METRICS

Planned activities and Budget Requests 2019

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

- *L. De Nardo*

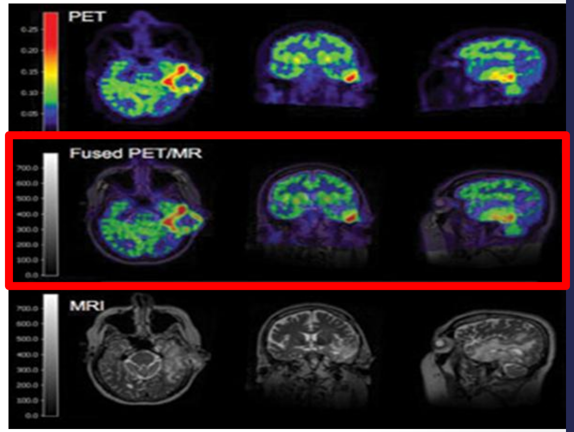
- PD, July 10th , 2018

METRICS 3 yrs (2018-2020) project

Responsabile Nazionale: J. Esposito, LNL

Background

- A breakthrough in Multi-Modal Imaging (MMI) diagnostic procedures may be achieved with a **genuine fusion between PET/SPECT and MRI analyses.** However that could be obtained only by using both a **radioactive and contrast agent based upon the same chemical compound.**
- **Hybrid PET/MRI** and **SPECT/MRI tomography**, combining at a later stage nuclear and magnetic resonance imaging, is currently the operative procedure followed. That turns out in **MMI mismatch,** because of the chemical diversity between the contrast and radioactive agents



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

- a contrast agent -> having **paramagnetic properties**
- radioactive tracer ->having **useful nuclear properties basically mimic ^{18}F**

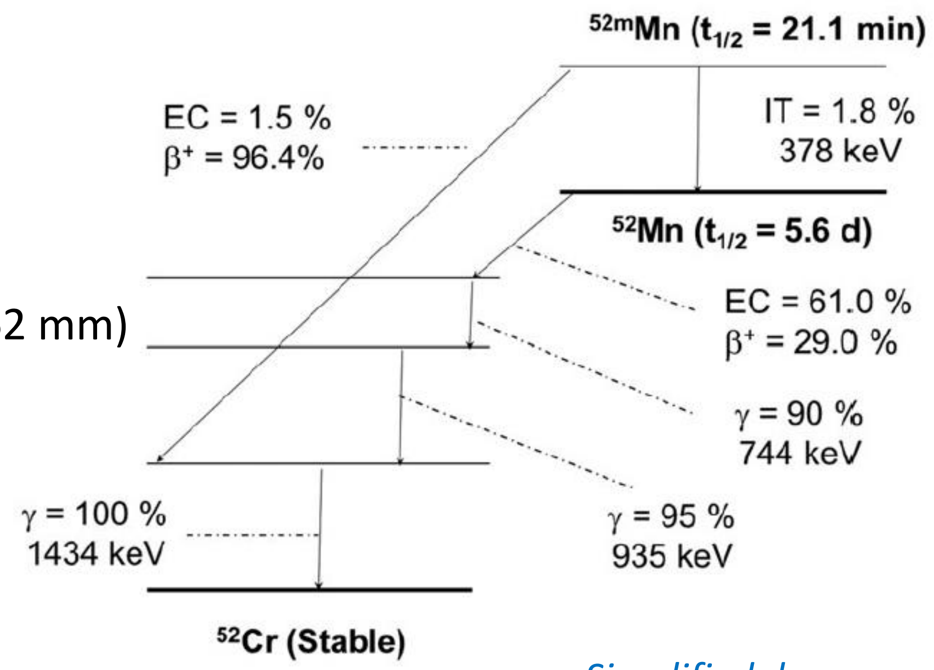
With the recent advances in PET/MRI scanner technology, **radio-manganese** may enable future dual modal imaging techniques, having both properties for MRI and PET.

METRICS

Mn positron-emitting isotopes suitable for use as a PET tracer:

^{52}Mn ($t_{1/2}$: 5.591 d, β^+: 29.4%, $E_{\beta+}$=244.6 keV, range=0.63 mm *)
^{52m}Mn ($t_{1/2}$: 21 min, β^+: 96.6%, $E_{\beta+}$ =1179 keV, range=5.288 mm
^{51}Mn ($t_{1/2}$: 46.2 min, β^+: 97.1%, $E_{\beta+}$ = 970.2 keV, range=4.275 mm

* comparable to ^{18}F ($t_{1/2}$: 110 min, β^+: 96.9% $E_{\beta+}$= 250 keV, range=0.62 mm)



Simplified decay scheme of ^{52}Mn

Possible NCA ^{52g}Mn production routes:

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

The simplest way is to produce ^{52g}Mn by using Cr natural basically exploiting all isotopes available…but other possible routes are under investigation by using medium/low-energy cyclotron (40-10 MeV) e.g. SPES cyclotron.

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...

INFN Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

Università degli Studi di Milano

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

INFN Istituto Nazionale di Fisica Nucleare

- Ferrara Branch
- Padua Branch
- Milan Branch
- Pavia Branch (new 2019)

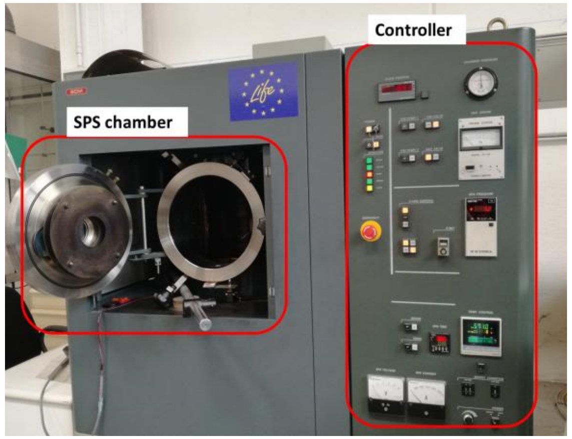
Università degli Studi di Ferrara

Ospedale Sacro Cuore Don Calabria
Presidio Ospedaliero Accreditato - Regione Veneto
Negrar - Verona

Resume on R&D activities performed (as of June 2018)

INFN -LNL

First Cr-nat metallic targets for 16-19 MeV class medical cyclotrons (up to ~2.1 kW) successfully produced by SPS (Spark Plasma Sintering) technique. Fruitful collaboration with K4Sint s.r.l. company (Trento).



