CSN5 INFN new research project proposal
(2015-2017)

TECHN-Osp

R&D activities aimed at an industrially-based technology for future homeland accelerator-^{99m}Tc production based on a selected cyclotrons' network in Italy:

May the the colllaboration network gathered around the APOTEMA research project have a role as the strategic center for the scientific/technical support?

The APOTEMA/ S. Orsola (Bo) Hospital collaboration network for the next TECHN-Osp project

LNL, June 19th , 2014

The daily need of ^{99m}Tc in Italy

Some facts and starting numbers....

- Based on a first meeting occurred with the medical physics head of the St. Orsola Hospital (Bologna)-Nuclear Medicine Dept., we have been aware that:

- ^{99m}Tc needs for S. Orsola Hospital only for routine diagnostic procedures : 1÷2 Ci/day

- Required ^{99m}Tc daily activity needed for the whole country estimated to be about S. Orsola Hospital x 150 ≅ **150-300 Ci**
- Is this range likely?

- Former information we had for **Veneto region** in past years: ~10 Ci/day
  Rough extrapolation: 10x 20 Italian regions =200 Ci

- Former information we had for **Ferrara Hospital** in past years: ~1 Ci/day
  Emilia Romagna region estimated ~ 15 times Ferrara needs = 15 Ci/day x 20 = 300 Ci/day

The average ^{99m}Tc daily need may thus be supposed ~200 Ci in the whole country

How many radioisotope production cyclotrons do we have in Italy?

- **~35 cyclotrons are currently running**, most of them located in the nuclear medicine depts of Hospital centers. The remaining (a few of them) located in private companies/ research centers (e.g. JRC-ISPRA).

- Basic role is to assure the daily PET-based radioisotope production. (basically ^{18}F-FDG and, at a lesser extent, (i.e. ^{11}C, ^{13}N- a few run per week)

- 2/3 of them are located in the continental area, the remaining 1/3 in the two big islands (Sicily, Sardinia)

- Cyclotron types (basically two):

IBA Cylone 18/9
18 MeV, up to 100 μA (1.8 kW) protons
9 MeV, 40 μA deuterons

Cyclone® 18/9 | Fitted with Vectio® external beam line for advanced research.

GE PetTRACE
16 MeV, up to 75 μA (1.2 kW) protons
8.4 MeV, 50 μA deuterons

^{99m}Tc production expected using next high-performance cyclotrons

^{99m}Tc in-target production yields estimated at EOB after:

- 3 h irradiation,
- at 15 and 20 MeV,
- 200 μA beam current
- 500 W/cm^2 mean areal power density
- 99.05% ^{100}Mo enrichment (optimized target configuration).

A series of quality parameters are listed at EOB. (Ref. 2 RCM report, IAEA 2013)

^{99m}Tc production	Ep=15 MeV	Ep=20 MeV
Beam power on target [kW]	**3.0**	**4.0**
Integral-target activity [Ci]	**2.85**	**5.56**
In-target activity [mCi/μA]	**14.25**	**27.8**
Specific Activity [GBq/g]	$3.84 \cdot 10^7$	$2.96 \cdot 10^7$
Tc / TOTAL activity	0.9848	0.9468
^{99m}Tc / TOTAL activity	0.3693	0.3926
^{99m}Tc / $^{99m+g}$Tc	0.1990	0.1665
Isotopic Purity (IP)	0.1970	0.1520
Radionuclidic Purity(RNP)	0.3750	0.4147

→ **reference for 100 μA current**

1.4 and 2.8 Ci expect to be yielded, removing **1.5 and 2.0 kW power** respectively

Basically, the daily production needed by a Hospital !!!

INFN Istituto Nazionale di Fisica Nucleare Laboratori Nazionali di Legnaro

A possible accelerator-^{99m}Tc production plan in Italy...

Let us suppose to have, from a mix of both cyclotron types available :

- 2 Ci average production per each 100 μA, 3 hrs run
- 2 Ci x 35 cyclotron available: 70 Ci

- 3 runs per day at each cyclotron station is therefore needed in the hypotheses to cope the full italian requirement of about ~ 200 Ci/day.

- This means the preparation of roughly 650-700 ^{100}Mo-enriched moly
- low power targets per week.
- A technology process covering all the production/recycling process and recovery of ^{100}Mo is therefore needed

- Possible **future business of roughly million Euro/year could be envisaged**

The key issue of ^{100}Mo-enriched moly recovery...

The ^{100}Mo-enriched (>99%) metallic moly cost in huge amonts (i.e. several hundreads grams) is currently around **800 Euro/gram .**

As comparison, cost for a few grams is ~1300 Euro/g

Coin target type	
Target diameter (coin type)	Φ = ~ 10 mm
^{100}Mo-enriched layer thickness required (i.e. optimized production for 18-20 MeV cyclotrons)	250 μm
Moly volume estimated	~ 20 mm^3
^{100}Mo-enriched moly metal bulk density	10.7 g/cc
moly mass estimated for any single target	214 mg

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The new research plan proposed....

- The is a growing interest all over the world in the new accelerator-based ^{99m}Tc production on a routine basis, exploiting the new high-performance cyclotrons now entering into operation

- The still ongoing APOTEMA project as well as the IAEA project launched at international level (CRP code F22062: "Accelerator-based Alternatives to Non-HEU production of Mo-99/Tc-99 m") has demonstrated the feasibility (i.e. physical-chemical constraints) for an accelerator-^{99m}Tc production quality as high as generator-^{99m}Tc.

