Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

CSN5 INFN new research project proposal
(2018-2020)

METRICS

Multimodal p**ET**/m**R**i **I**maging with **C**yclotron-produced $^{52/51}$Mn and stable paramagnetic Mn i**S**otopes

Presented by A. Fontana (INFN-Pavia)
Consiglio di Sezione INFN, Pavia, July 11th, 2017

Courtesy of J. Esposito on behalf of INFN/ S. Orsola.Malpighi Hospital (Bo) /Padua Hospital collaboration network for the METRICS project (proposal presented to CSN5 INFN, LNL, June 29th , 2017)

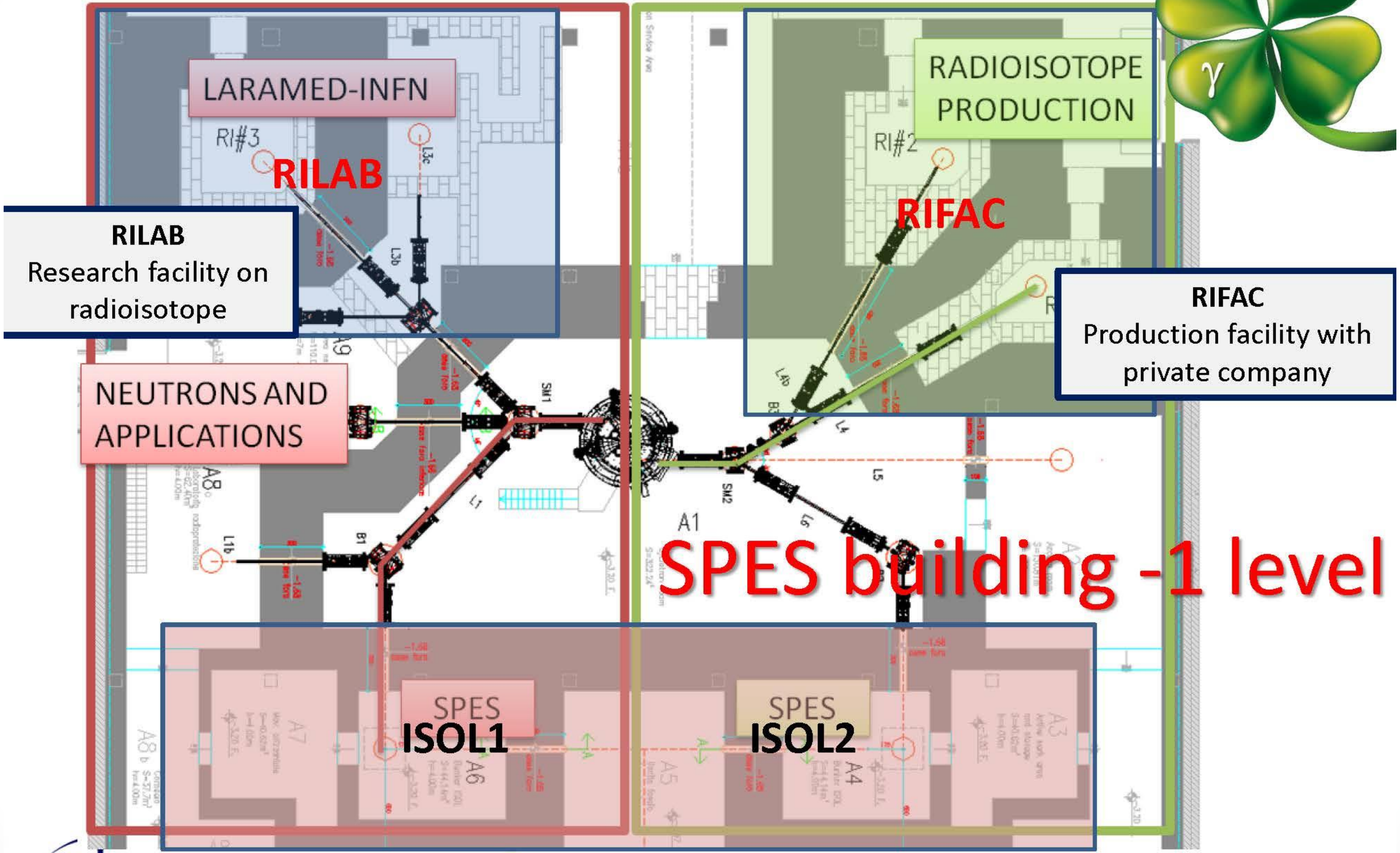
How LARAMED Project is planned

LAboratory of **RA**dionuclides for **MED**icine, granted as "competitive project" at national level includes:

- **A research laboratory (RILAB),** owned jointly by INFN and CNR for:
  - Nuclear cross section measurements (i.e. standard stack-foils activation technique)
  - A proving ground for high power target tests
  - Low-activity-production of experimental radioisotopes/radiopharmeceutical (^{99m}Tc, ^{64}Cu, ^{67}Cu, ^{89}Zr, ^{47}Sc...)

- **A production facility (RIFAC)**, operated by INFN and a private partner, to supply market demands for parent nuclides ^{82}Sr/^{82}Rb and ^{68}Ga/^{68}Ge generator systems

Final layout and cyclotron beams sharing foreseen



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LARAMED

J. Esposito, October 11, 2016

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Running R&D activities within LARAMED framework

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INFN already funded/running projects	Project name
Tc-99m/Mo-99 direct production routes using accelerators	APOTEMA (2012-2014) TECHN-OSP (2015-2017)
Participation to IAEA ' Coordinated Research Project ' (CRP) on "*Alternative, non HEU-based, Tc-99m/Mo99 supply*" (PI: J. Esposito)	CRP (F22062) (2011-2015)
Cu-67/Sc47 new (i.e. more efficient) production routes	COME (2016) PASTA (proposal)
Participation to IAEA ' Coordinated Research Project ' (CRP) on "*Radiopharmaceuticals Labelled with New Emerging Radionuclides Cu-67, Re-186, Sc-47*"	CRP (F22053) (2016-2019)
Sr-89 production with ISOL technique	SPES/ISOLPHARM
RILAB laboratory infrastructure set up	LARAMED comp. project (2013-2016)
High Power Target concepts R&D ($^{64/67}Cu$)	TERABIO comp. project (2016-2019)

LARAMED first radionuclides list of interest

Radioisotope	Half-life
Sc47	3.35 d
Cu-64	12.7 h
Cu-67	2.58 d
Sr-82	25.4 d
Ge-68	270.8 d
Tc99m	6.01 h
Sr-89	50.5 d

Theranostic approach

Starting radionuclides of interest for nuclear medicine. They can be produced by means of the SPES cyclotron. Additional ones are under examination → ^{52}Mn

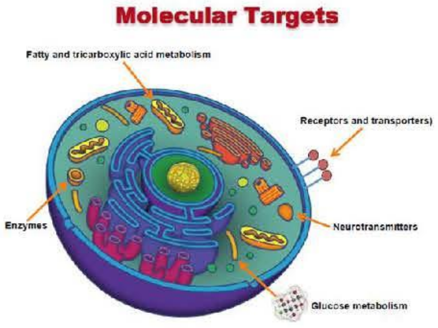
MultiModal Imaging (MMI): a new diagnostic imaging tool in medicine

MMI as a new standard approach nowadays to greatly improve diagnostic power *in vivo* with imaging modalities based on different physics processes.

