Production of Medical Radioniclides in Russia: Status and Future

B.L. Zhuikov

Institute for Nuclear Research of Russian Academy of Sciences, Moscow-Troitsk

3rd International Nuclear Chemistry Congress
Sicily - Italy, Sept. 18-23, 2011

Main Producers of Medical Isotopes in Russia

- **Kurchatov Institute of Atomic Energy (Moscow): cyclotron, liquid fuel reactor**
- **Production Association MAYAK (Ozersk, Ural region): nuclear reactor, hot cells**
- **Research Institute of Atomic Reactors (Dimitrovgrad): high flux reactor, hot cells**
- **Medical Preparations Plant (Moscow): hot cells**
- **Institute for Physicas and Power Engineering (Obninsk): hot cells**
- **Karpov Institute of Physical Chemistry (Obninsk): nuclear reactor, hot cells**
- **Cyclotron Co. (Obninsk): 23 MeV and 14 MeV cyclotrons**
- **Khlopin Radio Institute (St-Petersburg): cyclotron**
- **Central Research Institute of Radiology and Roentgenology (St-Petersburg)**
- **State Institute of Applied Chemistry (St-Petersburg): hot cells**
- **Institute for Nuclear Research of Russian Academy of Sciences (Troitsk): LINAC**

Kurchatov Intitute of atomic Energy, Moscow

"ARGUS" – 20 kW solution reactor
Fuel: UO_2SO_4 water solution (HEU)

SOLUTION REACTOR:
^{99}Mo (under development)
^{89}Sr via ^{89}Kr (under development)

CYCLOTRON 30 MeV:
^{201}Tl (^{203}Tl-targets)
^{123}I (via irradiation of ^{124}Xe)

Production Association MAYAK, Ozersk, Chelyabinsk region (URAL)

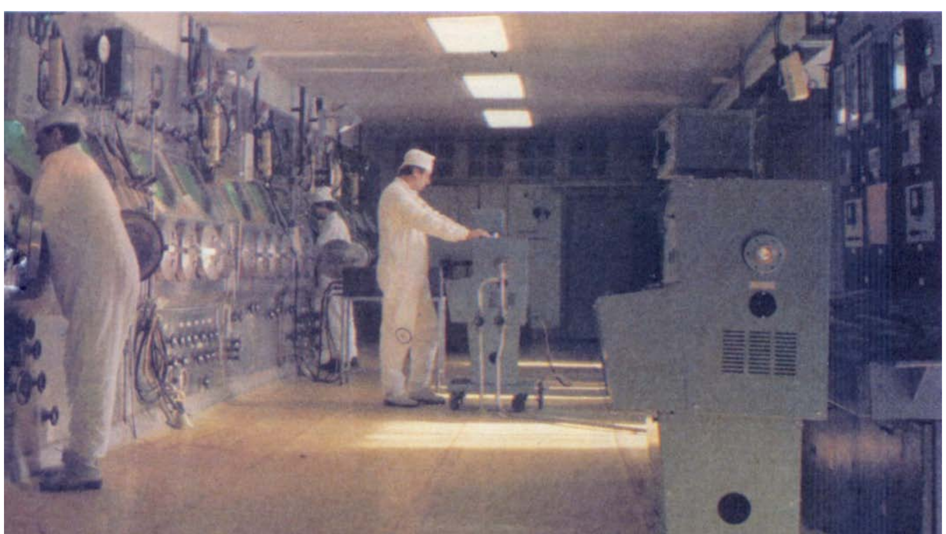
Reactors «Ruslan» and «Ludmila»

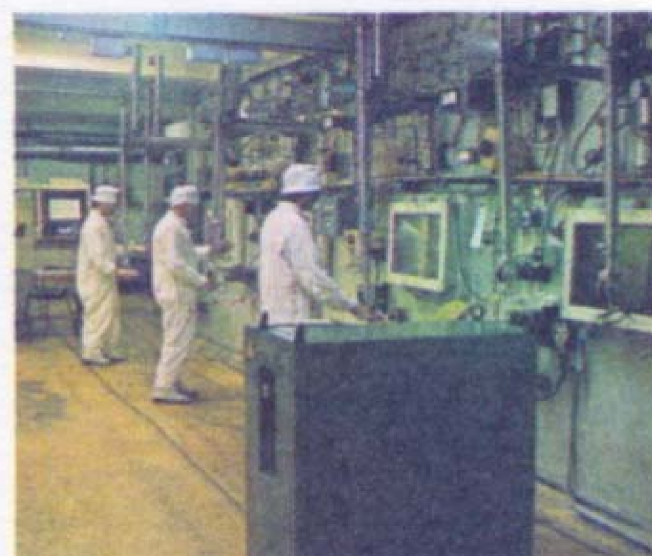
RADIOISOTOPE PLANT

Produced radionuclides:

$^{89,90}Sr$, ^{32}P, ^{35}S, ^{14}C, ^{99}Mo (under development)

Process facility for production of gamma-sources (Co-60, Ir-192, etc.) for medicine, sterilizers and flaw meters





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

Produced radionuclides:

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

^{99}Mo (starting up)

Nuclear reactors for isotope production: RBT-10/1 and 10/2

BOR-60 (fast neutrons)

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

Mo-99 Crisis and the Role of Russia

^{99}Mo (66 h) $\rightarrow$ ^{99m}Tc (6 h)

About 80% of all radiodiagnostic procedures are performed with ^{99m}Tc

Consumption of molybdenum-99 (6-day decay)

In the world: 12 000 Ci/week
in USA: 5 000 - 7 000 Ci/week
……
in Russia 200 Ci/week

Main producers:

MDS Nordion (Canada –NRU, Maple-1)	**40%**
Covidien (Netherlands - HFR, Belgium - BR2, France - Osiris)	**25%**
IRE (Belgium)	**20%**
NTR (South Africa)	**10%**
Others:	**5%**

Russia, Australia, Indonesia, Argentina, Chili, Poland, Romania, Pakistan, Egypt

NEAR FUTURE: China (2015), Japan (2014), South Korea (2016)

Russian project at RIAR (Dimitrovgrad) (2011-2012)

1st step: 800-1000 Ci/week, 2nd step: 2200-2500 Ci/week

(Alkaline technology of German company Isotope Technologies Dresden)

The most prospective ways solving the "Mo-99 crisis"

1. Targets from low enriched uranium (LEU), 19.9% or lower ^{235}U

Successful developments in Argentina, South Korea, Australia, South Africa, Belgium

2. Solution reactors

Developments in USA (Babcock &Wilcox - Covidien), Taiwan, Russia (KI-"ARGUS")

The most prospective challenge: LEU

3. Accelerators – mainly of electrons (γ, n)

also protons (p, n) IRE/IBA: Ta+p (350 MeV, 1000 μA)

4. Neutron capture $^{98}Mo\ (n, \gamma)\ ^{99}Mo$

Less effective local production in many places in small amounts

THERE ARE SEVERAL MORE APPROACHES

Karpov Institute of Physical Chemistry (Obninsk branch)