- All the experience and the knowledge acquired the **APOTEMA group** of people which is expected to be involved into the next **LARAMED project** at LNL , may now be usefully applied to a new step forward…

The need for a new technology process....

- It's **hard to think about the set up of an "extended cyclotron network" to ensure the supply of Tc-99m on the whole national territory**. It would surely be a **long logistic process to be put into operation…..**

- More reasonable is the **development of Tc99m closed loop technology for a number of selected centers (Hospital cyclotrons) instead**, that could routinely supply the accelerator-Tc-99m to other nearby Hospitals **in case of Mo-99 shortage**.

Basically the **TECHN-Osp pilot project** therefore aims at:

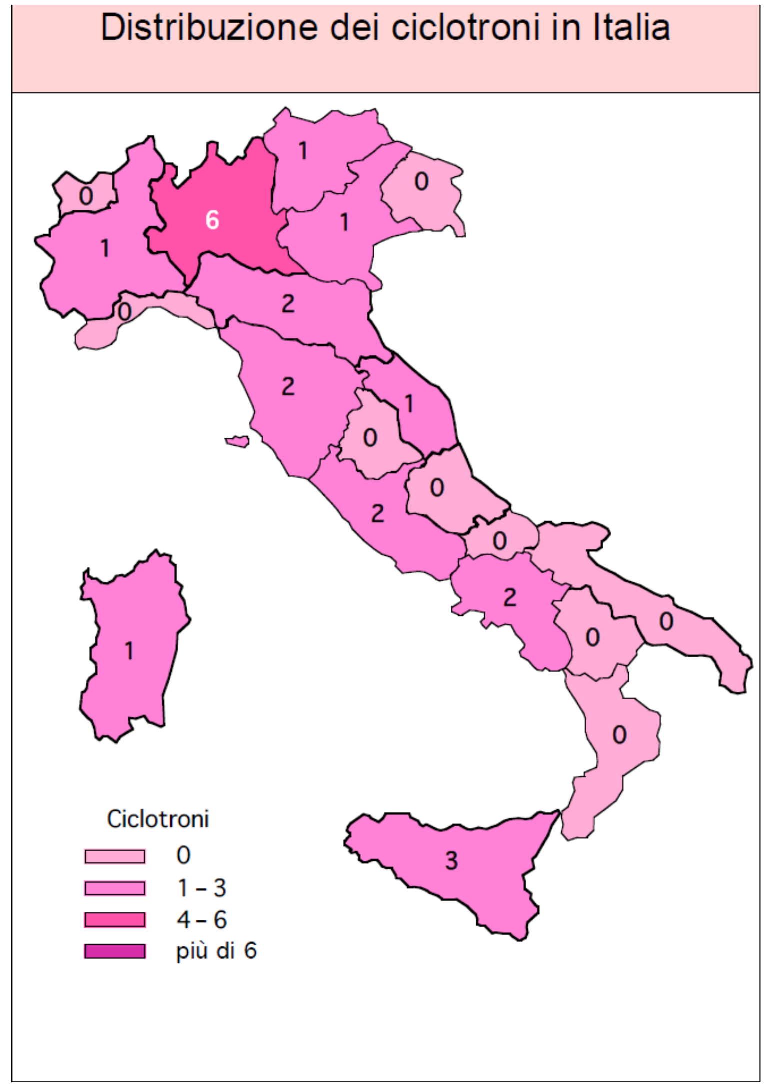
a) the very first research steps to set up the best **technology for a closed (^{100}Mo recovery step included) Tc-99m yield program;**

b) Setting up **a limited cyclotron network as well as** to provide both technology and procedures to yield Tc-99m if requested by another center in case of need