Currently, imaging modalities are based on the use of different physics processes:

a. X-rays **(CT)**;
b. β^+/γ-emitting radioisotopes **(PET and SPECT),**
c. fluorescence **(OPTICAL)**
d. Magnetic resonance **(MRI).**

CT / MRI



PET/SPECT/OPTICAL

Typically:

1. **CT / MRI** -> allow obtaining **anatomical images** of **organ tissues**
2. **PET/SPECT/OPTICAL** -> able to deeply penetrate the **inner cellular structure** and collect **molecular-type information (functional imaging)**

GOAL

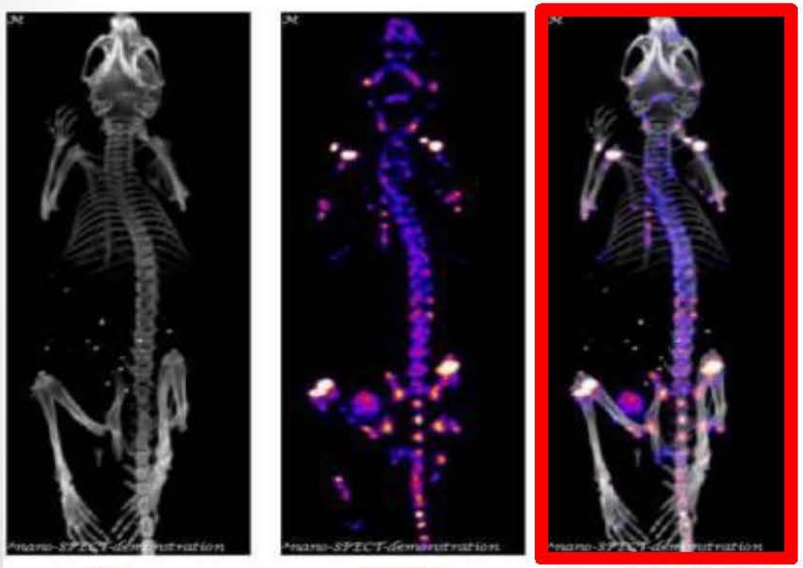
combining images with a different diagnostic content can significantly improve understanding of the clinical picture

Status of art for MMI technology

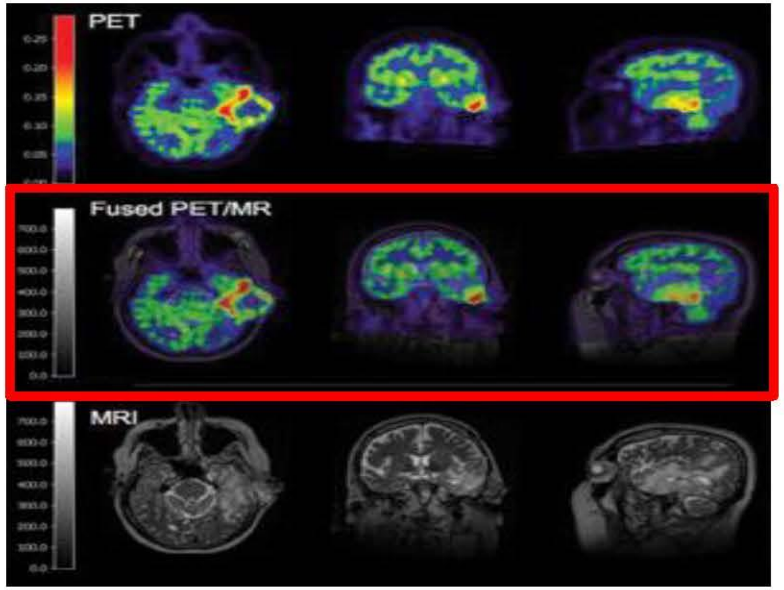
Already established technologies allow the acquired images, recorded by both systems in a unique gantry, to be combined later as **as superimposed images only by software procedures**.

- **PET** or **SPECT cameras** merged with a **CT scanner** **(PET/CT, SPECT/CT)**, combining X-rays and nuclear imaging.

- **hybrid PET/MRI** and **SPECT/MRI tomography**, combining nuclear and magnetic resonance imaging.



CT SPECT Fused SPECT/CT



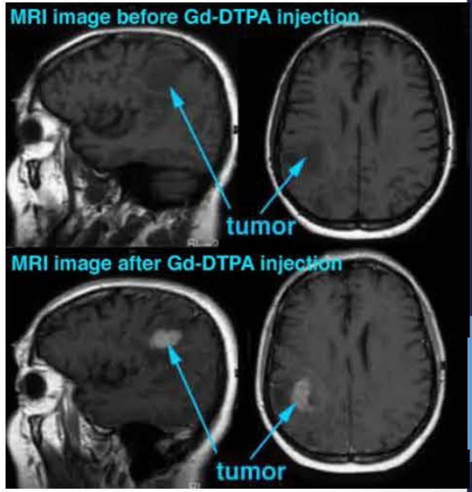
Main limiting issues in MMI

- **(PET and SPECT) ->** functional imaging always requires injection of a **radiolabeled tracer (e.g. ^{18}F-FDG for PET or ^{99m}Tc-HMPAO for SPECT,**
- **(CT and MRI) ->** anatomical imaging always involves administration of a **contrast agent (e.g. Gd-OMNISCAN)** to achieve the **highest spatial resolution**.


HOWEVER….

- basically impossible to tightly couple infos through:
  - **Functional or metabolic imaging** **(radioactive tracer)**
  - **Anatomical imaging** **(contrast agent)**

through a **simultaneous administration. Chemical species are always totally different**.

THEREFORE….how MMI is carried out in practice

- either **without administration** of the **contrast agent**
- when necessary, done in a **separate steps**

Corresponding images are **superimposed later only**

MAIN problem in MMI

a) Usefulness of **hybrid imaging** is **strongly limited**

b) **diagnostic imaging mismatch** because of the **chemical diversity between the contrast and radioactive agents**

An example: PET-MRI cardiac perfusion investigation

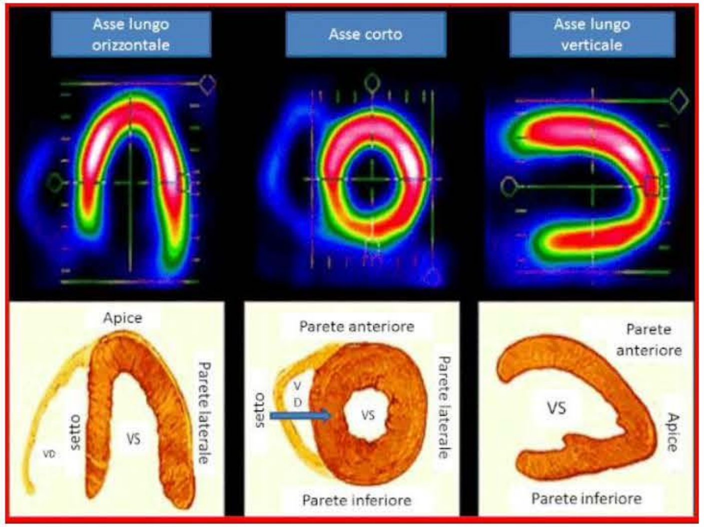
- **MRI** -> accomplished by injecting a **paramagnetic gadolinium contrast agent**
- **PET** -> evaluated by administration of **β^+ emitter ^{82}Rb** under the chemical form of Rb^+ ion.