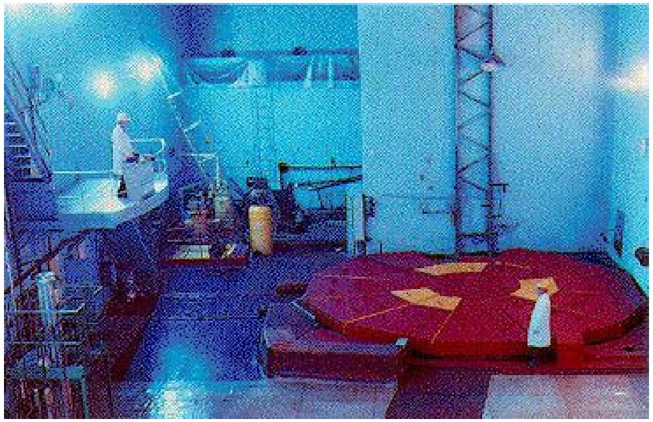
Nuclear reactor
Hot cells

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)
- ^{67}Ga-citrate
- ^{188}W/^{188}Re-generator (under development)
- ^{103}Pd (together with INR)

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

First world's nuclear power plant



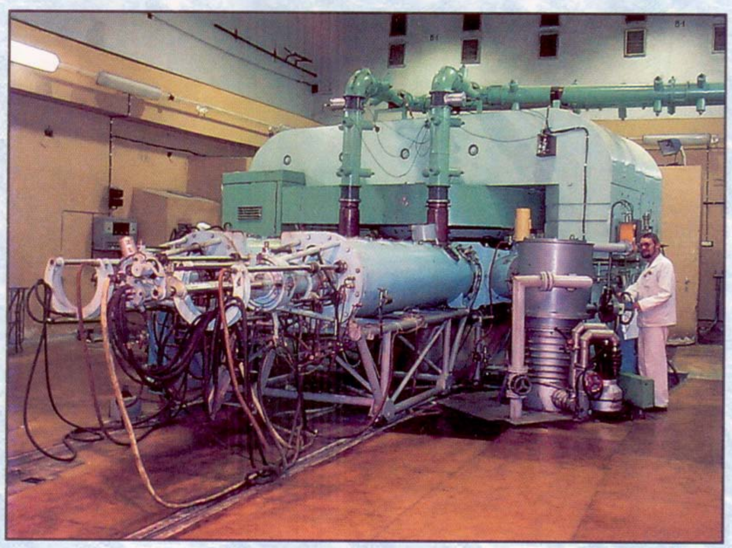
MEDICAL ISOTOPE PRODUCTION

- **^{125}I – microsources for prostate cancer therapy**
- **^{90}Sr – microsources for cardio-vascular therapy**
- **^{99m}Tc-generator (GMP in project)**
- **$^{188}W/^{188}Re$-generator**
- **^{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

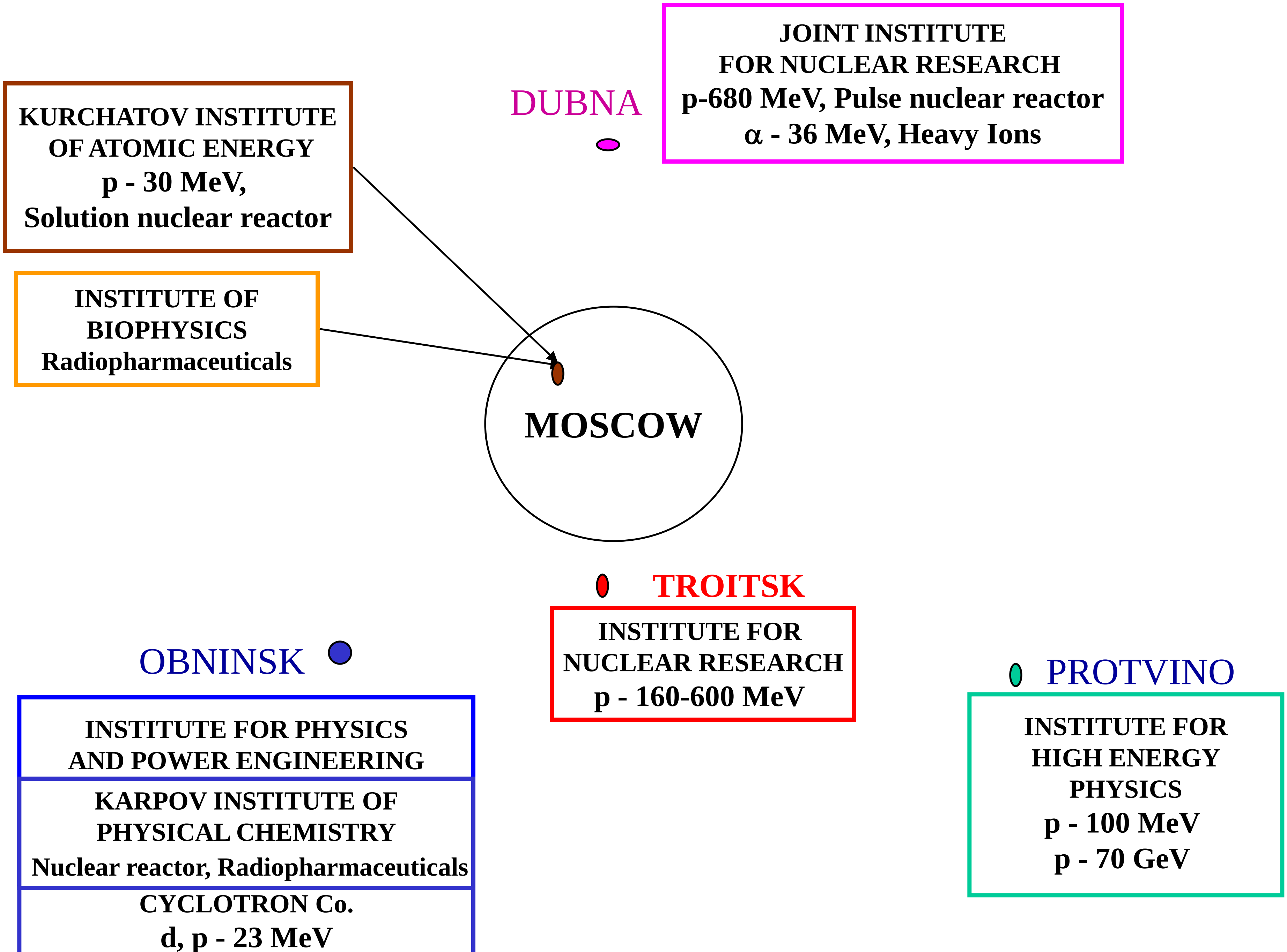
PRODUCED RADIONUCLIDES
^{67}Ga, ^{68}Ga, ^{103}Pd, ^{111}In, ^{85}Sr,
^{68}Ge/^{68}Ga-generator