The operating Cyclotron network in Italy

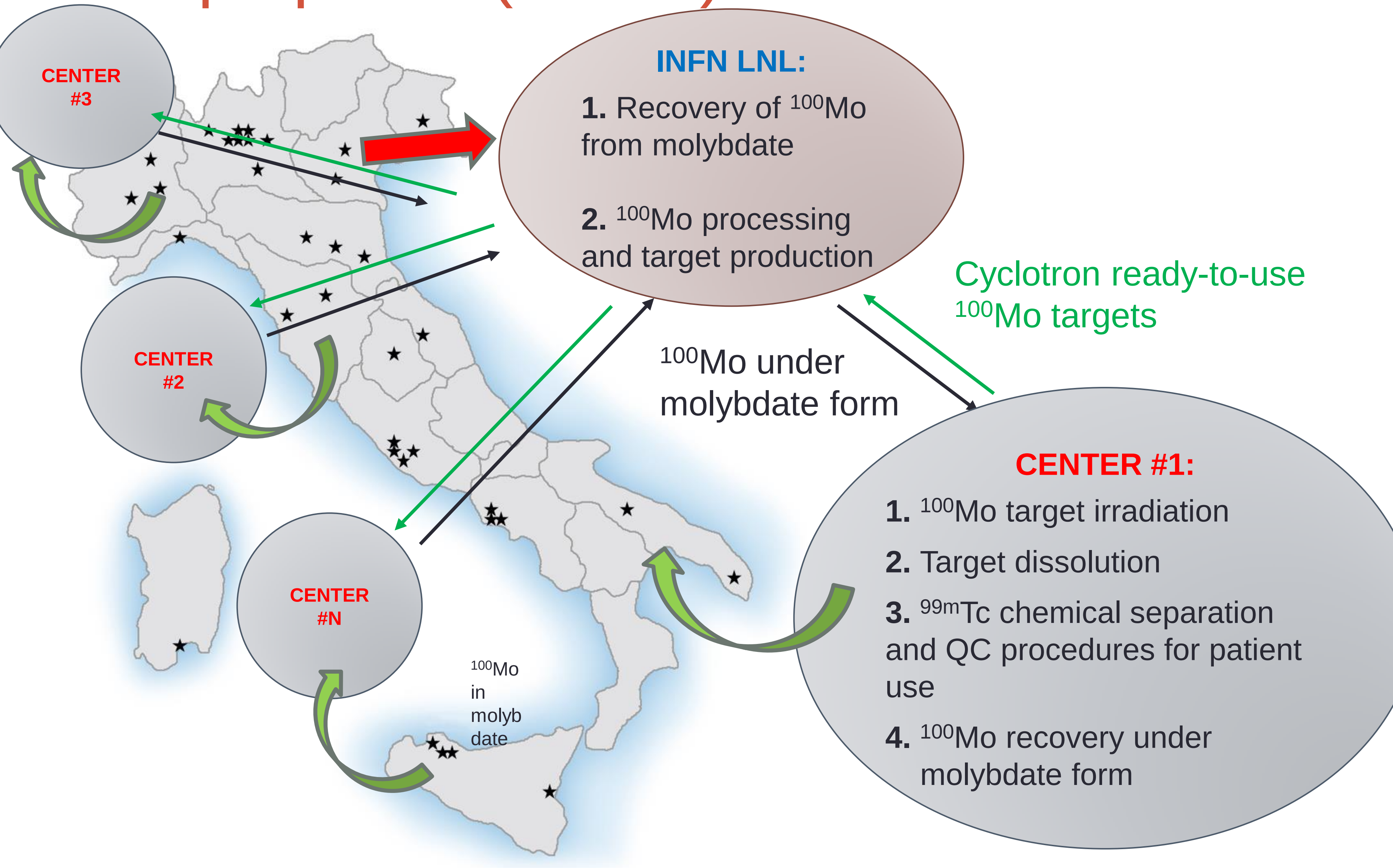
Public + Private centers: 36 cyclotron units

Public healthcare centers (Hospitals)



Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The proposed (limited) network scheme



Research units taking part...

INFN Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

Università degli Studi di Ferrara
1391
Ex labore fructus

INFN Istituto Nazionale di Fisica Nucleare

- Ferrara Branch
- Pavia Branch
- Padua Branch
- Milan Branch
- Bologna Branch

Servizio Sanitario Regionale Emilia-Romagna
Azienda Ospedaliero - Universitaria di Bologna
Alma Mater Studiorum Università di Bologna
Policlinico S. Orsola-Malpighi

Università degli Studi di Milano

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The TECHN-Osp (2015-2017) research project proposal

Basically a

4 step research program...