- **Main Result: Radically different biological pathways**
  - **MRI ->** passive diffusion through heart capillaries for **Gd contrast agent**
  - **PET ->** membrane channel transport for **$^{82}Rb^+$**, being Rb^+ a biologic analog of K^+, fundamental in the heart cells operation

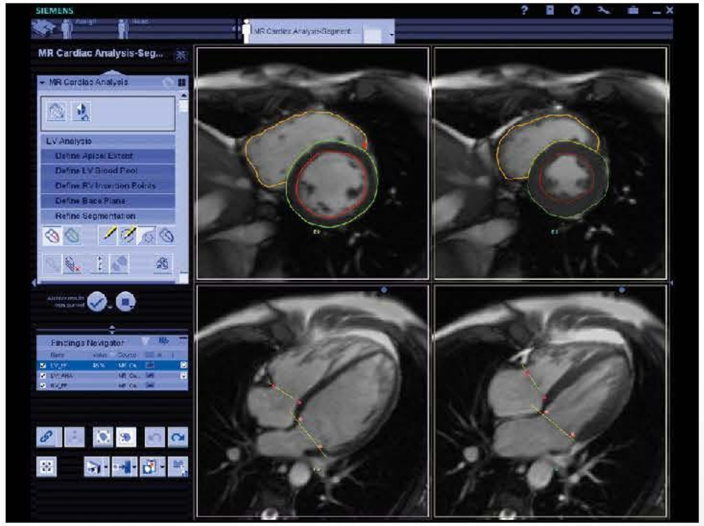
Diagnostic content of resulting images is immeasurably different.

To achieve a **genuine fusion between PET and MRI**, the **contrast and radioactive agents should be chemically identical !!!**

PET



MRI



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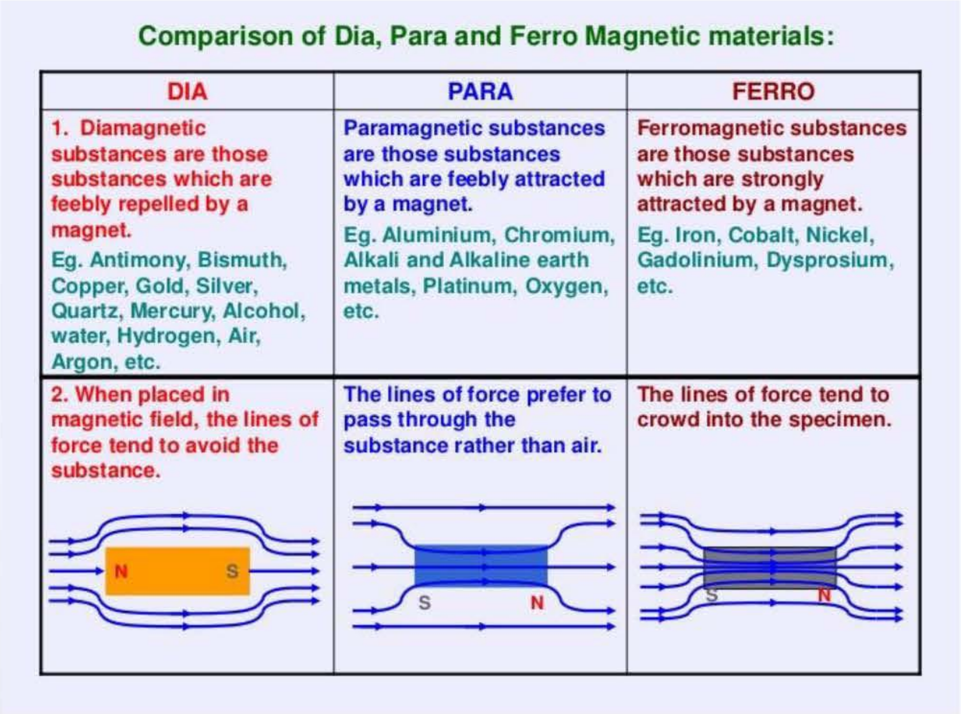
Does there exist any element/isotope having paramagnetic & nuclear properties for a combined PET/MRI?

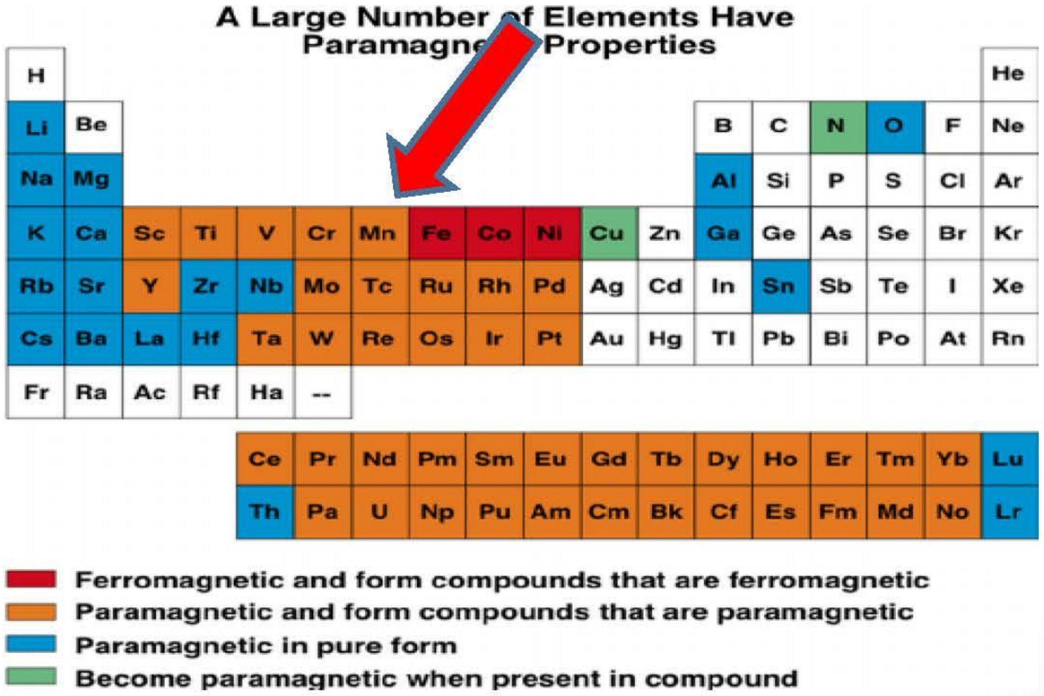
It's always **very challenging** to find out a chemical compound that can behave at the same time as:

- a contrast agent -> showing **paramagnetic properties**
- having some radioactive isotopes with **useful nuclear properties for PET imaging like ^{18}F**



Comparison of Dia, Para and Ferro Magnetic materials:

DIA	PARA	FERRO
1. Diamagnetic substances are those substances which are feebly repelled by a magnet. Eg. Antimony, Bismuth, Copper, Gold, Silver, Quartz, Mercury, Alcohol, water, Hydrogen, Air, Argon, etc.	Paramagnetic substances are those substances which are feebly attracted by a magnet. Eg. Aluminium, Chromium, Alkali and Alkaline earth metals, Platinum, Oxygen, etc.	Ferromagnetic substances are those substances which are strongly attracted by a magnet. Eg. Iron, Cobalt, Nickel, Gadolinium, Dysprosium, etc.
2. When placed in magnetic field, the lines of force tend to avoid the substance.	The lines of force prefer to pass through the substance rather than air.	The lines of force tend to crowd into the specimen.