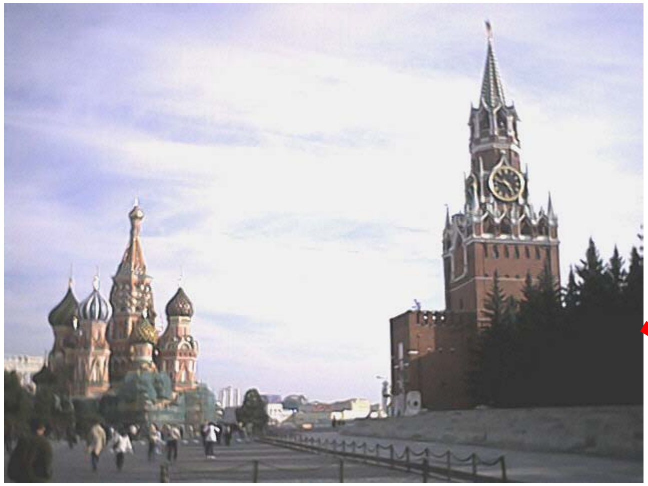
CYCLOTRON U-150

7 HOT CELLS

RADIOCHEMICAL SECTION


JOINT INSTITUTE
FOR NUCLEAR RESEARCH
p-680 MeV, Pulse nuclear reactor
α - 36 MeV, Heavy Ions
DUBNA
KURCHATOV INSTITUTE
OF ATOMIC ENERGY
p - 30 MeV,
Solution nuclear reactor
INSTITUTE OF
BIOPHYSICS
Radiopharmaceuticals
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 - 23 MeV
PROTVINO
INSTITUTE FOR
HIGH ENERGY
PHYSICS
p - 100 MeV
p - 70 GeV

MOSCOW, RUSSIA



TROITSK TOWN

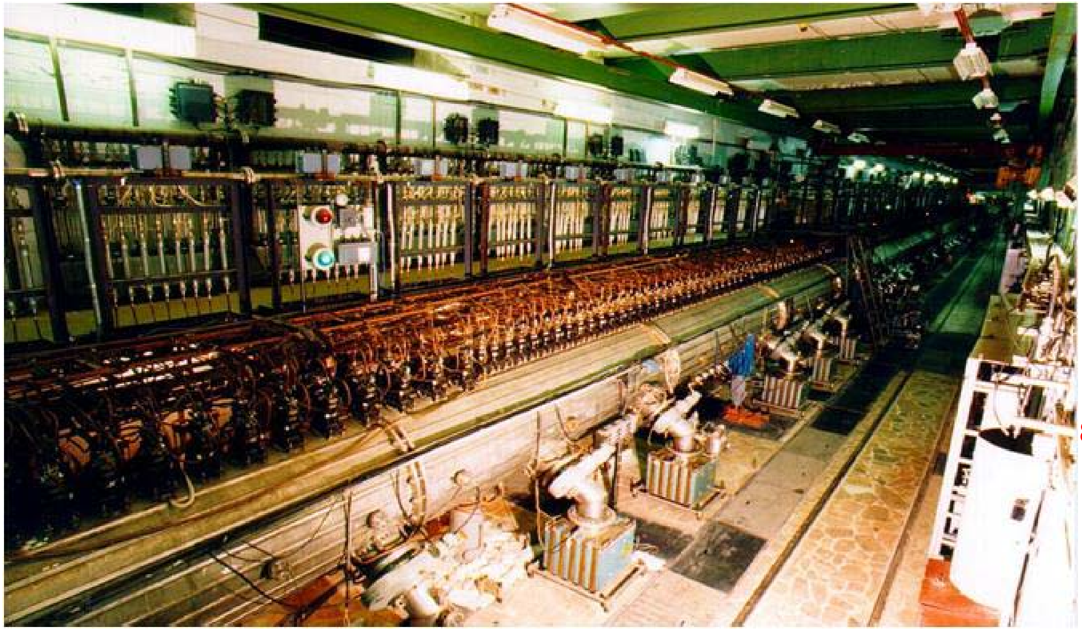
40 km

1 km

INR ACCELERATOR

ИЯИ
ЯNR
RUSSIAN ACADEMY OF SCIENCES
INSTITUTE
FOR NUCLEAR RESEARCH

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:

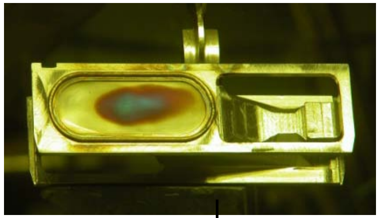
^{72}Se, ^{64,67}Cu, ^{225}Ac, ^{223}Ra

Isotopes exported by INR

Sr-82 | Pd-103 | Sn-117m | Ge-68 | Na-22 | Cd-109

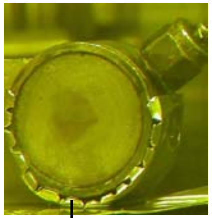
T a r g e t s

Rb

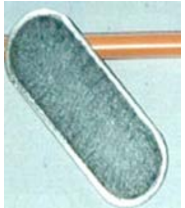


Ag

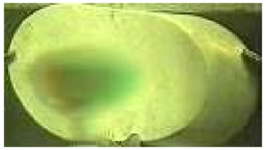
Sb



Ga



Al



In

-Los Alamos, USA
-IPPE, Obninsk

-Karpov,Obninsk
-Mayak, Ozersk

IPPE, Obninsk
Brookhaven, USA

-Cyclotron Co., Obninsk
-IPPE, Obninsk

-Los Alamos, USA

-Applied Chemistry,
St-Petersburg

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

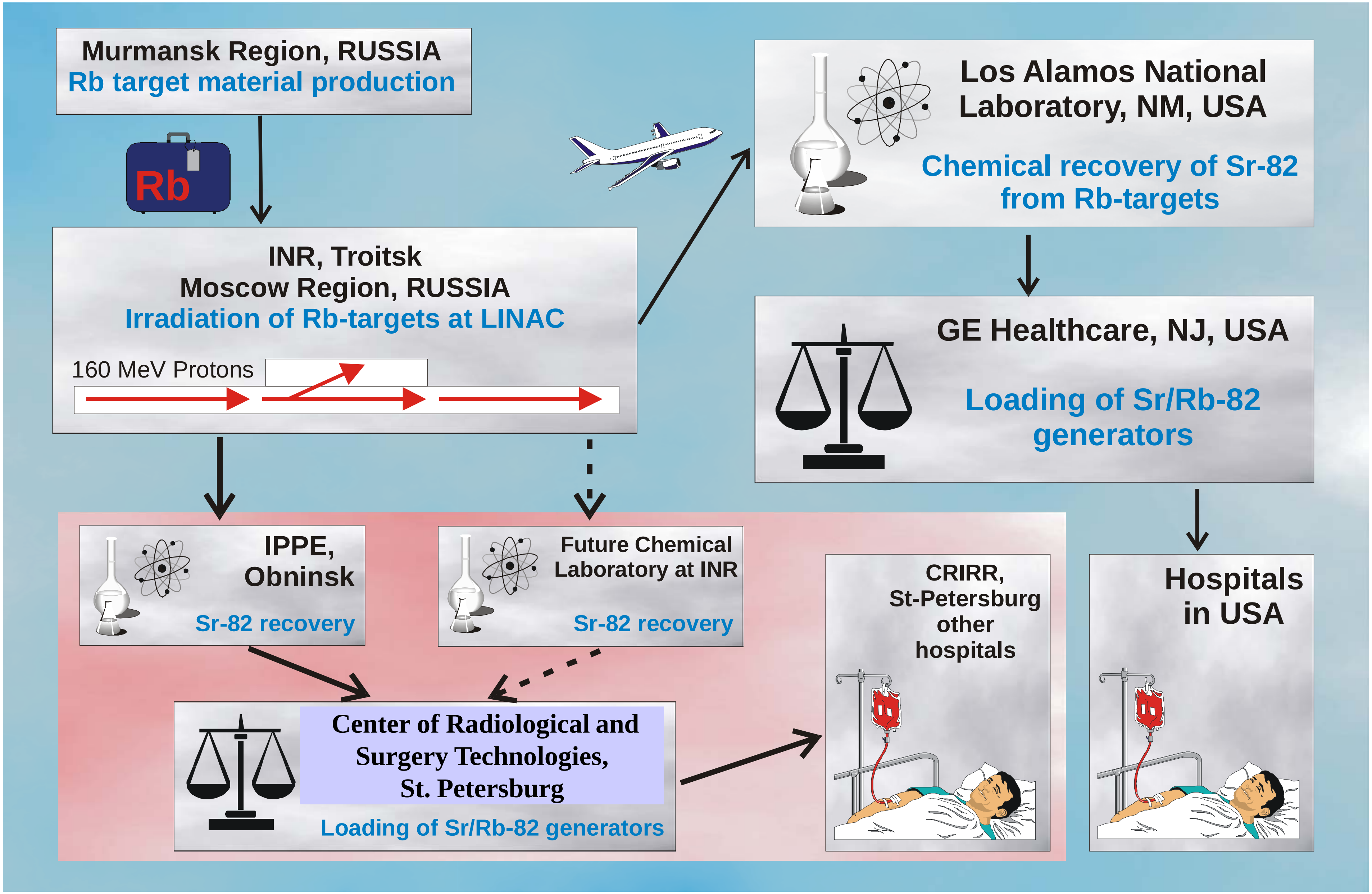
Radio-nuclide	Half life period	Target	Energy range, *MeV*	Bombardment period, *hr*	Activity produced in one run at EOB, *Ci*
Sr-82	25.5 d	Rb	100-40	250	5
Na-22	2.6 y	Mg, Al	150-35	250	2
Cd-109	453 d	In	150-80	250	2
Pd-103	17 d	Ag	150-50	250	50
Ge-68	288 d	Ga, GaNi	50-15	250	0.5
Sn-117m	14 d	Sb, TiSb	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

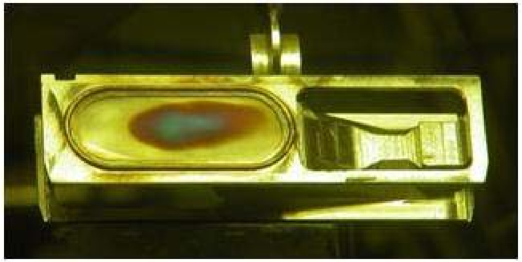
Red – production method developed, technology under development

Production and Transportation Scheme of Strontium-82



Processing of INR metallic rubidium target for recovery strontium-82 at Los Alamos

(successful GIIP project INR with LANL)



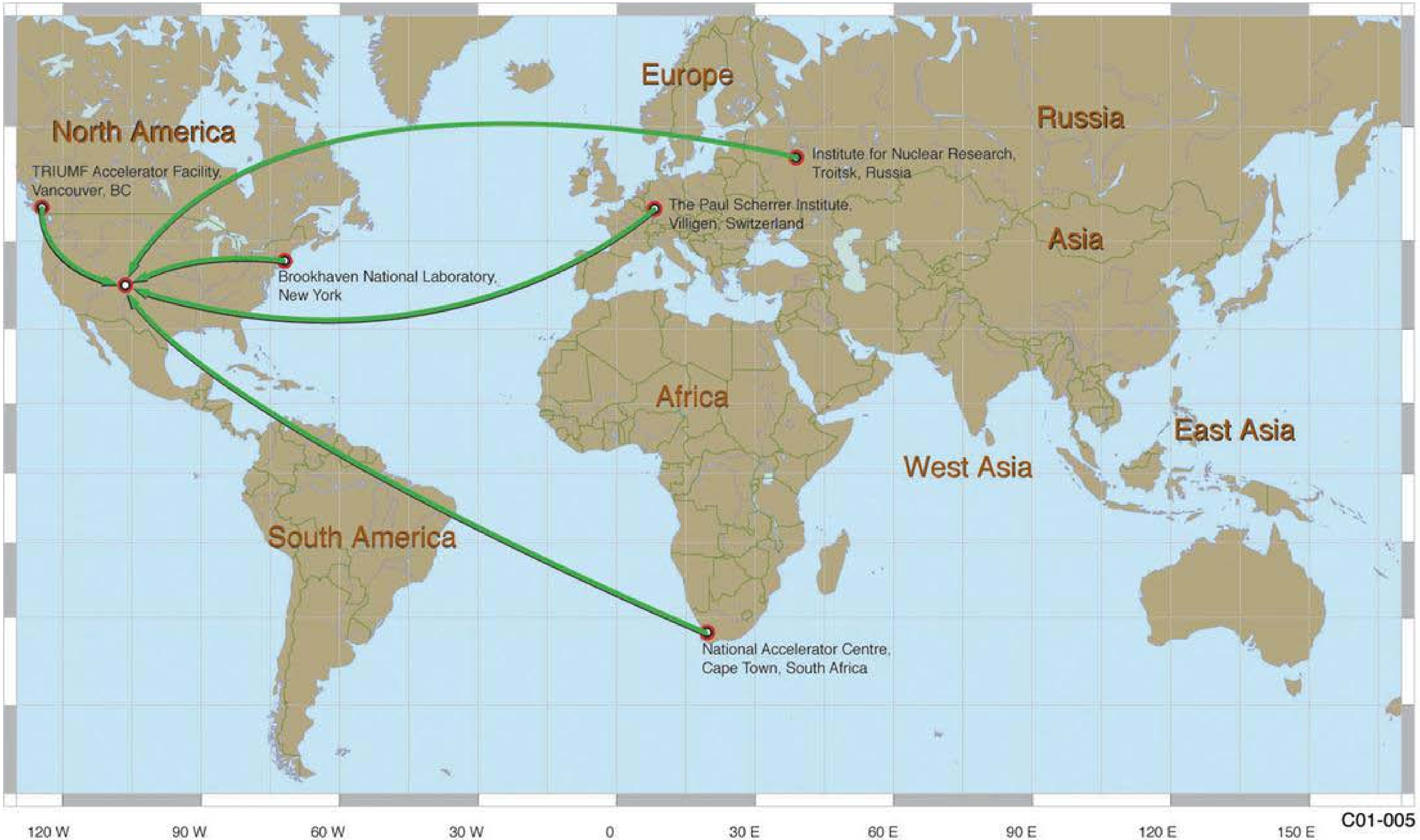
Total amount of irradiated and shipped target: more than 100