Development of an industrial process for in-hospital Tc99m production

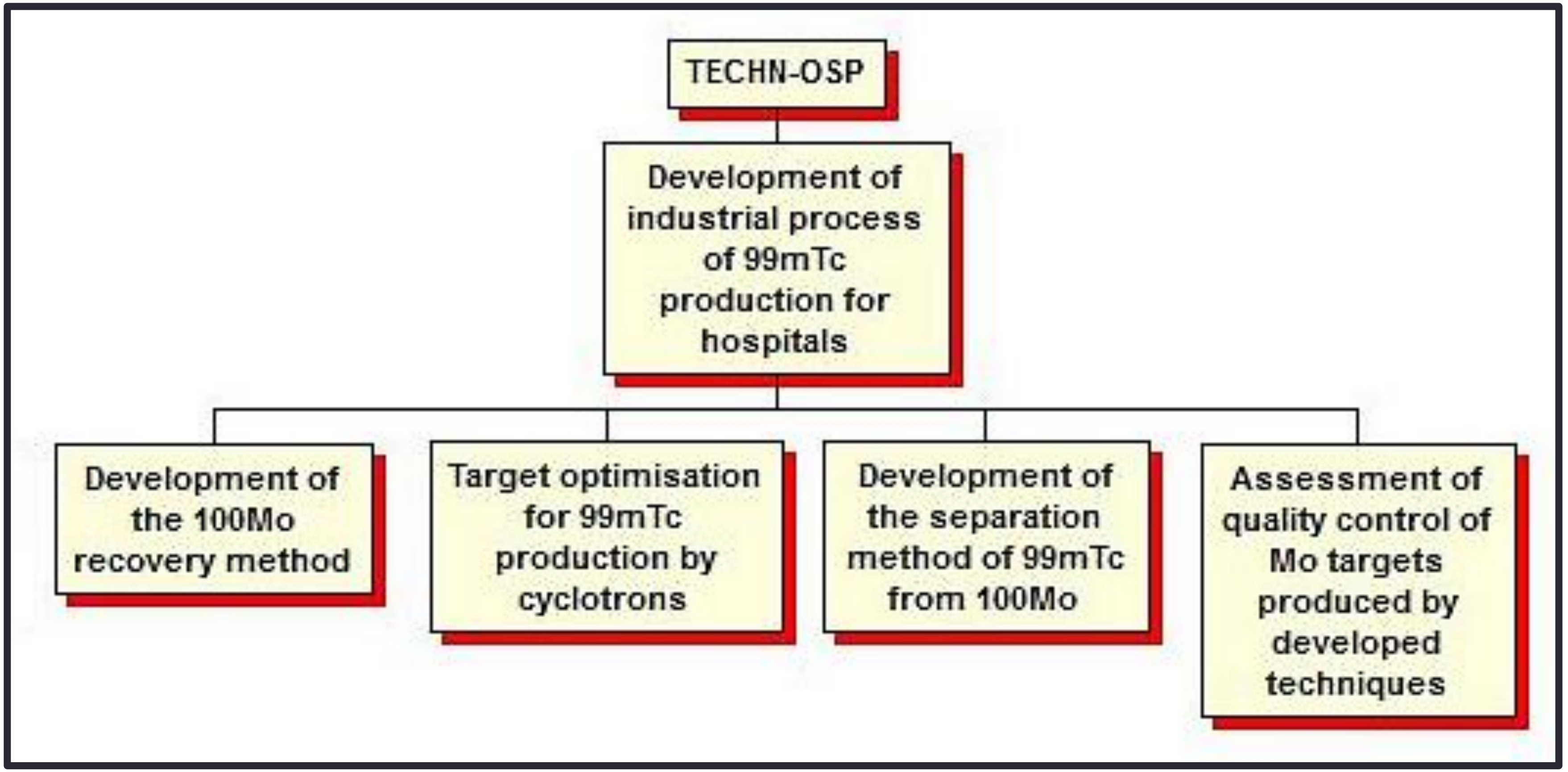
A
Development of a Mo100 recovery method in mass quantity

B
Optimisation of Mo100 target manufacturing for Tc99m production by (low and high current) Cyclotrons

C
Optimization of Tc99m chemical separation(s) methods from Mo100 targets

D
Quality Control (QC) procedures on both Tc99m and recovered Mo100 for targets manufacturing by developed techniques

TECHN-Osp research WBS structure proposed



A B C D

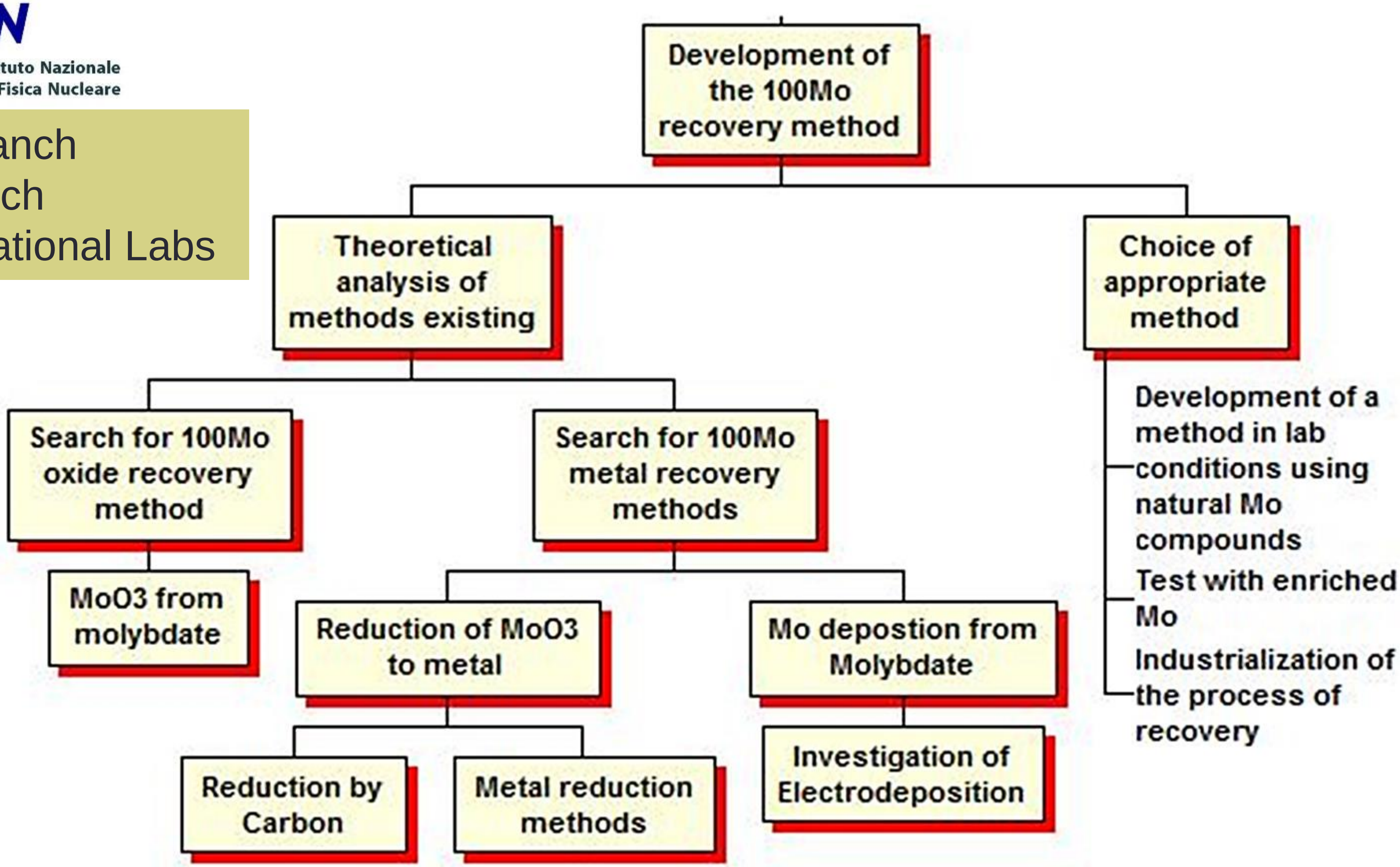
Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The role of different research units

