Cyclotron-Production of $^{51/52}$Mn Isotopes: the METRICS Project Final Report

J. Esposito[1], O. Azzolini[1], S. Cisternino[1,6], G. Keppel[1], A. Kotliarenko[1], P. Martini[1], L. Mou[1], G. Pupillo[1], G. Sciacca[1,6], A. Boschi[2], G. Di Domenico[3], A. Duatti[2], L. Marvelli[2], A. Taibi[2,3], L. Uccelli[2], F. Groppi[4,5], S. Manenti[4,5], L. De Nardo[6,7], L. Melendez-Alafort[1,8], M. Bello[1,7], A. Zorz[7,8], M. Paiusco[7,8], D. Cecchin[6,7], U. Anselmi-Tamburini[6,9] A. Fontana[9], A. Colombi[6,9], M.P. Carante[6,9], L. Canton[5], F. Barbaro[5,6], E. Cazzola[12], G. Gorgoni[12]

[1]INFN, Laboratori Nazionali di Legnaro, Legnaro (PD), Italy, [2]Università di Ferrara, Ferrara, Italy, [3]INFN Sezione di Ferrara, Ferrara, Italy, [4] Università di Milano, Milano, Italy, [5]INFN Sezione di Milano, Milano, Italy, [6]Università di Padova, Padova, Italy, [7]INFN Sezione di Padova, Padova, Italy, [8] Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy; [9]Università di Pavia, Pavia, Italy; [10]INFN Sezione di Pavia, Pavia, Italy, [12] Ospedale Sacro Cuore Don Calabria, Negrar (VR), Italy

INTRODUCTION

The METRICS (Multimodal PET/mRi Imaging with Cyclotron-produced 52/51Mn and stable paramagnetic Mn iSotopes) has been a 3+1 years (2018-2021) research project, funded by INFN-CSN5 and led by the Legnaro National Laboratories, which goal was to develop the R&D technology to get a cyclotron-driven $^{52/51}$Mn radionuclide production aimed at the so-called Multi-Modality Imaging (MMI), in the framework of LARAMED project at LNL [1]. We briefly recall here that MMI is the modern diagnostic approach in clinics which combines the different imaging modalities, due to different physical processes, to collect a better diagnostic information. As an exemplum giving, when combining PET (Positron Emission Tomography*)* or SPECT (Single Photon Emission Computed Tomography) with CT (Computed Tomography*)* or MRI (Magnetic Resonance Imaging), MMI allows to pair functional and molecular information, obtained by PET or SPECT, with anatomical information got by using imaging techniques, such as CT and MRI. While functional imaging through PET or SPECT always requires the administration of a radiolabeled tracer, anatomical imaging through MRI or CT involves the administration of a contrast agent to achieve the highest signal to noise ratio. However, so far radiolabeled tracer and contrast agent have always different chemical nature and therefore follow different biological pathways, which lead to an unavoidable mismatch about the content of the diagnostic information. The only way to achieve a genuine molecular fusion between PET/SPECT and MRI information, collected by both the contrast and the radioactive probe, is that they should be chemically identical. It is therefore interesting to seek for an element having paramagnetic properties, useful as an MRI contrast agent, and providing some radioactive isotopes as well, suitable for PET/SPECT scans. These requirements are met by the transition element manganese, having both paramagnetic properties and some β^+-emitting radioisotopes, such as ^{52}Mn ($t_{1/2}$=5.591d, I=29.6%, $E(\beta^+)_{avg}$= 244.6 keV), ^{52m}Mn ($t_{1/2}$= 21.1 min, I=96.6%, $E(\beta^+)_{avg}$ = 1179 keV) and ^{51}Mn ($t_{1/2}$= 45.59 min, I=97.1%, $E(\beta^+)_{avg}$ = 970.2 keV). Aim of METRICS project, has been therefore to seek for physics/chemistry/radiopharmaceutical conditions able to develop a perfect molecular matching between PET and MRI by using paramagnetic and radioactive manganese isotopes, to afford an unprecedented type of PET/MRI hybrid imaging modality. Moreover, to develop all the needed technology, i.e., dedicated targets, optimization of the proper radiochemical separation methods and, at last, the development of new Mn(II)-complexes, with the aim to get a cyclotron-based ^{52}Mn production. What follows is a concise summary of the project main outcomes achieved. Specific details of the METRICS project may be found in former editions of the Annual Report.