SPS (Spark Plasma Sintering) main advantages:

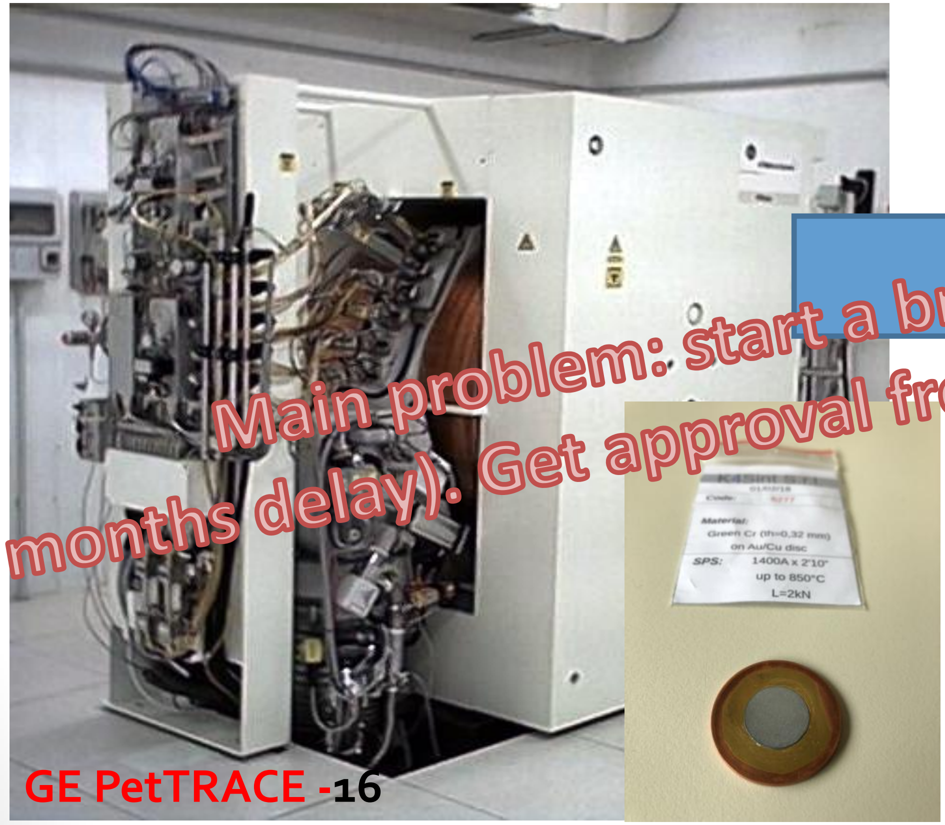
- takes only a few minutes to complete a sintering process compared to conventional sintering (e.g. HIP, DB, PVD)
- Possibility to get high melting point materials sintered (like Cr)
- NO any future ^{52}Cr-enriched material loss during manufacturing (100 % efficient)
- Possibility to produce easily 100-500μm thickness green pellets

Au protective layer

Cr green pellet	**D=15 mm, s=0.3mm (mass= 350 mg)**
Cu backing	D=23.5mm, s=1.7mm
Au protective layer in between (~25 μm) onto Cu disk	

Target Irradiation tests planned at S. Orsola Hospital (Bologna) suspended so far

- Experimental activities that were planned at the cyclotron in the first half of the year have adjourned. Cyclotron is not available in the near future for our activities due to unavailability of technical staff to support the target experimental tests.



GE PetTRACE -16
Protons: 16 MeV, up to 85 µA (1.3 kW)
Deuterons:8.4 MeV, 50 µA deuterons

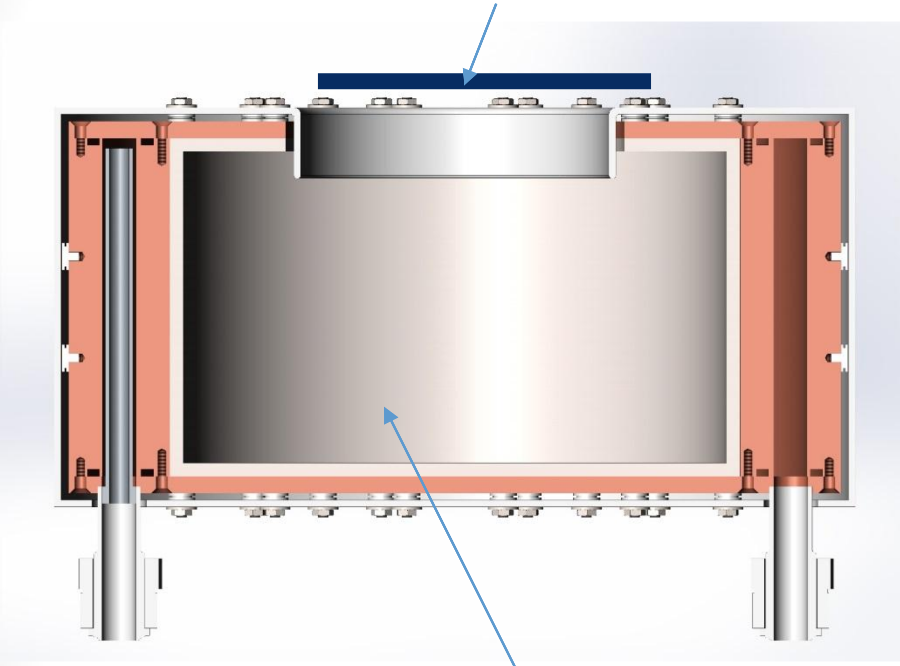
Main problem: start a brand new target manufacturing process (3 months delay). Get approval from Sacro Cuore Hospital for access to cyclotron