Step (A): Development of ^{100}Mo recovery method

Istituto Nazionale di Fisica Nucleare

Ferrara branch
Pavia branch
Legnaro national Labs



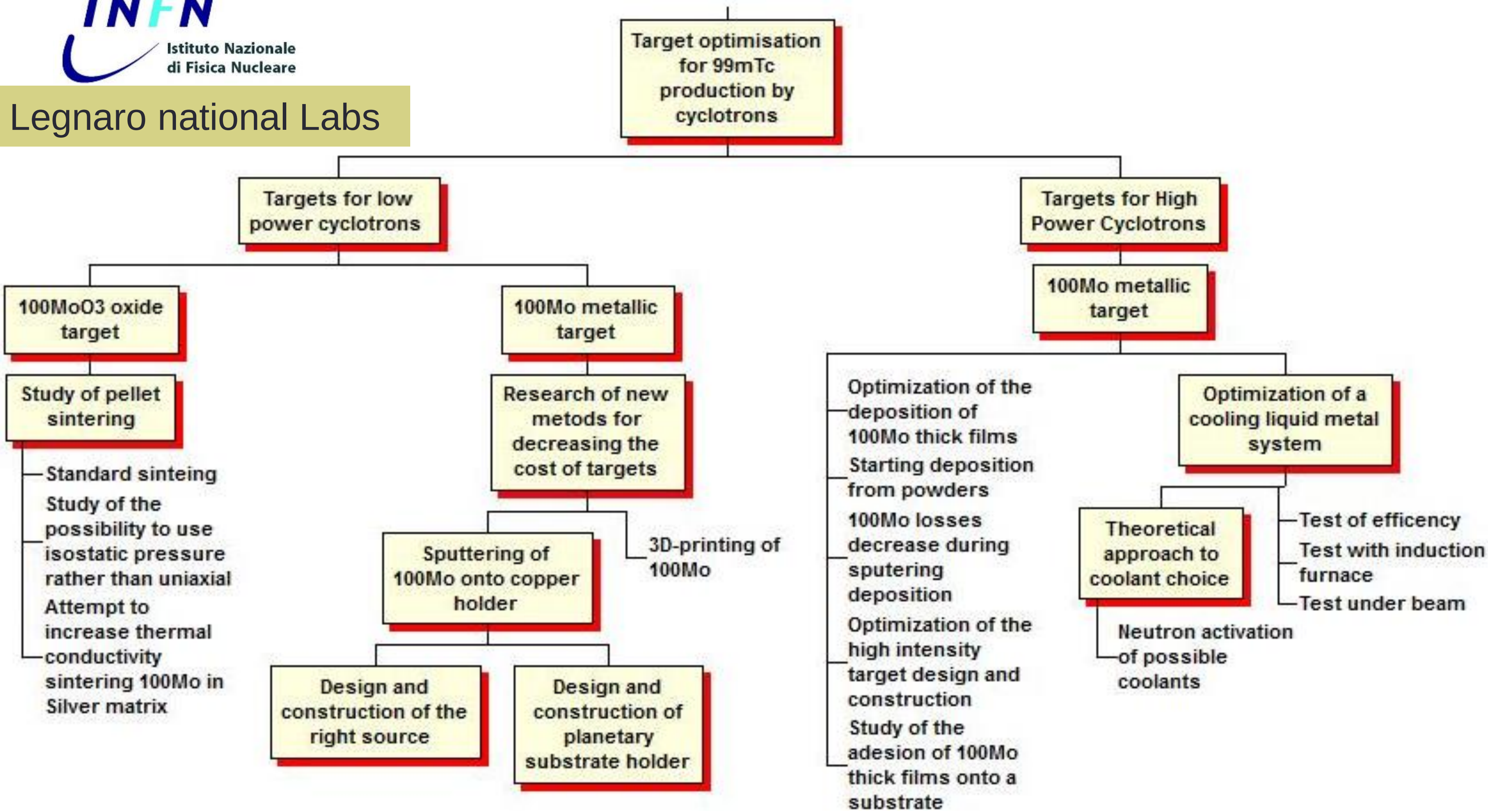
INFN Istituto Nazionale di Fisica Nucleare Laboratori Nazionali di Legnaro

