therapy, γ-diagnostics (bone cancer, cardio vascular disease)	14 d	10	30	1 000
^{67}Cu	Therapy (oncology)	62 h	20	100	1 000
^{64}Cu	Therapy, PET- diagnostics (oncology)	12.7 h	150	700	1 000
^{72}Se	PET- diagnostics (oncology)	8.5 d	15	60	80 000
^{103}Pd	Therapy (cancer of prostate, liver, mammary gland, rheumatoid arthritis)	17 d	200	800	10 000
^{225}Ac	Therapy (oncology)	10 d	8	(100)	(100 000)
^{223}Ra	Therapy (bone cancer)	11.4 d	20	(500)	(300 000)

Some problems in medical isotope production

1. To provide sufficient governmental funding to establish new facilities or upgrade the existing facilities

2. To get government/private funding for development new medical isotopes and application

3. To form a qualified and independent international committee for distribution of funds to create and realize isotope projects

4. To achieve sustainability (full cost recovery)

5. To provide reliability in isotope supply

6. To meet requirements for drug regulatory approval.

Some of References:

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