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

- **Brookhaven National Laboratory (NY, USA)**
  200 MeV, 100 μA
- **Los Alamos National Laboratory (NM, USA)**
  100 MeV, 200 μA
- **TRIUMF (Vancouver, Canada)**
  110 MeV, 70 μA
- **iThemba Laboratory (Cape Town, South Africa)**
  66 MeV, 150 μA
- **Institute for Nuclear Research (Troitsk, Russia)**
  160 MeV, 120 μA

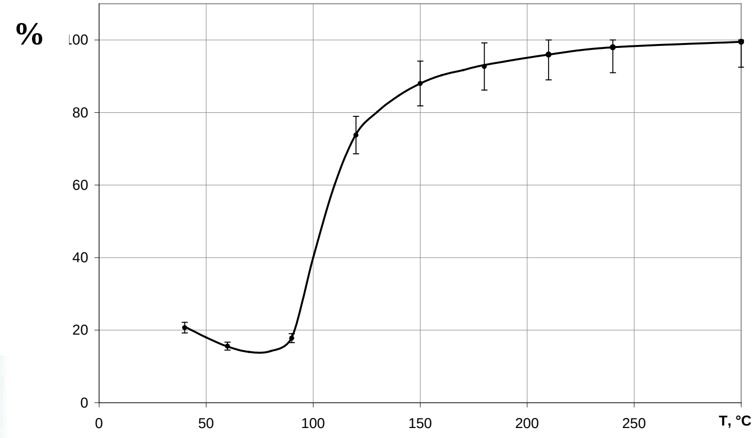
(Regular beam currents on typical targets)

Virtual Isotope Center- supplementing and extending existing availability



Radiochemical facility based on a new technology of strontium-82 sorption directly from liquid metallic rubidium (in hot cells at IPPE, Obninsk)

Temperature dependence of Sr-sorption



Short-lived radionuclides used in PET

- ^{18}F (110 min)
- ^{15}O (2 min)
- ^{13}N (10 min)
- ^{11}C (20 min)
- ^{82}Rb (1.3 min)

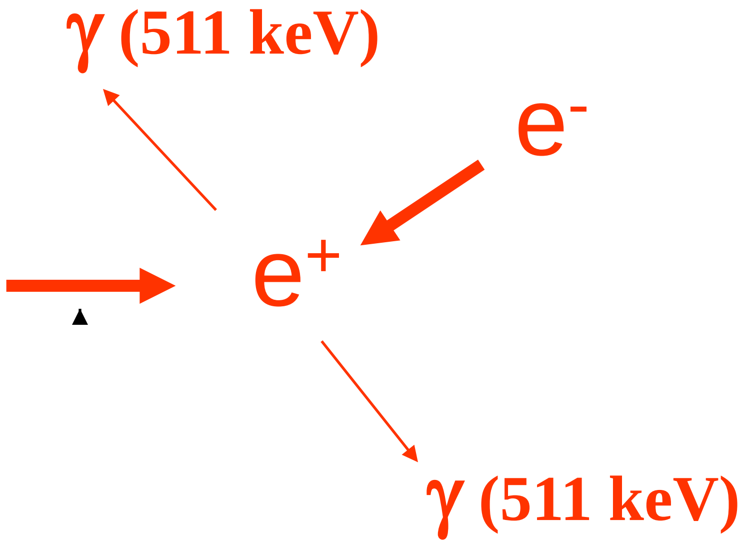
  ↑

  ^{82}Sr (25.5 d)

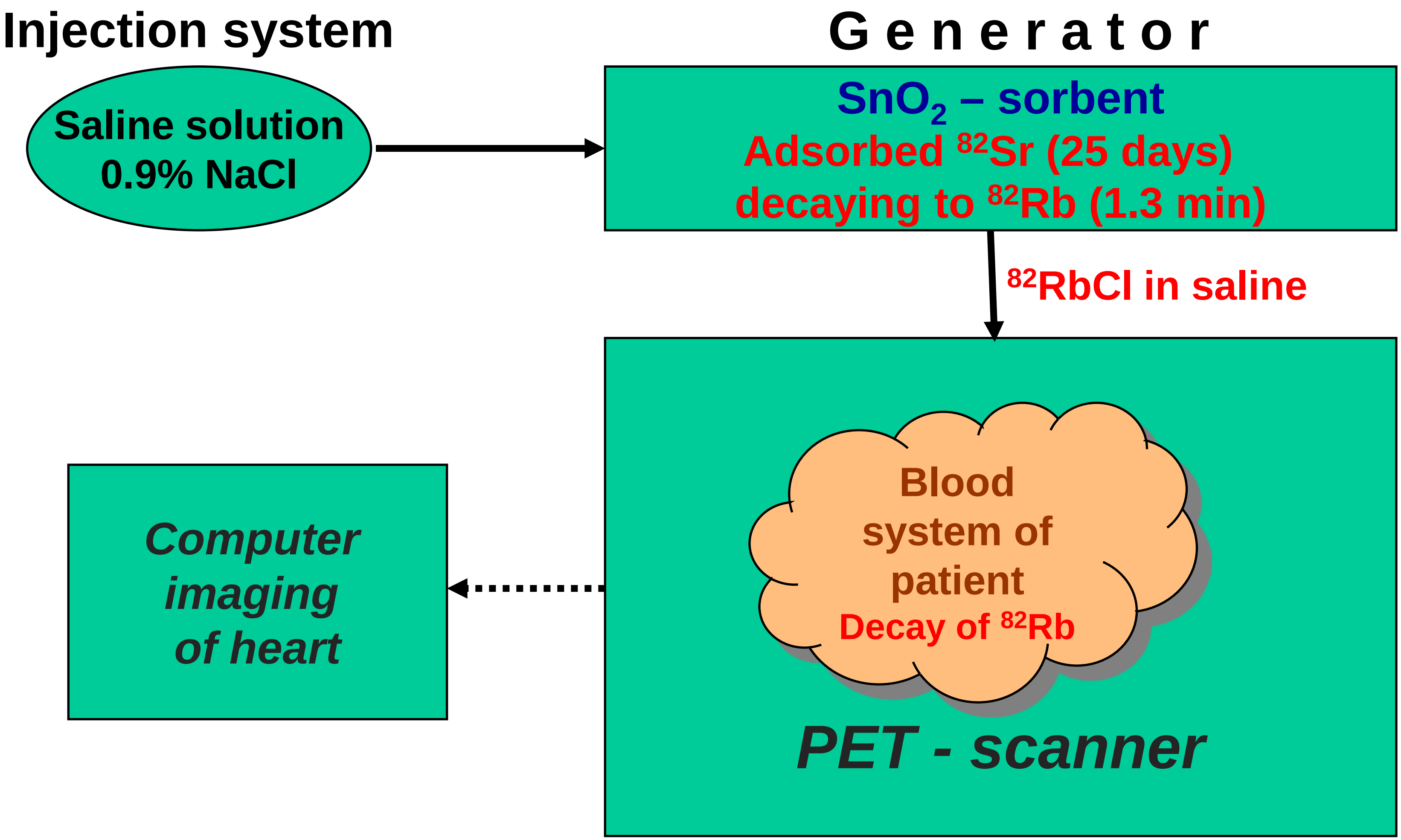
- ^{68}Ga (68 min)