The role of different research units

Step (B): Development of ^{100}Mo target production method

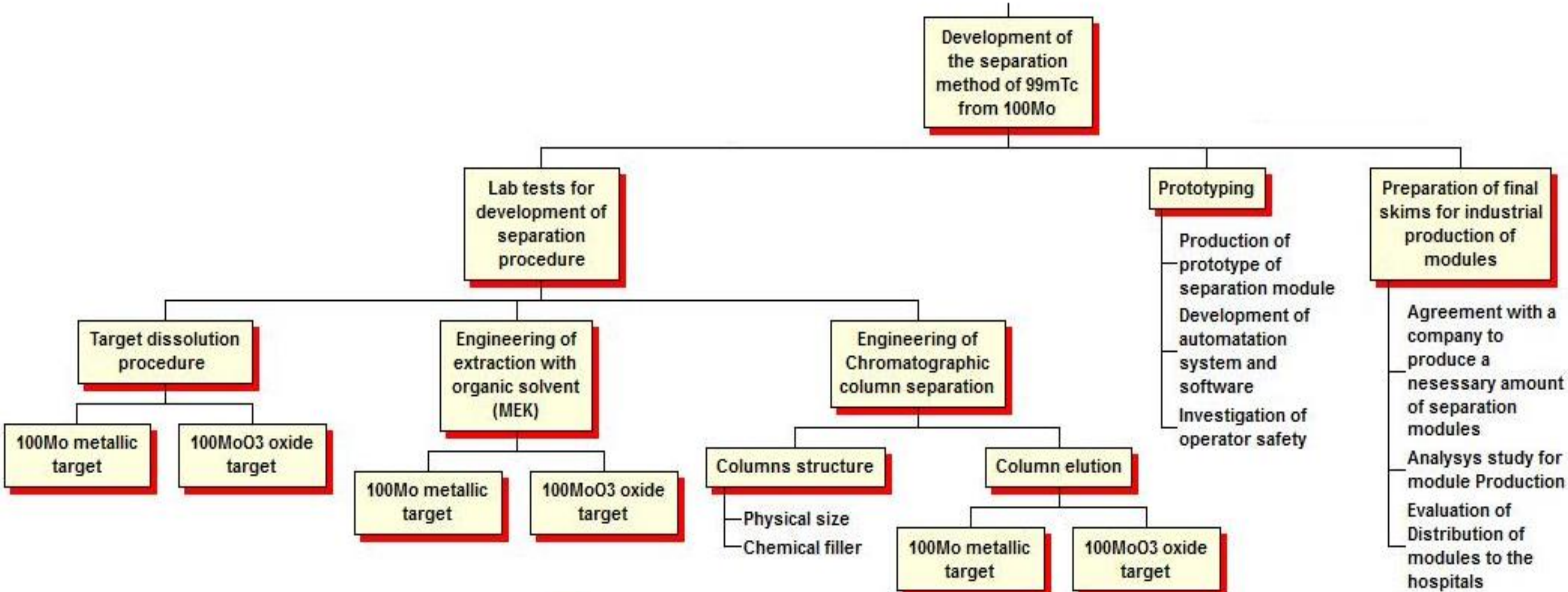
INFN Istituto Nazionale di Fisica Nucleare

Legnaro national Labs



The role of different research units

Step (C): Optimization of Tc99m separation(s) methods



- Legnaro National labs
- Pavia branch

INFN Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The role of different research units

Step (D): Quality Control (QC) procedures on both Tc99m and recovered Mo100

Assessment of quality control of Mo targets produced by developed techniques

- Theoretical predictions → INFN: Legnaro Nation labs; Milan branch — Università degli Studi di Milano
- Chemical analysis of recycled target → Università degli Studi di Ferrara; INFN: Ferrara Branch, Pavia Branch
- Isotopic composition analysis of recycled Mo targets → Università degli Studi di Milano; INFN: Pavia branch, Milan branch
- QC procedures through imaging activities with Tc99m-radiopharmaceuticals from recoved 100Mo targets → INFN: Padua Branch, Ferrara Branch — Università degli Studi di Ferrara; Servizio Sanitario Regionale Emilia-Romagna, Azienda Ospedaliero - Universitaria di Bologna, Policlinico S. Orsola-Malpighi

TECHN-Osp project INFN-LNL

PLANNED ACTIVITIES for 2015

Part B: Traget optimisation for ^{99m}Tc production by cyclotrons

- **Thick films technology development:**
  - Optimization of the deposition of Mo thick films
  - Starting deposition from Mo powders
  - Design and set up of a magnetron for depositing Mo onto large areas from a small target
- **Optimization of high intensity targets:**
  - Construction of High Conductivity Targets for future comparison of LM cooling and Water cooling
  - Study of impact of neutron activation (radioprotection and safety concern) of possible coolants

TECHN-Osp project
INFN-LNL

PLANNED ACTIVITIES for 2015 and budget quotation (80 K€)

Item	What is needed	Estimated cost K€
Optimization of the Mo thick-films deposition	New deposition system for a batch of targets simultaneously: materials, mechanical work	**24**
	New power supply	**10**
	Automation of stress free program	**15**
	Mo materials	**3**
	Gas of high grade purity for sputtering	**1**
Starting deposition from powders	Construction of magnetron source for powder sputtering: materials, mechanical work	**15**
Construction of High Conductivity Targets	High conductivity materials	**5**
	External mechanical work	**6**
Travels	Domestic travels Padua-Legnaro Padua-Ferrara, Padua-Bologna	**1**

TECHN-Osp project INFN-Padua

PLANNED ACTIVITIES scheduled in 2015 and budget quotation (16 K€)

- **Quality Control (QC) procedures** for Tc99m yielded by different cyclotrons (ISPRA, Bologna, Pavia?) through gamma spectrometry.
- ***In-vivo* imaging** of standard drugs marked with accelerator-Tc99m (MDP, MIBI, HMPAO TRACER etc) using a tomographic last generation microSPECT from IOV planned to be installed at LARIM lab in LNL in late 2014.