Does there exist any element/isotope having paramagnetic & nuclear properties for a combined PET/MRI?

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The **only radionuclide in 1<Z<92** having main **positron-emitting nuclear properties basically mimic ^{18}F** (i.e. average $E_{\beta+}$ ~ 250 keV and similar β^+ spectrum energy range) is **^{52}Mn only,** that could be conveniently employed as PET tracer. **^{51}Mn** is an alternative radionuclide PET candidate, although with a higher-energy β^+ spectrum.

The transition element Mn has moreover stable isotopes (**Mn^{2+}**) having **useful paramagnetic properties to be used as MRI contrast agents.**

You requested: 1 ≤ Z ≤92 h 1 ≤ $T_{1/2}$ ≤ 6 d Radiation 200 ≤ E ≤ 300 20 ≤ I ≤ 100 type β+ 400 ≤ E_B ≤ 700

Ground State | Levels | Gammas | Decay Radiation

Comments — Click on a column header to open the guide
Uncertainty for numeric values refers to the last digits of the value: 12.1 *23* means 12.1 ± 2.3

Data from: ENSDF Angeli & Marinova AME2012 Definitions and Sources ?

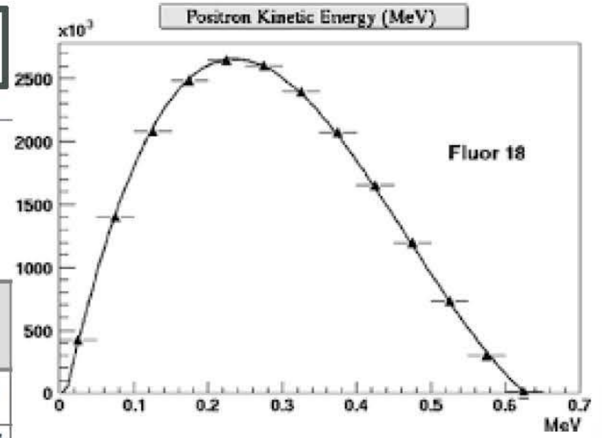
CSV

Nuclide	Energy [keV]	Jπ	$T_{1/2}$ Abund. [mole fract.]	$T_{1/2}$ [s]	Decay Modes BR [%]	Isospin	μ [μ_N]	Q [barn]	R [fm]	$Q_{\beta-}$ [keV]	Q_α [keV]
$^{18}_{9}F_{9}$	0.0	1+	109.77 min *5*	6.59E3 *3E0*	ec β+ 100	0				-4444.5 *6*	-4415.2 *5*
$^{52}_{25}Mn_{27}$	0.0	6+	5.591 d *3*	4.83E5 *2.59E2*	ec β+ 100			+0.50 *7*	3.6706 *128*	-2377 *5*	-8654.5 *21*

Click on a nuclide symbol to show the decay schema

Electron Capture and Beta+ CSV

$<E_{\beta+}>$ [keV]	$I_{\beta+}$(abs) [%]	E_{EC} [keV]	I_{EC}(abs) [%]	Daughter level [keV]	Jπ	Log *ft*	Transition type	Comments	Parent	$T_{1/2}$
249.8 *3*	**96.73 4**	(1655.5)	3.27 *4*	0	0+	3.5700 *19*			$^{18}_{9}F_{9}$	109.77 min *5*
241.59 *80*	**29.4 4**	(1597.3)	61.4 *6*	3113.883 *24*	6+	5.580 *5*			$^{52}_{25}Mn_{27}$	5.591 d *3*



radionuclide	T1/2
Mn-52m	21.1 min
Mn-52g	5.59 days
Mn-51	46.2 min

Mn-based dual-modality PET/MRI imaging: a new standard in diagnostic approach

- Mn compounds, having exactly the **same chemical composition**, can thus be prepared using paramagnetic and radioactive Mn isotopes for **both MRI and PET agents (Mn^{2+}/ $^{52}Mn^{2+}$)**
- Manganese is moreover an element essential to living organisms, regulating metabolic activities of central nervous system.

ADVANTAGES

- A new type of **unprecedented PET/MRI hybrid imaging** characterized by a **perfect matching between the chemical and biological properties** of the two imaging probes may therefore be achieved.

- It has already been used **preclinically as a potent MRI contrast agent** for *in-vivo* **MEMRI** (**Mn-Enhanced MRI**) /**PET** and *ex-vivo (***Autoradiography***)* neural imaging activity and neural stem cell tracking in rat brain. Importantly, this dual-modality manganese-based PET/MRI approach may be used in cell tracking in other anatomy(*).

DRAWBAKS

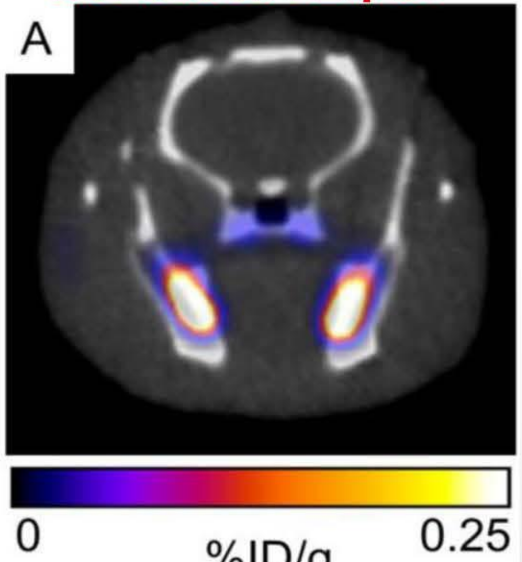
- As in itself **free manganese is toxic**, this fact has hindered the use of manganese MRI in clinical investigations, so far.