  ↑

  ^{68}Ge (271 d)



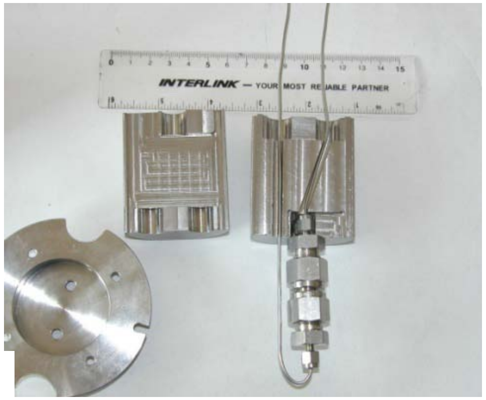
Principle of Operation with $^{82}Sr/^{82}Rb$- Generator: an alternative of ^{13}N and ^{99m}Tc in some cases



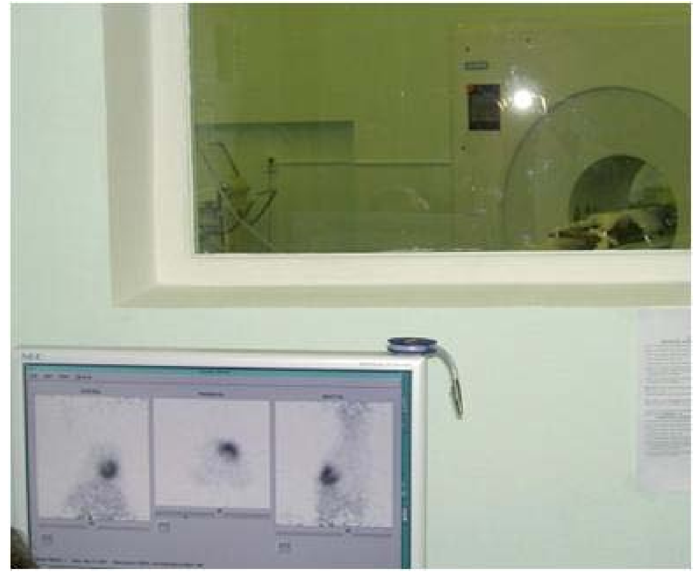
CardioGen-82® US Sr/Rb-82 Generator (10/30 kG, 100-120 mCi, 28-day operation)

RECALL in July 2011

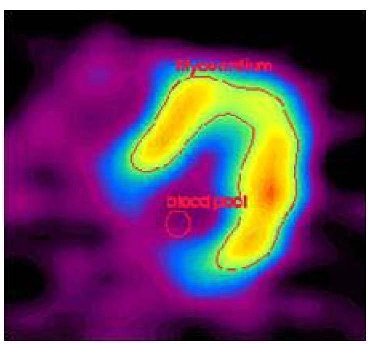
GR-01 Russian Sr/Rb-82 Generator in tungsten container (21/38 kG, 50-160 mCi, 60-day operation)



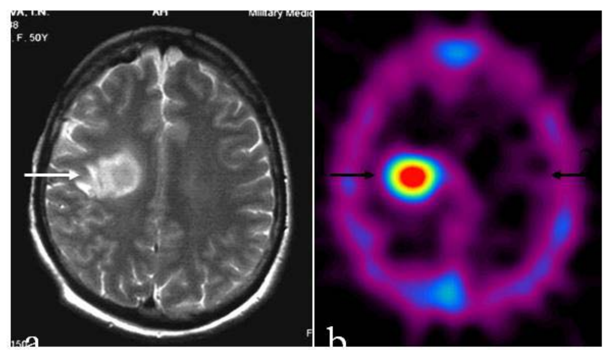
Preclinical and clinical tests of Russian Sr/Rb-82 generator for cardio diseases at PET facility in Center of Radiological and Surgery Technologies, St. Petersburg



Heart of the first patient



Ameboid glioma of right parietal lobe



More than 150 patients have been treated within the clinical trials

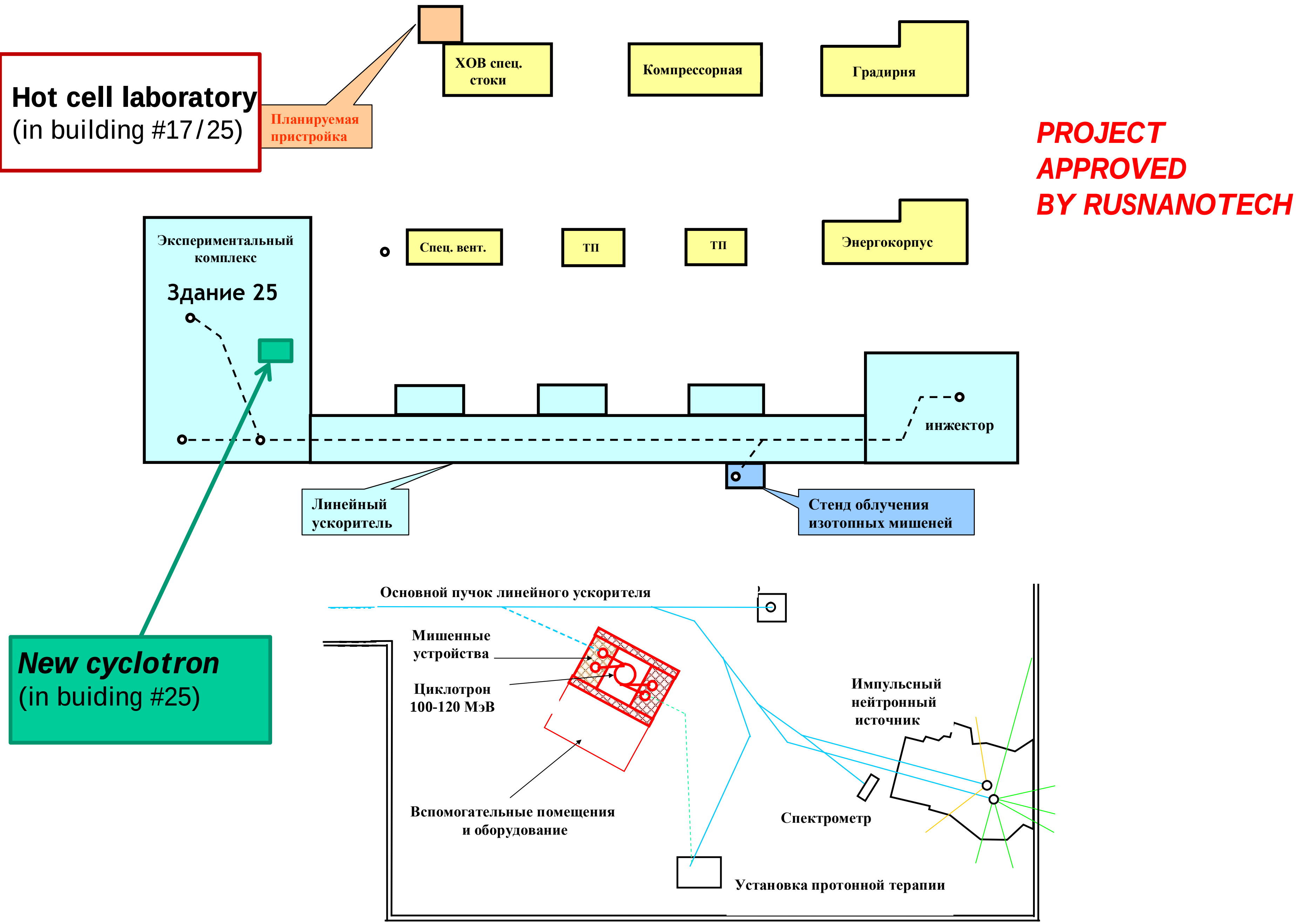
Expected approval for routine use in Russia: December, 2011