Item	What is needed	Estimated Cost
1. Electronics for Gamma spectrometry meaurements	Amplifier	**3.0 k€**
	Multichannel system	**3.5 k€**
	HV power supply system for low background (for ex-vivo measurements)	**2.5 k€**
	NIM crate	**3.0 k€**
2. Travels	Domestic travels Padua-Legnaro Padua-Ferrara, Padua- Bologna	**1.0 k€**

TECHN-Osp project INFN-Ferrara

PLANNED ACTIVITIES scheduled in 2015

- R&D activities aimed at the **Automatic Module optimization to enhance the** remote Mo/Tc chemical separation-purification processes at better efficiency and higher radioactivity levels

Experimental activities scheduled:

a) Irradiation of ^{100}Mo-enriched targets at high radioactivity levels;
b) chemical separation-purification tests with the automated system;
c) preparation of radiopharmaceuticals;
d) Imaging in vivo scans:
e) ^{100}Mo recovery process studies **(collaboration with Pavia branch)**

n. 5 accelerator-Tc99m production/imaging tests at S. Orsola Cyclotron (Bologna) planned the first year using Ceretec pharmaceutical. **4 ^{100}Mo-material recovery steps.**

- Starting activities aimed at upgrading the SPECT-CT scan system performance for small animals (currently based on NaI detector crystal not able to properly detect gammas from a mix of Tc isotopes). Coupling of a PMT system in order to improve field of view and energy resolution
- Improvement of the β-Spectrometer developed in the APOTEMA project including a third PMT for the TDCR (Triple to Dual Coincidence Ratio) method implementation. System optimization to measure samples with very low radioactivity (< 1Bq ^{99g}Tc) for xs measurements;

to Nazionale
ica Nucleare
li di Legnaro

TECHN-Osp project INFN-Ferrara

PLANNED ACTIVITIES for 2015 and budget quotation (29.3 K€)

Item	What is needed	Estimated Cost
1. Automatic Module optimization activities	Set of Valves	**4.0 k€**
	Flanges, Fittings	**0.5 k€**
	Sep-Pak allumina/silice	**0.5 k€**
	Solvents	**0.2 k€**
	Helium/Nitrogen bottles	**0.4 k€**
	Glassware	**0.2 k€**
2. n. 5 Imaging in vivo tests	CERETEC Pharmaceutical kit (5 vials)	**1.1 k€**
	rats for in vivo imaging scans	**1.30 k€**
3. SPECT system upgrade plan	PMT tube and related electronics	**11.0 k€**
4. Radioactive transport service (5 travels Fe-PD + 10 travels new Cona Hospital-Fe)	Authorized carrier	**4.0 k€**
5. Travels + subumission papers to congress	Travels Fe- Legnaro, Pe- Pavia + Travels for congress	**6.0 k€**

APOTEMA project INFN-Pavia

PLANNED ACTIVITIES scheduled in 2015 and budget quotation (18 K€)

- Studies aimed at **the Optimization of of Tc99m separation(s) methods** with an automated system at high activity levels. Determination of Radiochemical purity **(step C)**
- laboratory chemical studies aimed at the **development of high performance ^{100}Mo recovery method** (Step process A) and separation through the **Automatic Module for high** Tc99m activities (to be performed in collaboration with Ferrara branch)
- Starting Radiochemistry Research activity on a new radioisotope of interest for LARAMED project (in collaboration with Milan Univ. and INFN branch

Item	What is needed	Estimated Cost
1. Products for chemical separation-purification processes	• chemical reagents, • glassware standards, • standards, • exchange resin, • columns, etc. ..	**10.0 k€**
2. Radioactive transport service	• Irradiations to JRC Ispra to LENA Pavia	**2.0 k€**
2. Travels to perform experiments	Domestic between Pavia and Milan, Legnaro, Ferrara, Rome	**2.0 k€**
	international travels (Arronax)	**4.0 k€**

PROGETTO TECHN-Osp
Distribuzione FTE partecipanti al progetto

LNL	FTE
Esposito J.	0.2
Palmieri V.	0.2
Skliarova H.	0.7
Azzolini O.	0.3
Ramones M.	0.8
Rappo S.	1.0
	3.2

INFN-Pd	FTE
De Nardo L.	0.2
Bello M.	0.8
Uzunov N.	0.5
Melendez L.	0.1
Rosato A.	0.1
Sartori P.	0.2
	1.9

INFN-Mi	FTE
Groppi F.	0.8
Bonardi M.	1.0
Manenti S.	1.0
Gini L.	0.5
Bazzocchi A.	0.8
	4.1

INFN-Fe	
Gambaccini .M	0.2
Taibi A.	0.2
Di Domenico G.	0.2
Duatti A.	0.5
Pupillo G.	1.0
Uccelli L.	0.5
Pasquali M.	1.0
Boschi A.	1.0
Giganti M.	0.5
Martini P.	1.0
	6.1

INFN-Pv	FTE
Salvini A.	0.3
Oddone M.	0.5
Prata M.	0.3
Magrotti G.	0.3
Strada L.	0.8
	2.2

INFN-Bo	FTE
Marengo M.	0.2
Cocoria G.	0.3
????	
	0.5

TOTALE FTE 18.0

Additional slides

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The key issue of ^{100}Mo-enriched moly recovery...