- **Positron emission tomography (PET) imaging of $^{52}MnCl_2$ at tracer doses has the potential to allow similar MEMRI studies while providing quantitative results and avoiding toxic effects**

(*) C. M. Lewis *52Mn Production for PET/MRI Tracking Of Human Stem Cells Expressing Divalent Metal Transporter 1 (DMT1)- Theranostics* 2015, Vol. 5, Issue 3

Rat brain MEMRI

^{52}Mn-based PET/CT



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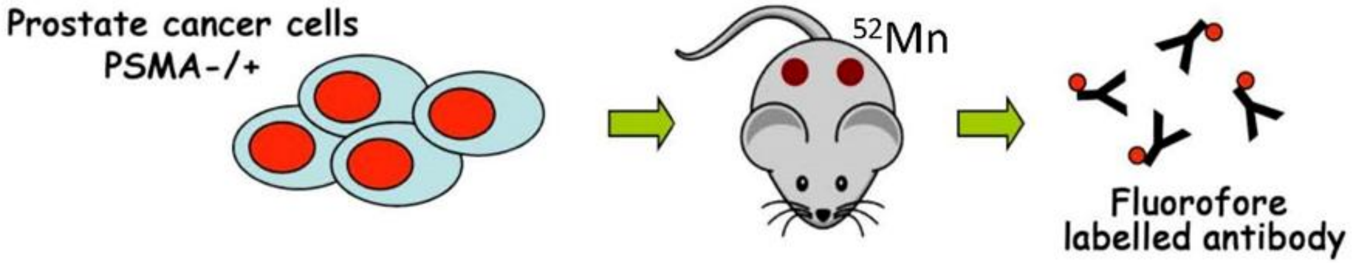
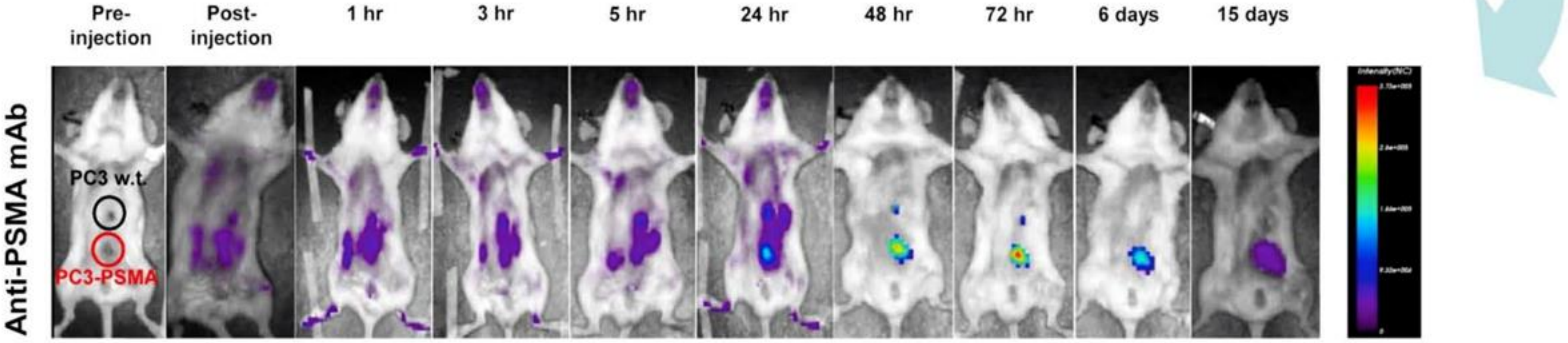
Main application fields of MEMRI/PET: a new window to monitor bio processes on a days-scale basis

- Mn interests comes from several important role it has in biology for mammals and in medicine
- Mn radioisotopes could easily be used for *in vivo* studies based on manganese as a radiotracer for antibodies, nanoparticles, etc. or as a means to image biodistribution of manganese cations Mn^{2+} .
- Due to the **longer ^{52}Mn $T_{1/2}$ (5.6 day)** than ^{18}F labelled compounds also makes it useful for the study of all that **biological processes and for radioimmuno PET applications** that have **similar time scales.**





J. Esposito on behalf of collaboration network for METRICS (2018-2020) project proposal CSN5 INFN

26.09.2017

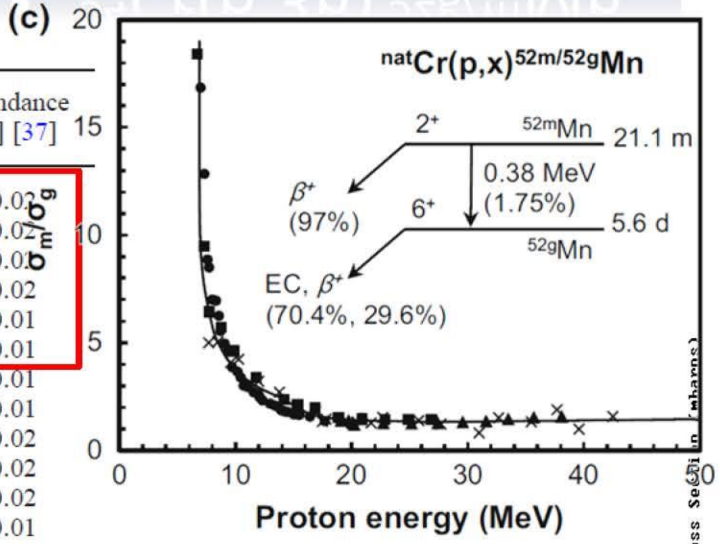
Possible NCA ^{52g}Mn production routes

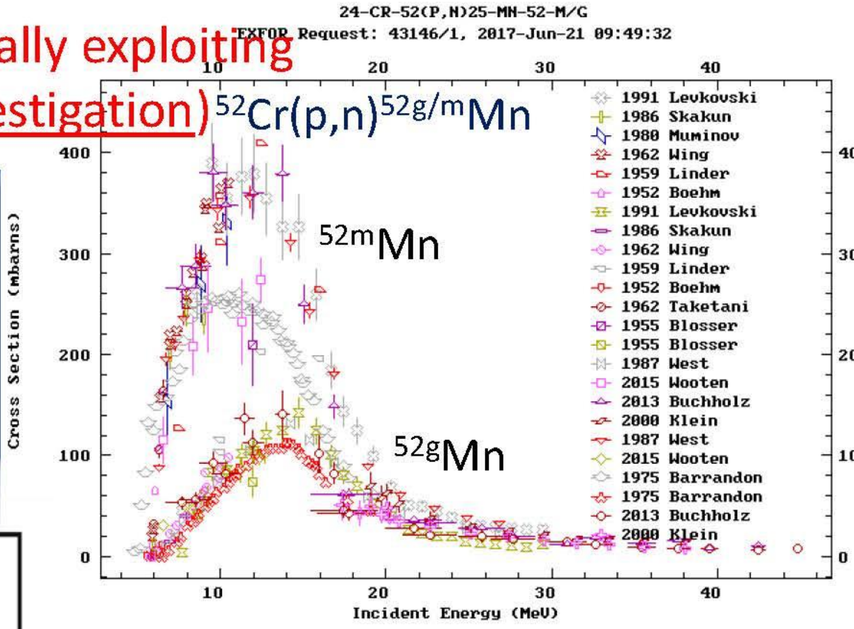
The simplest way is to produce ^{52g}Mn by using Cr natural basically exploiting all isotopes available…but <u>other possible routes are under investigation</u>)