MAIN METRICS PROJECT OUTCOMES

Following an earlier agreement achieved with INFN-Pavia unit, a first SPS prototype machine based upon LNL specification was jointly developed (INFN innovative technology), as shown in Figure 1. That to achieve the "in house" full control for radioisotopes solid targets manufacturing exploiting the SPS (Spark Plasma Sintering) process, under study at LNL since the TECHN-OSP research project (2015-2017). In the past, this step was conducted in collaboration with the K4Sint s.r.l. company in Trento, albeit without having all the information [2]. The construction of the SPS machine, started at the end of 2019, has continued during all the 2020 year long [3,4]. At the end

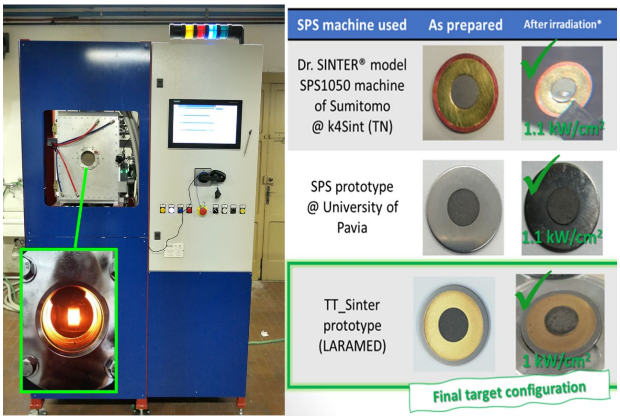

Figure 1: (Left) The SPS TT SINTER machine prototype, which will be installed in the LARAMED target laboratory at LNL. (Right) comparison of fist Cu/Au/Cr, Nb/Cr, Nb/Au/Cr solid targets produced with three different SPS machine used during the METRICS project and maximum beam power areal density achieved during irradiation test at the TR19 cyclotron of SCDCH.

of the year, the machine underwent the commissioning phase, improving all the sintering aspects still needed to be tuned. In May 2021, the SPS machine was assessed for the first time, fully meeting the specifications. Moreover R&D activities on new solid targets with the prototype SPS machine there available was conducted. At the end of 2019, some targets production tests with Nb backing, with and without the gold layer included in between (Nb/Cr) and (Nb/Au/Cr) were produced. In the second half of 2021 the first good-quality ^{52}Cr-enriched (~99%) targets were at last successfully produced.

About the development of an efficient Cr-Mn separation procedures for cyclotron-produced $^{52/51}$Mn, studies and laboratory tests were conducted in collaboration with Cyclotron and Radiopharmaceutical unit of Don Calabria Sacro Cuore Hospital (SCDCH) in Negrar (VR). They have continued for all the project period, with a dedicated radiochemistry separation-purification system developed for ^{5x}Mn from Mn-Cr liquid mixtures. Two different versions (prototypes), for the fully automated and remote-controlled chemical reactor have been realized and tested by making some technical modifications to an automatic module already available on the market (Ekert&Ziegler), which moreover allows for performing the on-line dissolution and purification processes with a cassette-based system, as shown in Figure 2.