ACSI TR 19
Protons: 14-19 MeV, >300 µA (up to ~6 kW)
Possible dual particle accelerations

Cr Target production via Magnetron Sputtering/Diode Techniques

PLANNED ACTIVITIES 2019

Deposition Substrate

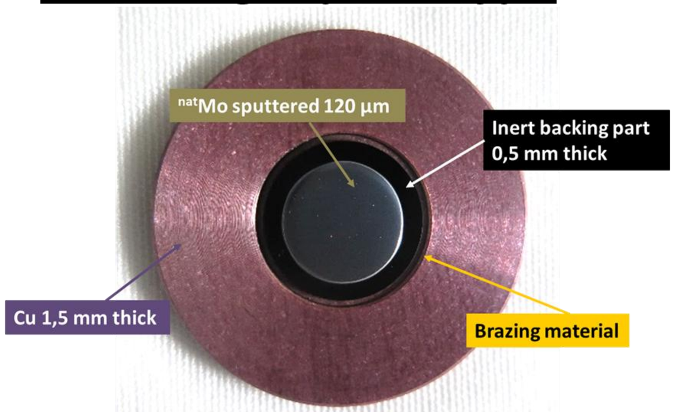


Evolution of inverted magnetron source technology

Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali di Legnaro

Innovative diode/magnetron source for material loss reduction.

New target prototype



INFN patent N. 102017000102990*
"Solid Target with chemically inert baseplate for radiopharmaceuticals production through cyclotrons". **New target production technologies under studies…**

- Validation of magnetron/diode sputtering techniques for irradiation target production
  - WP1 – Deposition of thick natural Cr with standard 2" source optimized for non material dispersion. Minimization of target-substrate distance, shielding design for material recovery. Measurement of lost material and estimation of sputtering efficiency (2019).
  - WP2 – Rescaling of innovative diode/magnetron source for irradiation target production. Machining and assembly (2019).
  - WP3 – Deposition test with innovative diode/magnetron source. Measurement of lost material and estimation of sputtering efficiency (2019-2020).

Comparison between the 2 sputtering source and validation of sputtering techniques

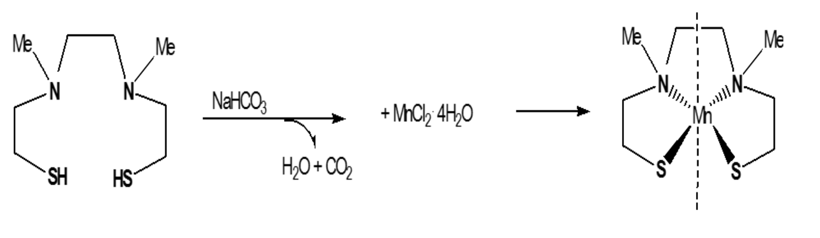
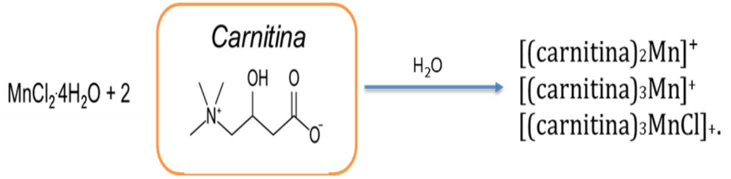
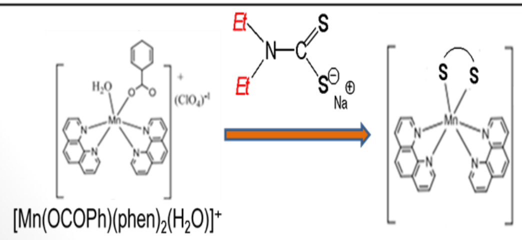
INFN-FE and UNIFE

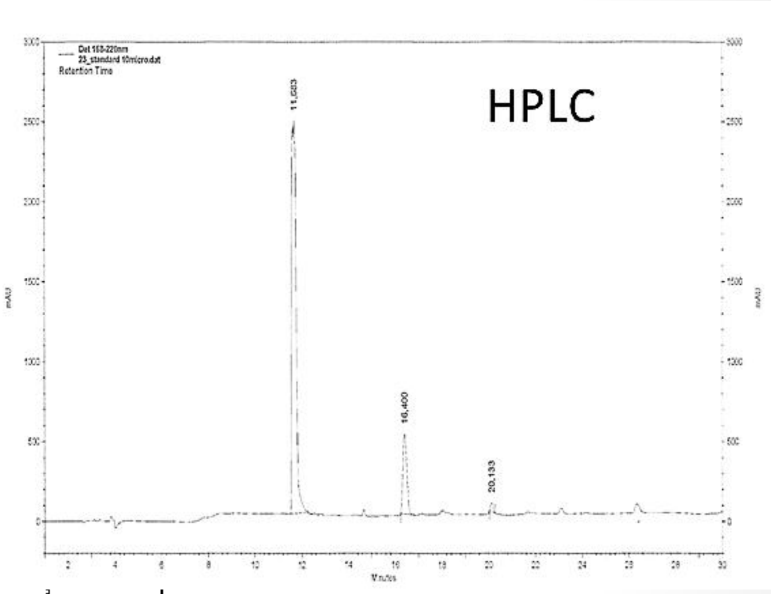
Radiopharmaceutical studies:

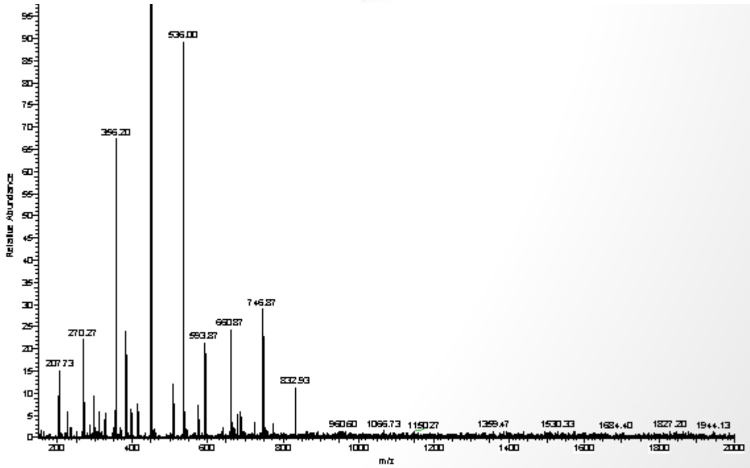
- ✓Mn-ligands coordination chemistry
- ✓characterization of the Mn(II)-complexes (ICPMS, IR, HPLC)

OBJECTIVES

- **Radiopharmaceutical studies** :
  - Mn(II)-complexes as contrast agent -> having **paramagnetic properties**
  - ^{52}Mn(II)-complexes radioactive tracer ->having **useful nuclear properties**

	Studi sulla reattività di Mn(II) con leganti tetradentati N_2S_2 Tendenza del Mn, a formare composti polimerici Occorre studiare metodi di sintesi di complessi «monomerici»
	Studi sulla reattività di Mn(II) con bidentati monoanionici O-O- buona reattività nei confronti di sistemi chelanti bidentati del tipo O-O
	Studi sulla reattività di Mn(II) con leganti neutri N-N e monoanionici O-O-

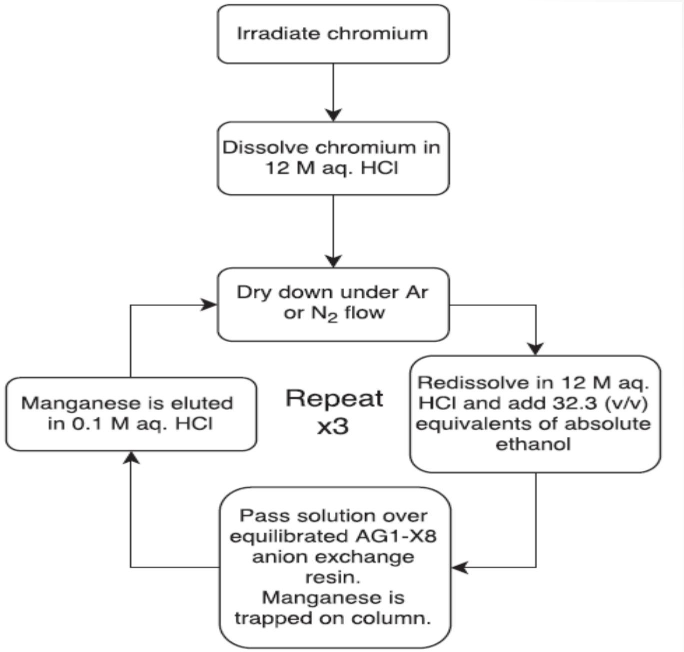




INFN-FE and UNIFE

OBJECTIVES

- Mn-Cr radiochemistry **extraction process**
  - ➢ Target Dissolution studies
  - ➢ Separation procedure development
  - ➢ Procedure automation and optimization
  - ➢ Product Quality Controls



(J. Fonslet et al. *Applied Radiation and Isotopes 121 (2017) 38–43)*

- Extraction process:
  - ✓ Literature study on Mn-Cr separation techniques

    ✓Anion exchange resin: chromium eluting in early fractions and manganese eluting in later fractions

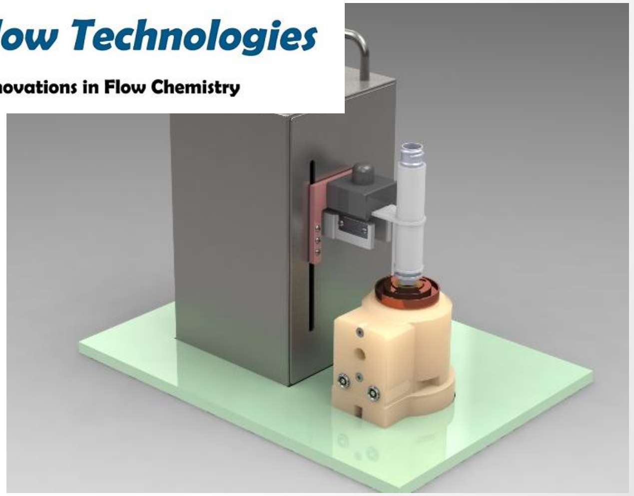
    ✓Solvent extraction: permanganate MEK extraction under evaluation (CONFIDENTIAL)

    ✓Applicability evaluation of the membrane –based innovative technology for liquid-liquid radionuclides separation (CONFIDENTIAL)

  - ✓ Design of a reactor heater suitable for solid target dissolution (CONFIDENTIAL))

Zaiput Flow Technologies

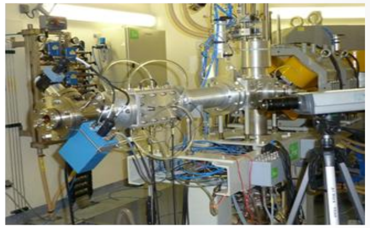
Groundbreaking Innovations in Flow Chemistry



INFN-Mi

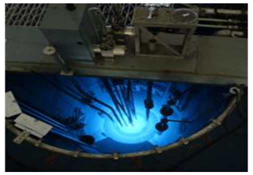
Involved Laboratories

Beam particles → ARRONAX Cyclotron (Nantes)
deuterons energy range: 15-35 MeV
Protons energy: up to 70 Mev