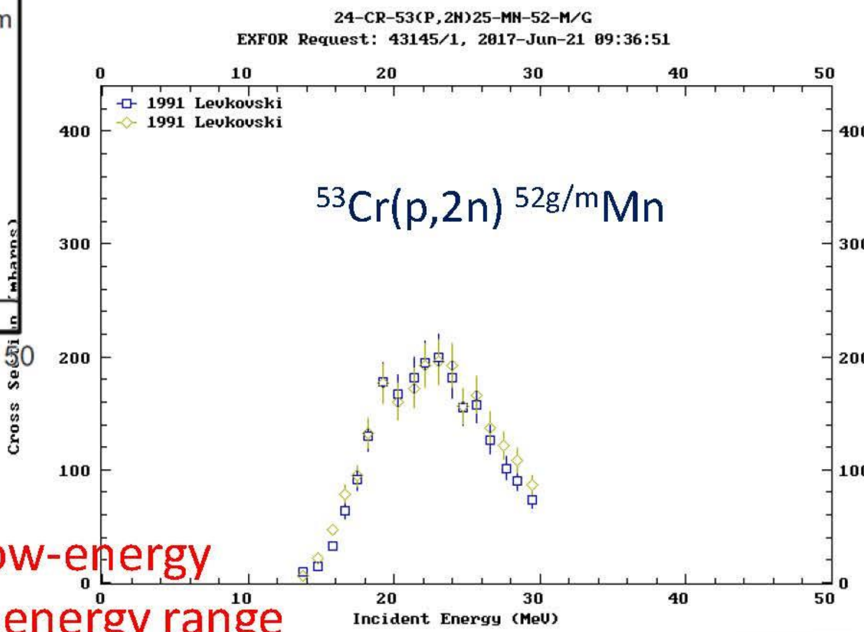
Naturally occuring isotopes
Cr-50 (4.345% , 1.8E+17yrs)
Cr-52 (83.789%)
Cr-53 (9.501%)
Cr-54 (2.365%)

- ^{52}Cr(p,n)$^{52g/m}$Mn
- ^{53}Cr(p,2n) $^{52g/m}$Mn
- ^{54}Cr(p,3n) $^{52g/m}$Mn

Reaction channel	Energy threshold [MeV] [30]	Natural abundance in ^{nat}Cr [%] [37]
^{52}Cr(p, n)^{52g}Mn	5.5	83.79 ± 0.02
^{52}Cr(p, n)^{52m}Mn	5.9	83.79 ± 0.02
^{53}Cr(p, 2n)^{52g}Mn	13.4	9.50 ± 0.02
^{53}Cr(p, 2n)^{52m}Mn	13.8	9.50 ± 0.02
^{54}Cr(p, 3n)^{52g}Mn	23.2	2.37 ± 0.01
^{54}Cr(p, 3n)^{52m}Mn	23.5	2.37 ± 0.01
^{50}Cr(p, p2n)^{48}Cr	23.6	4.56 ± 0.01
^{50}Cr(p, pn)^{49}Cr	13.0	4.56 ± 0.01
^{52}Cr(p, p3n)^{49}Cr	34.3	83.79 ± 0.02
^{52}Cr(p, pn)^{51}Cr	12.0	83.79 ± 0.02
^{53}Cr(p, p2n)^{51}Cr	20.0	9.50 ± 0.02
^{54}Cr(p, p3n)^{51}Cr	29.7	2.37 ± 0.01
^{50}Cr(p, He-3)^{48}V	21.6	4.56 ± 0.01
^{52}Cr(p, αn)^{48}V	14.1	83.79 ± 0.02
^{53}Cr(p, α2n)^{48}V	22.1	9.501 ± 0.02







Such reaction routes may be favorably obtained by a medium/low-energy cyclotron (40-10 MeV) e.g. SPES cyclotron working at the lowest energy range

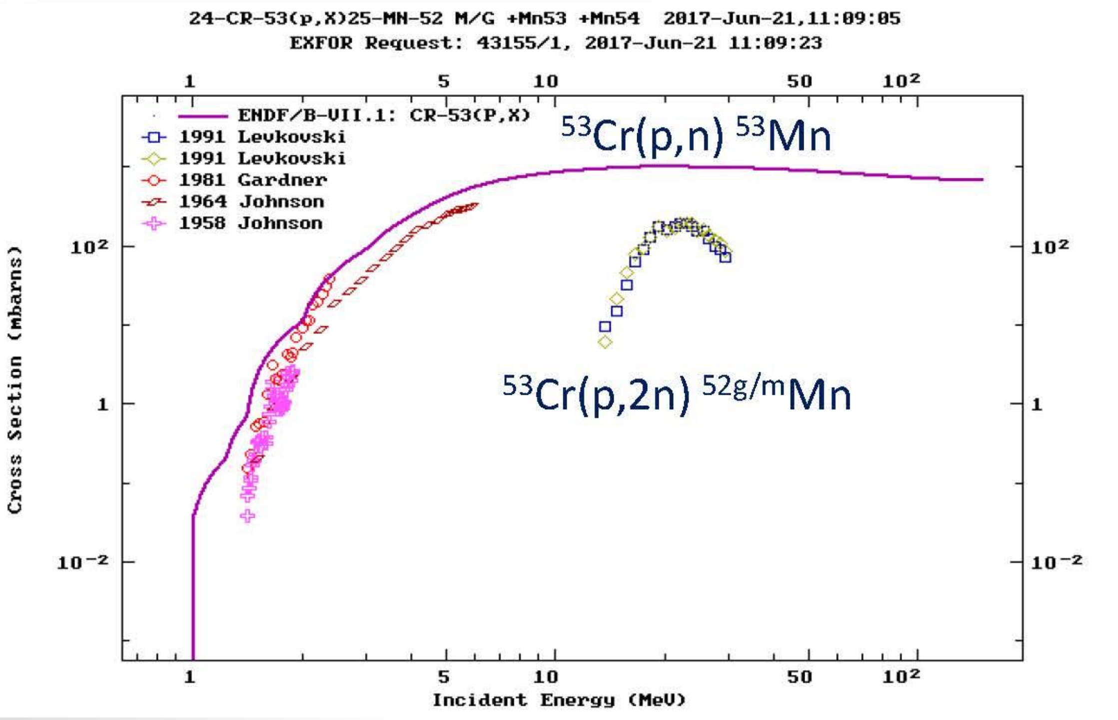
Main IP/RNP contaminations to be investigated