6 PET centers only in Russia are ready to consume; 31 – in near future

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

- **ARRONAX/IBA (Nantes, France)**
  H^- Cyclotron - 70 MeV, 2x375 μA
- **Institute for Nuclear Research (Troitsk, Russia)**
  H^- Cyclotron - 120 MeV, 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)
- **Legnaro National Laboratory, INFN (Padova, Italy)**
  Cyclotron - 70 MeV, 2x400 μA
- **Positron Corporation (Illinois, USA)**
  H^- Cyclotron - 70 MeV, 2x375 μA: ^{82}Sr production
- **Proton Engineering Frontier Project (Gyoungju, South Korea)**
  LINAC - 100 MeV, >300 μA
- **National Institute for Radioelements, IRE and IBA (Belgium)**
  Cyclotron - 350 MeV, 1000 μA (Ta-target to produce neutrons for ^{99}Mo)
- **TRIUMF (Vancouver, Canada)**
  Existing H^- cyclotron - 500 MeV. Isotope separator facility: ^{99}Mo from ^{98}Mo-targets

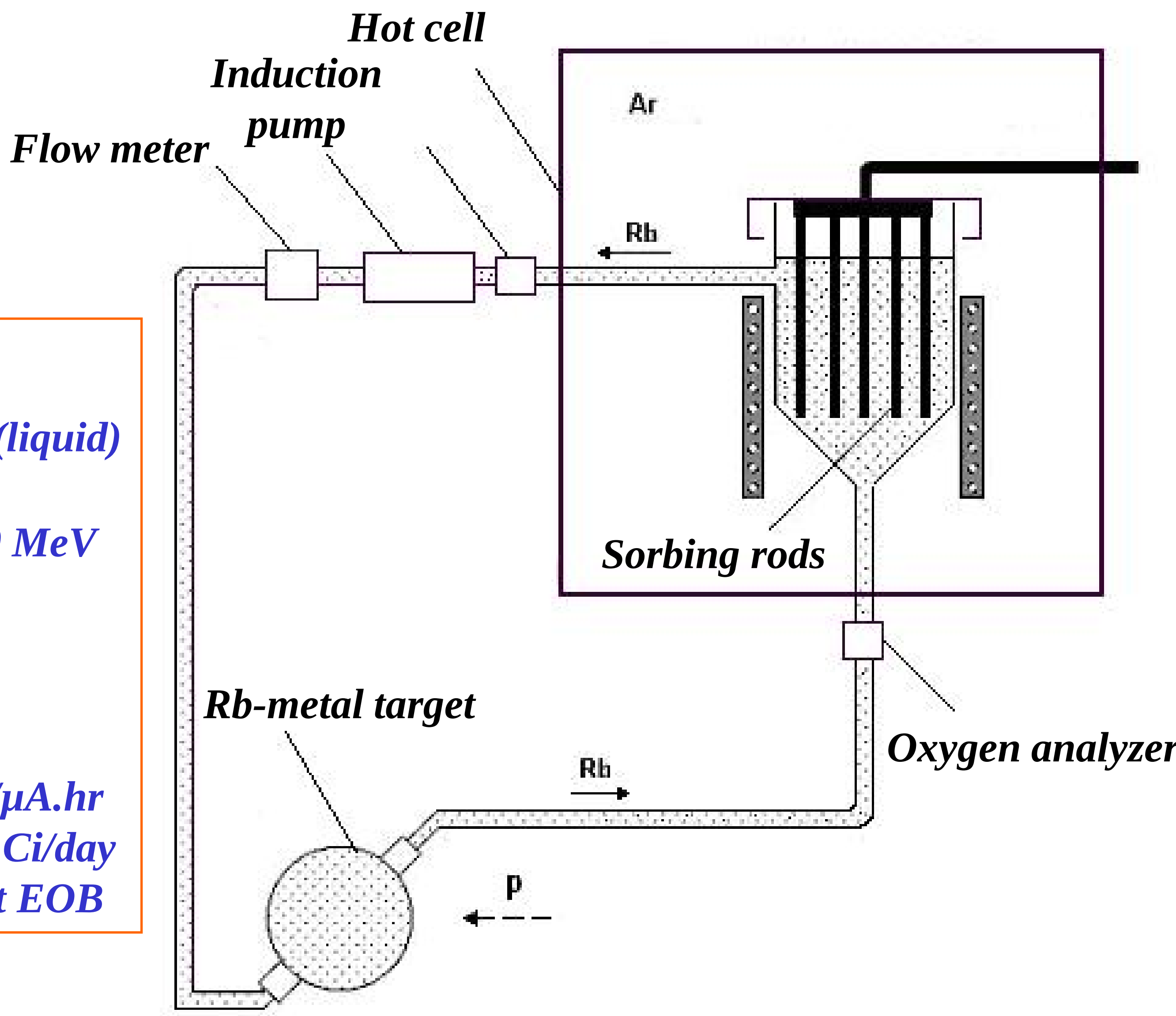
Existing and future installations for isotope production at INR



Prospect Facility for On-Line Sr-82 Production

Main Parameters:

Target material: Rb+3% O (liquid)
Beam current: ≥ 300 μA
Proton energy range: 80-40 MeV
Energy release: 12 kW
Rb volume: ~1.5 L
Rb flow: ~5 L/min
Target diameter: ~8 cm
Production yield: 0.45 mCi/μA.hr
Production capacity ^{82}Sr: 3 Ci/day at EOB