LASA → Radiochemistry Laboratory
→ Physics and Chemistry Measurements Laboratory

LENA - Pavia →



Nuclear Reactor TRIGA MARK II

First 6 months activity

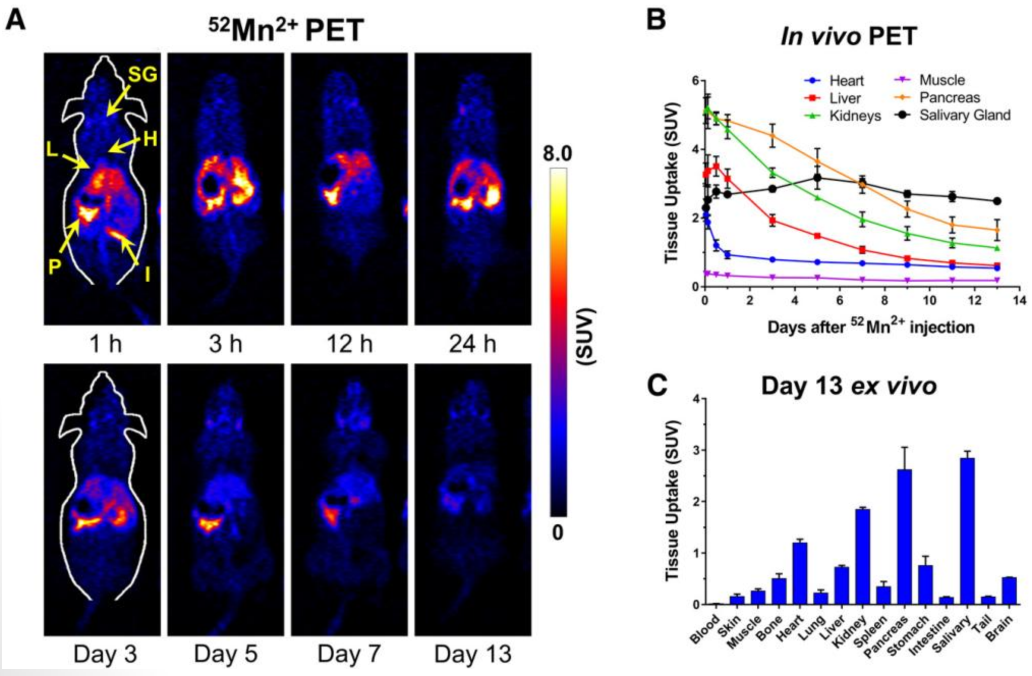
a) Simulation with **ALICE code** for the production of **Mn-52 by irradiation of Cr targets by deuterons and protons particles.**
b) Found some **difficulties in the preparation of the thin targets of chromium** to be irradiated for the determination of the **experimental cross sections**
c) just accepted **beam time request at ARRONAX Cyclotron** for irradiation with **deuterons of thin targets:** the final schedule will be between the end of **September and the first days of October 2018**

INFN-PD

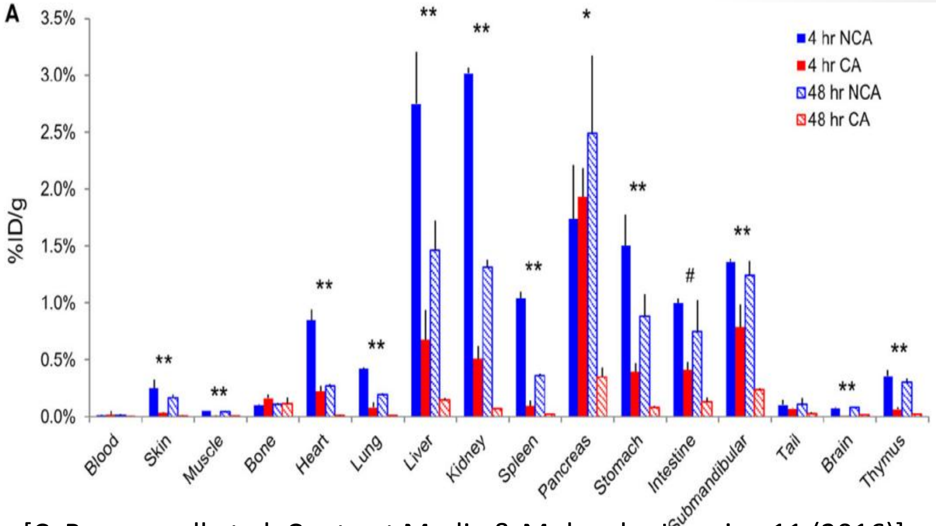
OBJECTIVES: Computational dosimetry

Biodistribution and organ uptake data of Mn-radiopharmaceuticals are scarce in the literature (small number of animals, limited number of time points, …).

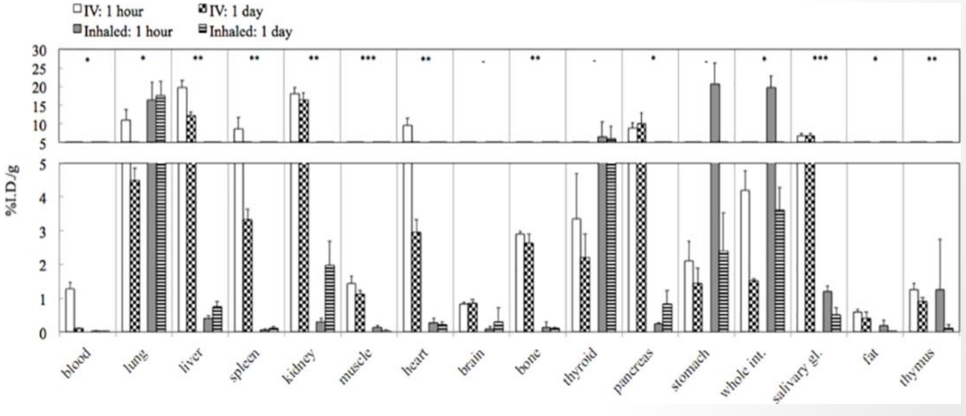
The most **complete biodistribution data available on the literature were data of Hernandez et al. [Diabetes 66, 2017]** regarding $MnCl_2$ biodistribution in normal mice, investigated non-invasively with PET and ex vivo gamma counting performed between 1 h and 13 days after i.v. injection of 3.7 MBq (100 mCi) of $^{52}Mn^{2+}$**.**



[Hernandez et al. Diabetes 66, (2017)]



[C. Brunnquell et al. Contrast Media & Molecular Imaging 11 (2016)]



[A. L. Wooten et al. PLoS ONE 12(3): e0174351(2017)]

INFN-PD

- Preliminary Dosimetry calculations of $^{52/51}MnCl_2$

✓ Biodistribution data of $MnCl_2$ in mice of Hernandez et al. were used to calculate the cumulated activity in the main source organs (pancreas, kidneys, liver, heart, and salivary glands).