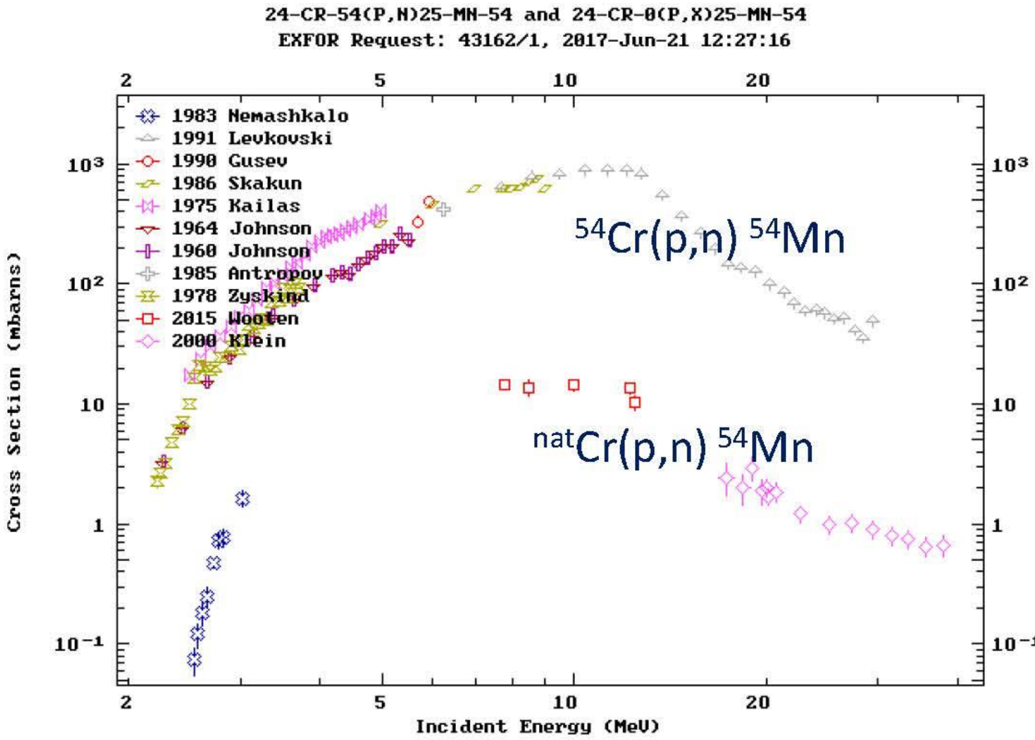
Other possible competing reactions have to be investigated in order to determine the final Isotopic (IP) and Radionuclidic (RNP) purity

Naturally occuring isotopes
Cr-50 (4.345% , 1.8E+17yrs)
Cr-52 (83.789%)
Cr-53 (9.501%)
Cr-54 (2.365%)

- $^{53}Cr(p,n)\,^{53}Mn$ ($T_{1/2}$= 3.75E+6yrs)
- $^{54}Cr(p,2n)\,^{53}Mn$
- $^{54}Cr(p,n)\,^{54}Mn$ ($T_{1/2}$ =312 days)

Such reaction routes might be favorably obtained by a medium/low-energy cyclotron (40-10 MeV) e.g. SPES cyclotron working at the lowest energy range





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The METRICS (2018-2020) research project proposal

MAIN project GOALS:

a) Investigate the best irradiation parameters and Quality control (QC) procedures in order to get an **as pure as possible ^{52}Mn** radionuclide **aimed at** the **new dual-modality PET/MRI investigations** using the **same injected radionuclide/contrast agent**.

b) **Design and construct proper targets** able to sustain the **related power levels for a production able to fulfill the Hospitals needs and nearby regions**

c) **Develop/optimize the proper radiochemistry** method to minimize chemical reagents & target material recovery

Research units taking part...

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ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA
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- Ferrara Branch
- Padua Branch
- Milan Branch
- Pavia Branch (new 2019)

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The METRICS (2018-2020) research project: timeline proposed

YEAR 2018	Research units involved
a) Design and construction of **low power Cr-nat targets for experimental investigation** following the know-how gained from APOTEMA/TECHNOSP past projects	**LNL/FE**
b) Early experiments on the ^{52}**Mn/nat-Cr radiochemistry extraction process**	**Fe**
c) **Irradiation tests and spectrometry** at a low-energy cyclotrons (Ep < 20 MeV), e.g. Sant'Orsola (BO), Negrar (VR) Hospitals or at ARRONAX (Ep > 20 MeV) to test conditions near to new LNL cycl.	**LNL-FE-MI**
d) Early studies on **computational dosimetry with the OLIDA tool** taking in to account the ^{5x}**Mn and contaminant nuclides**	**PD**

YEAR 2019	Research units involved
a) Progress and optimization about the ^{52}**Mn/**^{nat}**Cr radiochemistry extraction/separation/purification process**	**FE**
b) Theoretical/Experimental nuclear physics studies on alternative production routes (e.g. ^{52}**Cr(d,2n)**$^{52m/g}$**Mn**; ^{56}**Fe(p,αn)**$^{52m/g}$**Mn**; ^{56}**Fe(d,α2n)**$^{52m/g}$**Mn**; ^{54}**Fe(p,3He)** $^{52m/g}$**Mn**; ^{54}**Fe(d,α)** $^{52m/g}$**Mn** either with proton or deuteron beams	**LNL-MI** **PV/PD (new 2018)**
c) Studies about the improvement on the beam parameters optimization, prompted by the refinement of dosimetry computational studies with OLINDA tool on human phantom modeling	**PD**

The METRICS (2018-2020) research project: timeline proposed

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YEAR 2020	Research units involved
a) Radionuclide ^{52}Mn **production in enough quantity** for **PET imaging investigations** using **phantoms** and possibly *in-vivo* studies with a **small animal scanner (YAP-SPECT -PET) at LARIM (LNL) laboratory** and **PET/MRI** systems (Padua Hospital) ; comparison with same images taken by **^{18}F**	LNL-PD-FE
b) Design and construction of a dedicated **module prototype for 52Mn/natCr radiochemistry extraction/separation**	Fe
c) Completion of **experimental excitation functions measurements** on **alternative production routes**	LNL-MI PV/PD (new 2018)