No Mo-100 enriched moly recovery strategy

Note	Symbol		unit
Mo-100 enriched moly starting mass	M	1000	g
Mo-100 enriched (>99%) cost	C	800	€ / g
Enriched moly mass estimated for any single target	m	0.214	g
Number of one-shot targets manufactured	n	4673	targets
Mo-100 enriched flat cost per each target		171	€/target
Estimated Mo-100 supply cost per year	I	6.2244	M€ / year

Effective Mo-100 enriched moly recovery plan

Mo-100 loss rate per each recovery step	r	10	%
No. of recovering steps	Rs	80	
TOTAL no. of targets manufactured		46682	
Target manufacturing Enhanced Ratio (TMER)		9.99	
Mo-100 effective Flat cost per target		17.14	€/target

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

The key issue of ^{100}Mo-enriched moly recovery...

Hospital average charged costs for any 2 Ci Tc99m daily consumption in routine diagnostic procedures

Tc-99m activity yielded per single target	A	2	Ci
Activity needed by standard diagnostic procedure	Ap	30	mCi
Tc99m patient dose imparted cost		15	€ / dose
Number of dose available		66.7	dose
Hospital charged costs for Tc99m procedures supply		1000	€ /day

Gain expected by Mo-100 enriched moly recovery plan

Proposed target cost to customer (Hospitals) (chemistry, recovery, manufacturing costs included)	C1	100	€/target
No. of targets per week required	Nt	600	
TOTAL targets to be manufactured per year		31200	
Production time covered	T	1.5	year
Net Sales (Mo-100 material cost included)		3.87	M€
Yearly turnover		2.58	M€

^{99m}Tc production expected using high-current high-power cyclotrons in a production facility (e.g LARAMED)

Table 4: The ^{99m}Tc production yields estimated at EOB for different irradiation times at 15 and 20 MeV proton beams on 99.05% ^{100}Mo-enriched metallic molybdenum and optimized target configuration. 500 μA proton current and 500 W/cm^2 mean areal power density are considered on target. A series of production quality parameters are calculated and listed (see body text).

^{99m}Tc production	**E_p = 15 MeV**			
Beam power on target (kW)	**7.5**			
Beam power deposited inside Mo sample (kW)	**1.41**			
Irradiation time	1 h	2 h	3 h	6 h
Integral yield (mCi/μA)	5.32	10.05	14.28	24.38
In-target activity (Ci)	2.66	5.03	7.14	12.2
Specific activity (Ci/g)	$1.16 \cdot 10^6$	$1.10 \cdot 10^6$	$1.04 \cdot 10^6$	$8.86 \cdot 10^5$
Tc/Total activity	0.9877	0.9853	0.9848	0.9861
^{99m}Tc/Total activity	0.1809	0.2929	0.3693	0.4984
^{99m}Tc/$^{99m+g}$Tc	0.2224	0.2103	0.1990	0.1699
Isotopic purity (IP)	0.2200	0.2081	0.1970	0.1682
Radionuclidic purity (RNP)	0.1831	0.2973	0.3750	0.5055
^{99m}Tc production	E_p = 20 MeV			
Beam power on target (kW)	10.0			
Beam power deposited inside Mo sample (kW)	3.95			
Irradiation time	1 h	2 h	3 h	6 h
Integral yield (mCi/μA)	10.35	19.58	27.81	47.56
In-target activity (Ci)	5.17	9.79	13.90	23.78
Specific Activity (Ci/g)	$8.96 \cdot 10^5$	$8.47 \cdot 10^5$	$8.01 \cdot 10^5$	$6.84 \cdot 10^5$
Tc/Total activity	0.9573	0.9488	0.9468	0.9491
^{99m}Tc/Total activity	0.2006	0.3162	0.3926	0.5190
^{99m}Tc/$^{99m+g}$Tc	0.1862	0.1760	0.1665	0.1420
Isotopic purity (IP)	0.1698	0.1606	0.1520	0.1297
Radionuclidic purity (RNP)	0.2095	0.3333	0.4147	0.5468

For next generation high powerful cyclotrons (i.e 500 μA)

10 Ci/day ^{99m}Tc may be produced on a routine basis

Table extracted from the paper
J. Esposito, G. Vecchi, G. Pupillo, A. Taibi, L. Uccelli, A.Boschi, M. Gambaccini, "Evaluation of ^{99}Mo and ^{99m}Tc Productions Based on a High-Performance Cyclotron,"

Science and Technology of Nuclear Installations, vol. 2013, Article ID 972381, 14 pages, 2013. doi:10.1155/2013/972381