✓ Results were then extrapolated from animals to humans.

✓ We assume that any activity not accounted for in the main source organs is distributed uniformly throughout all other body tissues and is removed from the body only by radioactive decay (quite **conservative assumption**).

✓ Equivalent dose in the main organs and the total effective dose (ED) were calculated with OLINDA/EXM software version 1.1 and 2.0, using the adult male/female reference phantoms.

$^{52}MnCl_2$

ED (mSv/MBq)	Male	Female
Olinda 1.1 (ORLN model/ICRP60)	2.2	2.6
Olinda 2.0 (NURBS model/ICRP103)	1.8	2.4

$^{51}MnCl_2$

ED (mSv/MBq)	Male	Female
Olinda 1.1 (ORLN model/ICRP60)	0.0127	0.0164
Olinda 2.0 (NURBS model/ICRP103)	0.0125	0.0161

Using ^{52}Mn for PET imaging patients would be exposed to relatively large doses, compared with shorter lived traditional PET radionuclides such as ^{18}F (ED=0.019 mSv/MBq), due to:

✓ the relatively long physical half-life (5.6 days)

✓ the high energy gamma emissions

✓ the long-term retention in the organism

A **possible alternative for Mn imaging in humans** is the **radionuclide ^{51}Mn,** which has a relatively short half-life, 46.2 min, which would make radiochemistry and tracer delivery more difficult than for ^{52}Mn isolation, but which would substantially reduce the total radiation dose required to have sufficient rate of decays immediately after administration for imaging.

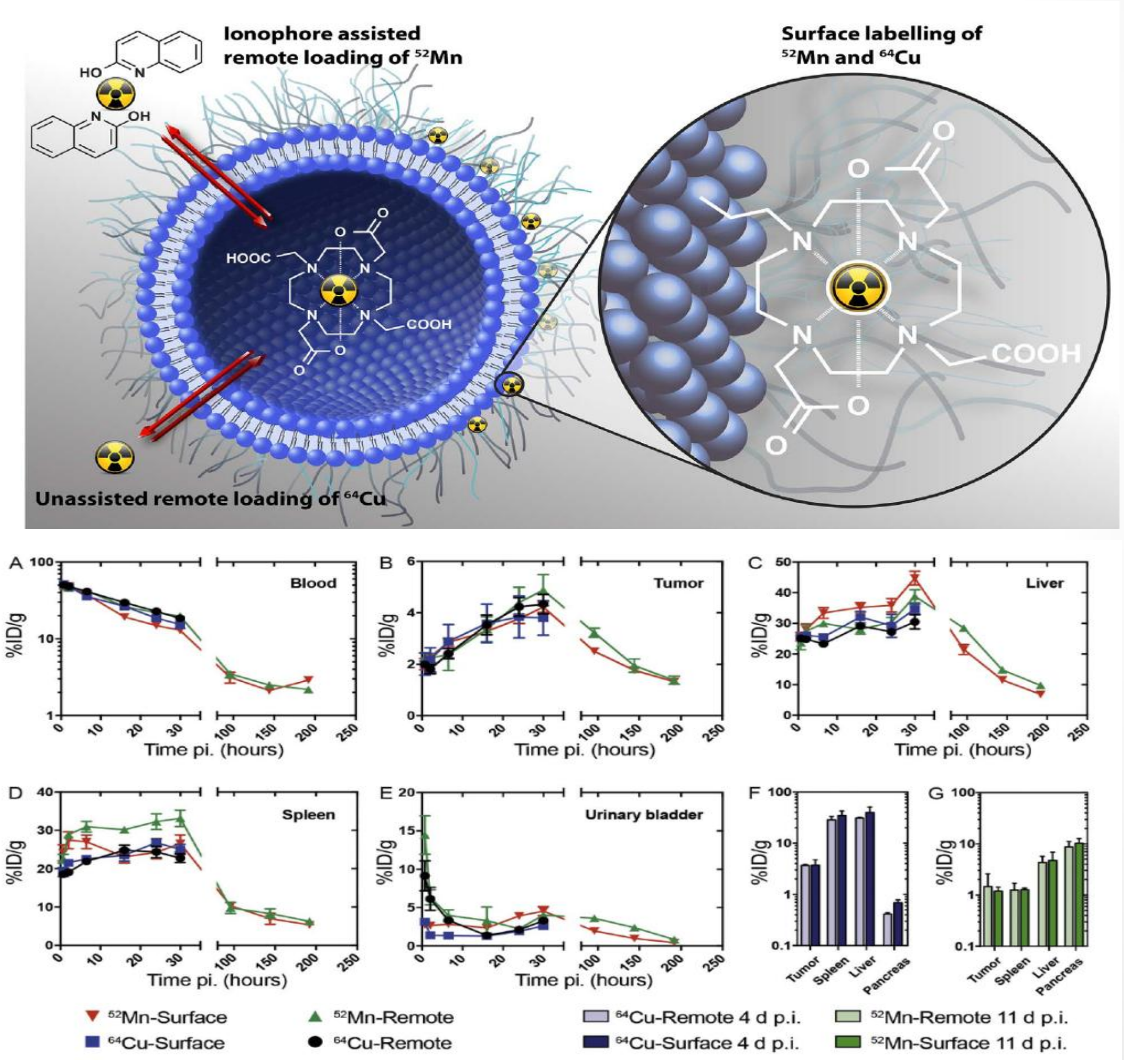
INFN-PD

- Future activity: dosimetry with other Mn-radiopharmacuticals

Liposomes are nanoparticles used in drug delivery that distribute over several days in humans, requiring long-lived radionuclides to be traced by PET.