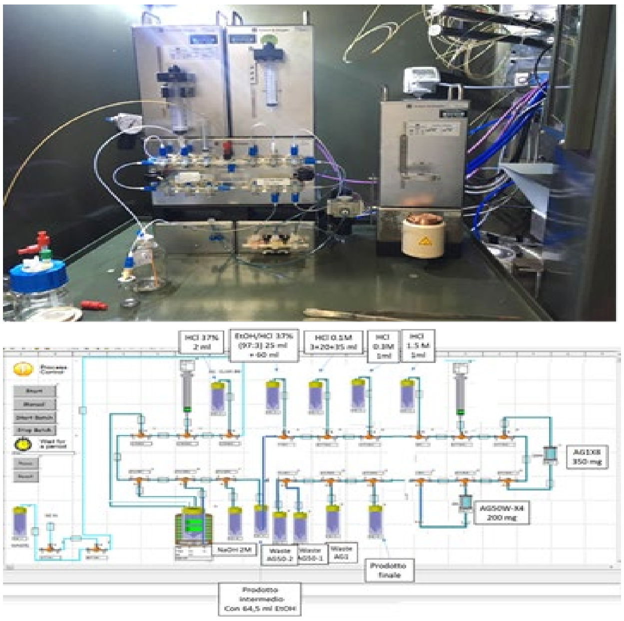

Figure 2: the PLC-controlled automatic prototype system developed for radiochemistry Mn-Cr separation-purification assembled in a hot cell of SCDCH, by using Eckert&Ziegler cassette-based modular units. On the right one of the two automatic solid target dissolution reactors developed and successfully tested.

They both worked according to design specification and were tested either in "cold" conditions, or with irradiated targets at one of the hot cells of SCDCH. As know method, a double Ag1X-8 anion exchange chromatography-based procedure has been selected as the most performing and thus used for the automation of a Mn/Cr separation protocol, albeit an original approach has also been tested based upon a first anion and a second cation exchange resins arranged in series (Ag1X-8 +AG50W-X4) which gave good performance during cold test in terms of Mn separation yield. The optimized automatic dissolution and purification process was used during a series of irradiated tests at the ACSI TR19/300 cyclotron (Ep=16 MeV, Ip=10μA Tirr=15 min) to evaluate the extraction yield of manganese from γ-spectrometry analysis of the final samples eluted. Results confirmed the presence of chromium and cobalt isotopes in load and wash samples, while no contamination being found in the final product (see also Figure 3). These results confirmed the efficiency of the separation process selected, allowing a recovery yield of Mn equal to 87.9%. [5,6]

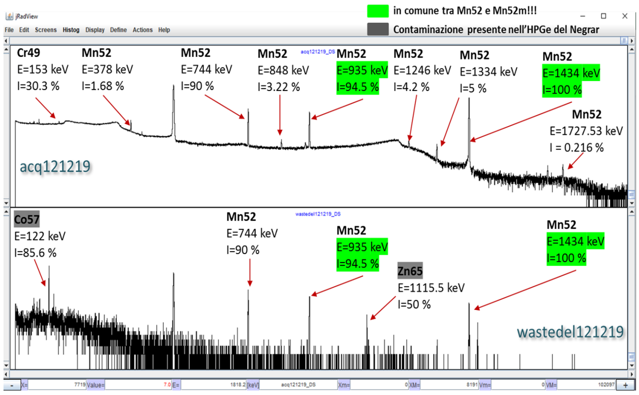

Figure 3: Gamma spectrometry measurements on first ^{52}Mn batches of radioactive manganese solution produced at the TR19/300 at HSCDC from radiochemistry procedure at Ep=16 MeV.

On the other hand, parallel activities, conducted at Ferrara University, aimed at selecting the most robust arrangement able to stabilize the Mn^{2+} ion in a biological environment, led to the development of a series of a new class of Mn(II)-dithiocarbamates complexes, potentially used as magnetic resonance imaging contrast media. They were characterized by HPLC chromatography, IR spectroscopy, elemental analysis and mass spectrometry, as well as relaxivity studies carried out in collaboration with Preclinical Imaging Laboratory - Dept. of Molecular Biotechnologies and Health Sciences, University of Turin (IT). A first series of studies with standard phantoms were conducted to evaluate the properties of paramagnetic imaging in water, by using the 1.5T clinical MRI at the Ferrara Hospital. Results showed that the contrast produced by the complex $[Mn(II)(L')_2]x2H_2O$ is comparable to that produced by gadolinium complexes currently used in medicine as a paramagnetic contrast agent. Given the absolute novelty, a patent application process has begun at CNTT.

[1] J. Esposito et al. Molecules 2019, 24, 20
[2] J. Esposito et al., LNL Annual Report (2018)
[3] S. Cisternino et al., LNL Annual Report (2019)
[4] S. Cisternino et al., LNL Annual Report (2020)
[5] P. Martini et al., LNL Annual Report (2019)
[6] P. Martini et al., LNL Annual Report (2020)