Production ^{117m}Sn from antimony targets

$^{121,123}Sb\ (p;\ 2p\ xn)\ ^{117m}Sn$

$T_{1/2}$=14.0 d

Low energy conversial Auger-electrons 127 and 152 keV

Range in water: 0.22 и 0.29 mm

Metallic Sb-target in graphite shell covered with nickel

Target from intermetallic compound TiSb

Mutual development of INR and BNL, USA (S. Srivastava et al.) with participation of MSU (Moscow) and IPPE (Obninsk), supported by GIPP foundation

Application of α-active actinium-225 and radium-223 for therapy of oncology diseases:
directly or via short-lived bismuth-213 and lead-211

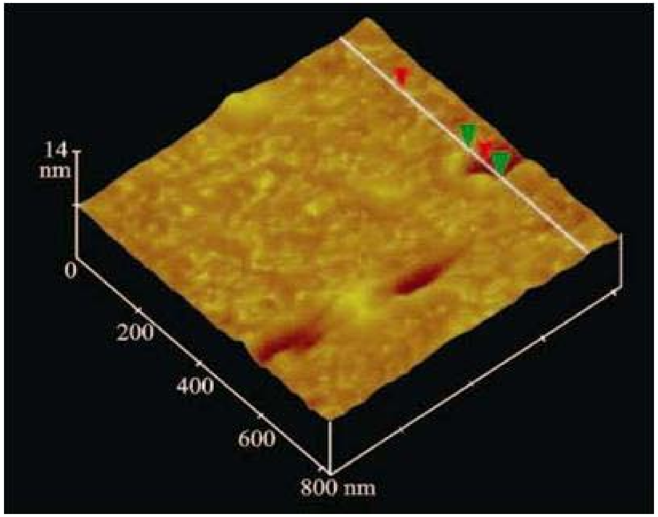
- **Prostate cancer, mammary gland, brain, bone, stomach, pancreas, ovaries cancer**

- **Melanoma**

- **Celothelioma**

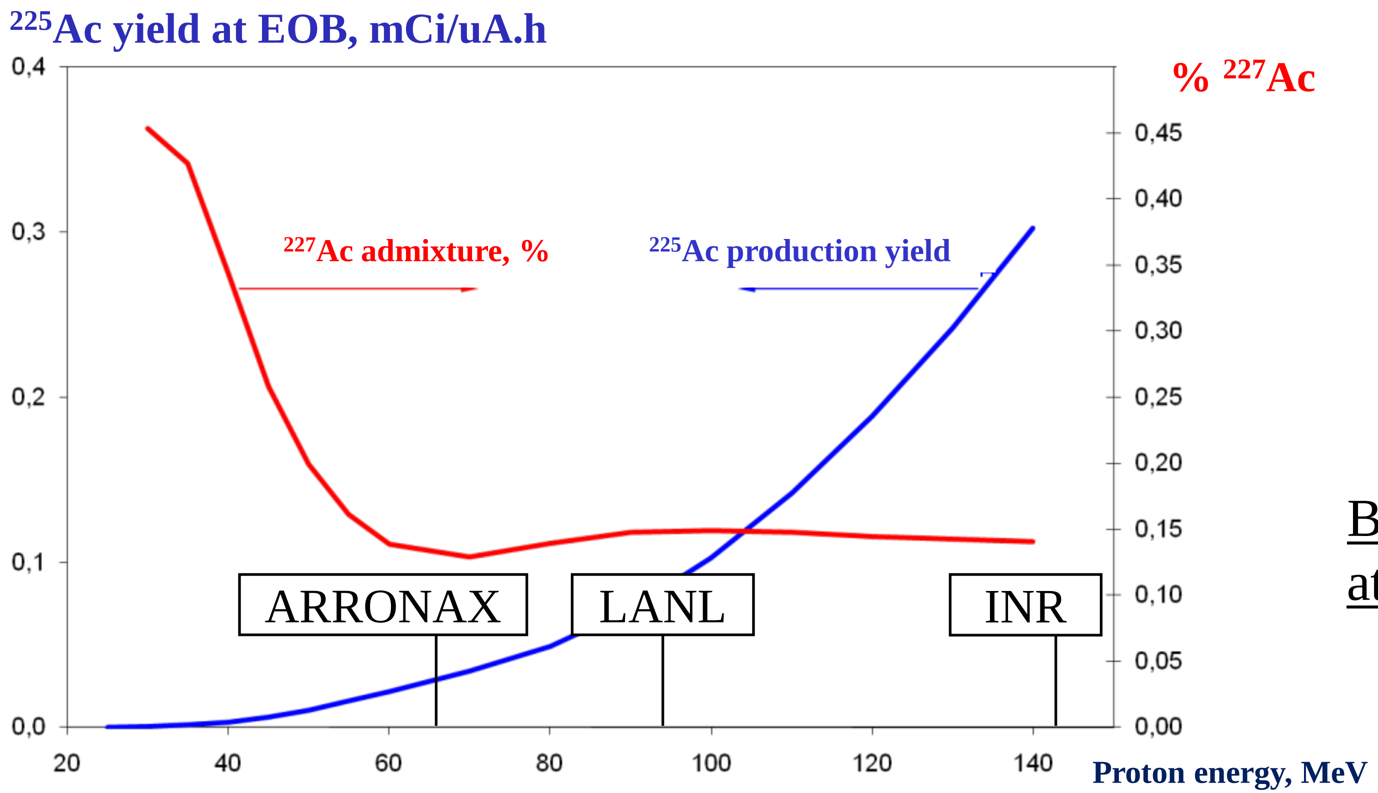
- **Leukemia**

By Institute of Gene Biology of RAS – A.S.Sobolev et al.



The radionuclides are incorporated into artificial modular NANOTRANSPORTERS (platforms) of polypeptide structure providing the address delivery of the radionuclide to the cells and the given cell component, e.g., to nucleus

Production of ^{225}Ac from nat. Th irradiated with protons



Backup production at BNL (200 MeV) is reasonable

Potential production at 160 MeV
(at customer's calibration time):

2 Ci per week ^{225}Ac after 10-day decay
(current world production is about 0.15 Ci per month)

4 Ci per week ^{223}Ra after 16-day decay

Possibility of Medical Isotope Production at INR

RADIO-NUCLIDE	APPLICATION	HALF-LIFE	ANNUAL PRODUCTION, *Ci*		PATIENT AMOUNT (per year)
			Linear accelerator	New cyclotron	
^{82}Sr	PET- diagnostics (cardiology)	25 d	30	400	500 000
^{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

Problems to be Solved in Isotope Production and Investigations

1. Efficient international collaboration

2. Government funding is necessary

3. Disposition of funds for R&D: overcoming agency barriers

4. Enough qualified and independent international committee for distribution of funds in realization of isotope projects is necessary

5. Improvement the system for transportation logistics

6. To reduce bureaucratic regulations (not reducing safety)

7. Severely growing rates for electricity power, heat, leasing, wastes management, etc.

THANK YOU !