As Mn can be chelated by DOTA (1,4,7,10-tetraazacyclododecane- 1,4,7,10-tetraacetic acid) to liposomes, **the long half-life of ^{52}Mn may permits injection of substantially lower amounts of initial radioactivity** with respect to other PET isotopes for liposomes tracking, making ^{52}Mn attractive for clinical imaging in certain scenarios, despite its high gamma dose.

Recently published biodistribution data of ^{52}Mn-DOTA liposomes **[Jensen et al. *Journal of Controlled Release 269 (2018)]*** will be used to perform computational dosimetry evaluation.



INFN-PD

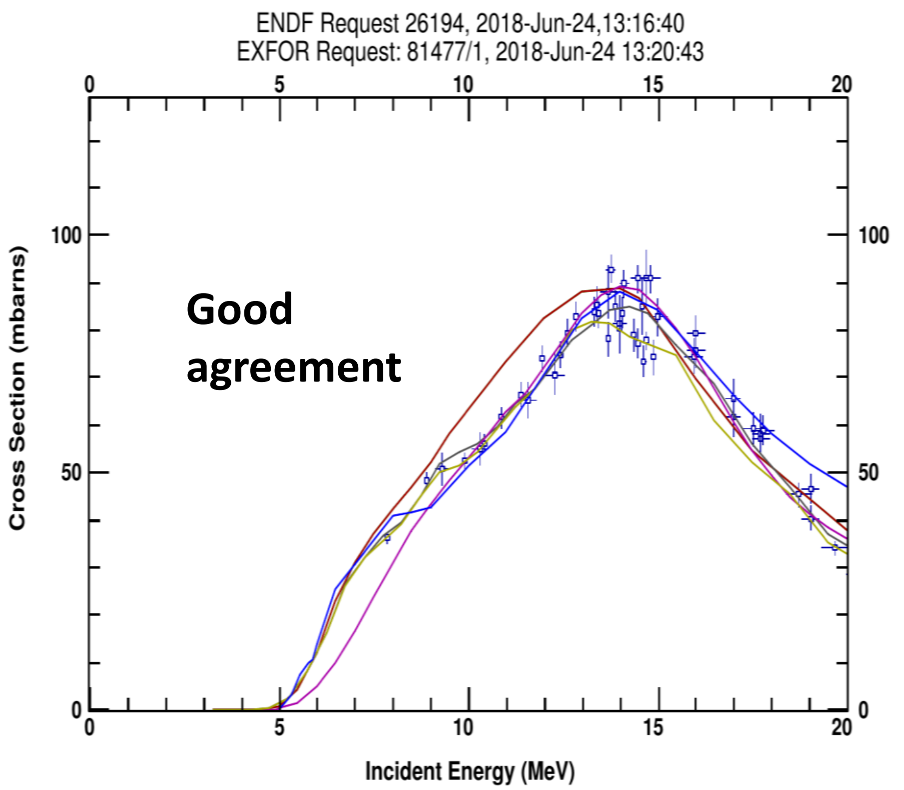
Theoretical/Experimental nuclear physics studies on alternative production routes

Theoretical studies of alternative routes for the production of Mn-52 (L. Canton in Collaboration with INFN Pavia) --Study of Cr52(d,2n), Fe56(p,an), Fe56(d,a2n), Fe54(d,a), Fe54(p,He3) etc --Extension of higher energies (range of SPES/LARAMED)

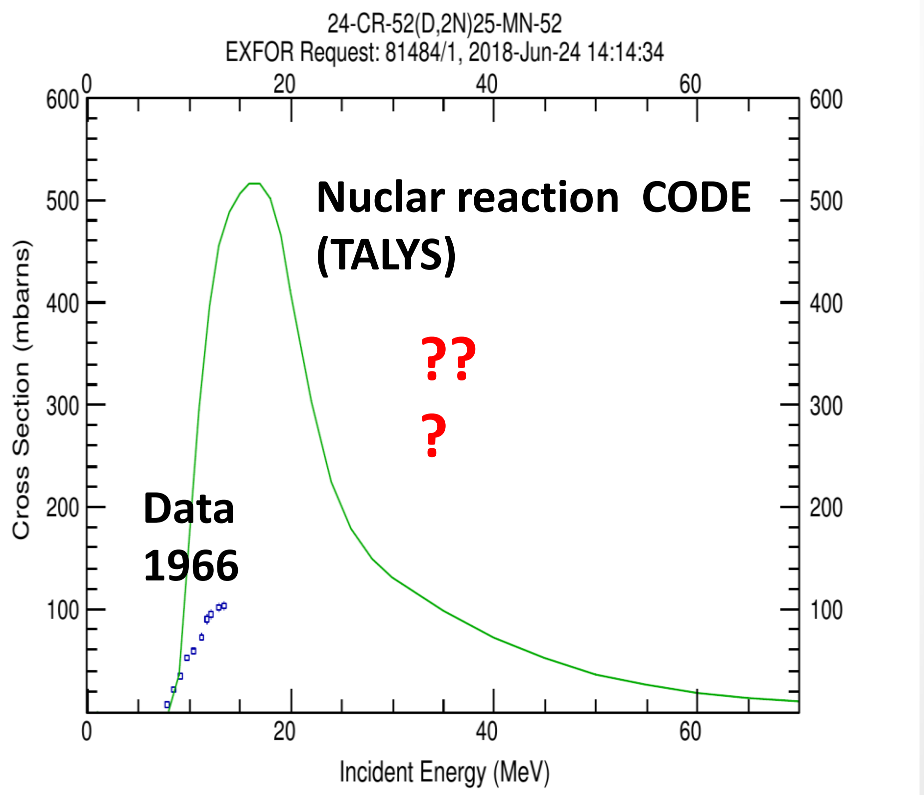
--Study of coproduction of contaminants (stable, radioactive)

FOR EXAMPLE:

"STANDARD" ROUTE Cr52 (p,n)Mn52



"ALTERNATIVE" ROUTE Cr52 (d,2n)Mn52



INFN-PV (newcomer 2019)

- Theoretical nuclear physics studies on alternative production routes with state of art nuclear codes: TALYS, EMPIRE, FLUKA.
  Possible reactions:
  $^{52}Cr(d,2n)^{52m/g}Mn$;
  $^{56}Fe(p,\alpha n)^{52m/g}Mn$;
  $^{56}Fe(d,\alpha 2n)^{52m/g}Mn$;
  $^{54}Fe(p,3He)^{52m/g}Mn$;
  $^{54}Fe(d,\alpha)^{52m/g}Mn$)
- either with proton or deuteron beams. Collaboration with INFN-PD.
- Study of fast neutron reactions (n,X).