METRICS project
INFN-Pavia

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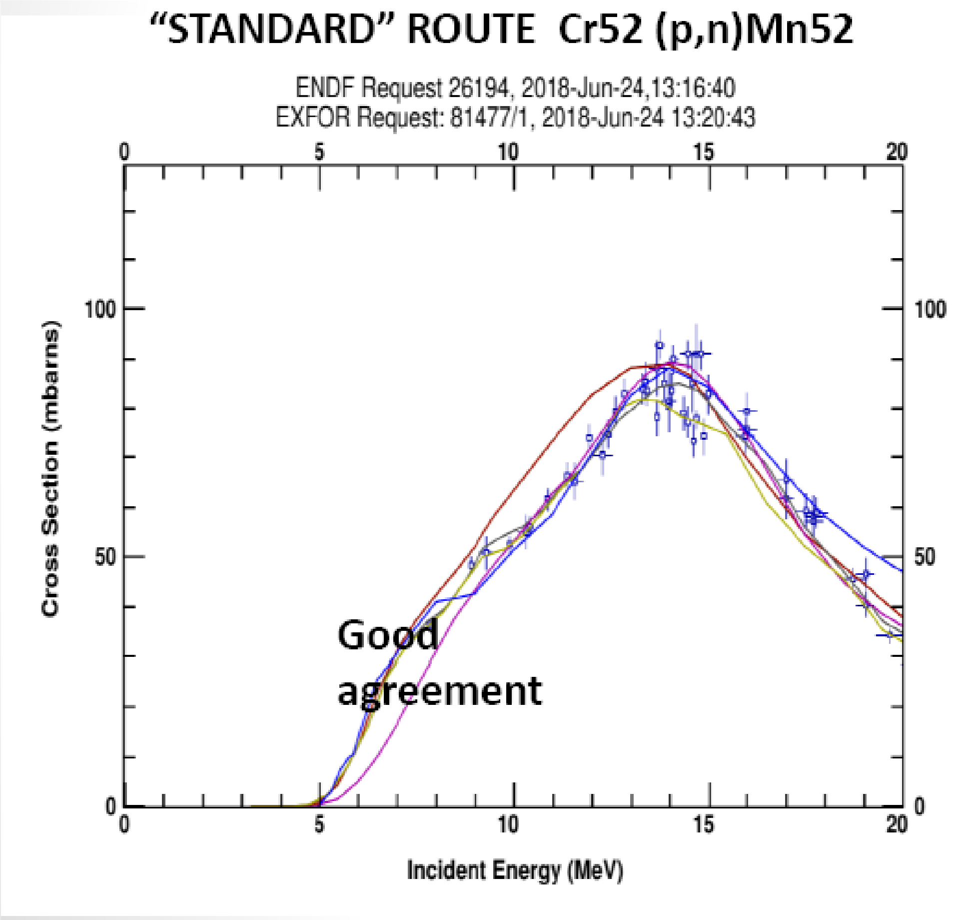
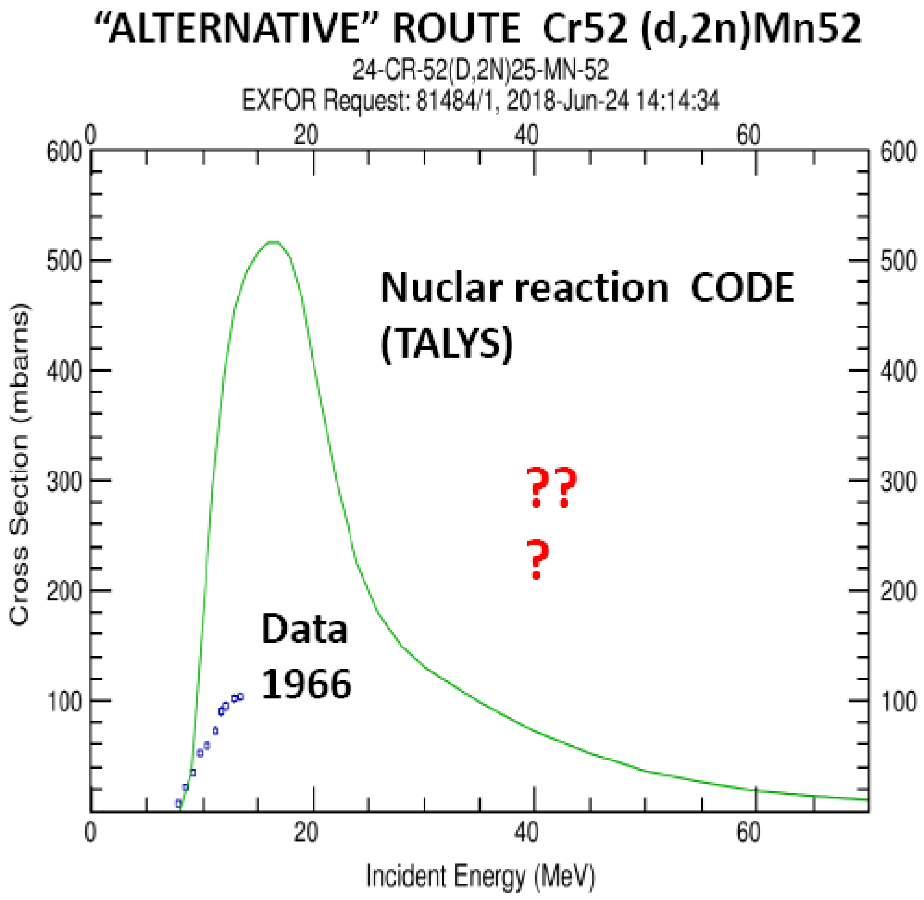
PLANNED ACTIVITIES for 2019 and budget quotation (8.5 K€)

Item	What is needed	Estimated cost K€
Activity INFN	• Theoretical nuclear physics studies on alternative production routes with state of art nuclear codes: Talys, Empire, Fluka. Possible reactions: **^{52}Cr(d,2n)$^{52m/g}$Mn; ^{56}Fe(p,αn)$^{52m/g}$Mn; ^{56}Fe(d,α2n)$^{52m/g}$Mn; ^{54}Fe(p,3He)$^{52m/g}$Mn; ^{54}Fe(d,α)$^{52m/g}$Mn)** either with proton or deuteron beams. Collaboration with INFN-PD. • Development of tools for activity calculation in thick targets considering radioactive decay of contaminants. Collaboration with INFN-PD/INFN-LNL.	
Activity LENA	• First tests of radiochemical separation, in collaboration with INFN-FE. • Study of recuperation and reprocessing techniques, by exploiting the experience gained during the APOTHEMA/TECHN-Osp. • Study of fast reactions (n,X) on Fe and Co.	**6.0**
Travels	• Domestic travels: Padova, Legnaro, Pavia • International travels: Conferences	**2.5**
	TOTAL	**8.5**

METRICS project
INFN-Pavia

Example:





METRICS project 2019
Distribuzione FTE partecipanti al progetto

LNL	FTE
Esposito J. (R.Naz.-Loc)	0.6
Bello M.	0.8
Pasquali M.	0.2
Sciacca G.	0.8
Mou L.	0.5
Pupillo G.	0.5
Martini P.	0.5
Keppel G.	0.1
Azzolini O.	0.1
Kotliarenko A.	0.4
	4.5

INFN-Fe	FTE
Taibi A. (R. Loc)	0.4
Gambaccini .M	0.2
Di Domenico G.	0.1
Duatti A.	0.2
Uccelli L.	0.2
Boschi A.	0.1
Fiorentini G.	0.5
	1.7

INFN-Pd	FTE
De Nardo L. (R. Loc)	0.8
Canton L.	0.1
Zorz A.	0.1
Paiusco M.	0.2
Cecchin D.	0.1
	1.3

INFN-Mi	FTE
Groppi F. (R. Loc)	0.4
Manenti S.	1.0
Bazzocchi A.	0.2
Harki G.	1.0
Bianch F.	1.0
	3.6

INFN-Pv	FTE
Fontana A. (R. Loc)	0.6
Salvini A.	0.2
Oddone M.	0.2
Strada L.	0.2
Alloni D.	0.2
Ballarini F.	0.2
Carante M.	0.4
(Calzaferri S.)	(1.0)
	2.0(3.0)

TOTALE FTE **13.1(14.1)**

Summary overall budget request METRICS FY2019

Sezioni / Lab	Missioni	Consumo/ Altri consumo	Trasporti	Manutenzione	Inventario	apparati	Sp- servizi	Tot. per sez/lab	FTE previsto
LNL	2.0	12.0					14.0	**28.0**	**4.5**
Fe	1.0	9.0	1.5					**11.5**	**1.7**
Pd	0.5	1.0					5.0	**6.5**	**1.3**
Mi	8.0	8.0	6.0	4.0				**26.0**	**3.6**
Pv	2.5	6.0						**8.5**	**2.0(3.0)**
TOTALE	14.5	36.0	7.5	4.0			19.0	72.0	**13.1(14.1)**

Budget request outlook METRICS FY2019 ~ 60 kEuro
FY2019 ~ 55 kEuro

TOTAL BUDGET request 3yrs ~ 187 kEuro