- Development of tools for activity calculation in thick targets considering radioactive decay of contaminants. Collaboration with INFN-PD/INFN-LNL.

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
	4.4

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
	1.6

INFN-Pd	FTE
De Nardo L. (R. Loc)	1.0
Canton L.	0.1
Zorz A.	0.2
Paiusco M.	0.2
Cecchin D.	0.1
	1.6

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

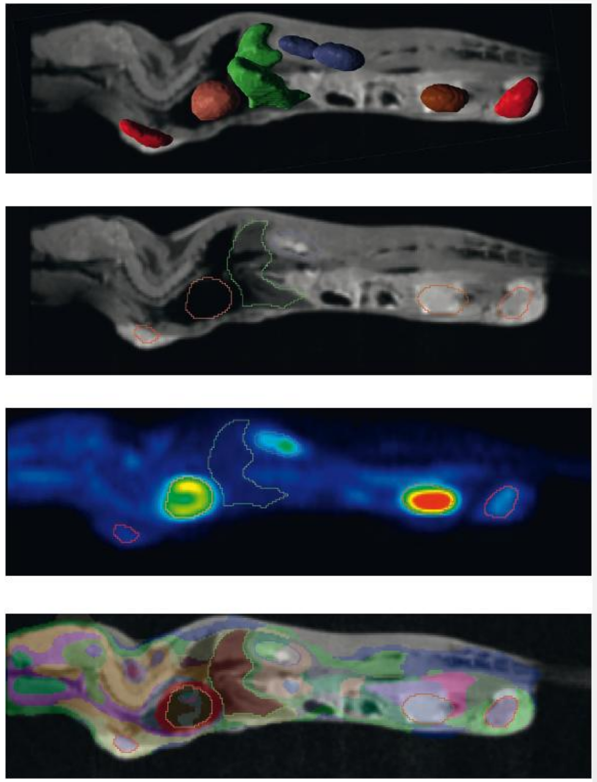
INFN-Pv	FTE
Fontana A. (R. Loc)	0.6
Salvini A.	0.2
Oddone M.	0.2
Strada L.	0.2
Alloni D.	0.2
(Calzaferri S.)	(1.0)
	1.4(2.4)

TOTALE FTE **12.6(13.6)**

INFN-PD
Budget quotation 2019

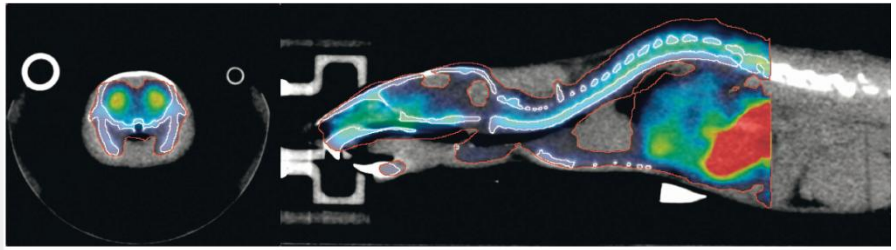
Item	What is needed	Estimated cost K€
Software tools for (PET/SPECT/CT) Small animal scanner	Modules PFUS and PSEG of the PMOD software.	**6.0**
Consumables	for PET scanner use	**0.5**
Travels	Domestic travels Padua-Legnaro - Pavia	**1.0**
TOTAL		**7.5**

PMOD Image Segmentation Tool (PSEG)

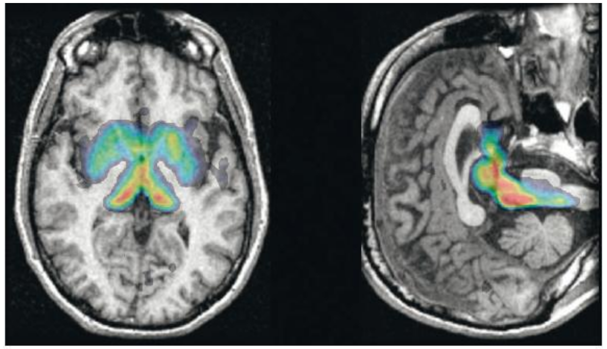


Organs and lesions derived by segmentation of dynamic FDG PET, shown in overlay on sagittal mouse MR sections.

PMOD Image Fusion (PFUS)



PET-derived dopamine D2/D3 map matched to CT (20 g mouse images).



PET-derived serotonin transporter map automatically matched to individual's MRI.

Summary overall budget request METRICS FY2019

Sezioni / Lab	Missioni	Consumo/ Altri consumo	Trasporti	Manutenzione	Inventario	apparati	Servizi	Tot. per sez/lab	FTE previsto
LNL	3.0	12.0					7.0	**22.0**	**4.4**
Fe	1.5	8.0	1.5			8.0		**19.0**	**1.6**
Pd	1.0	0.5					6.0	**7.5**	**1.6**
Mi	9.5	9.0	6.5	4.0				**29.0**	**3.6**
Pv	2.0	6.0						**8.0**	**1.4 (2.4)**
TOTALE	**15.5**	**34.0**	**7.5**	**4.0**		**8.0**	**13.0**	**75.5**	**12.6(13.6)**

FY2020 ~ 55 kEuro

TOTAL BUDGET request 3yrs (est.) ~ 190 kEuro