RESEARCH ACTIVITIES ON THE CYCLOTRON-BASED RODUCTION OF INNOVATIVE RADIONUCLIDES: THE EXPERIENCE AT THE LEGNARO NATIONAL LABORATORIES OF INFN

G. PUPILLO
Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro (INFN-LNL)
Legnaro (Padova), Italy
Email: gaia.pupillo@lnl.infn.it

A. ANDRIGHETTO
INFN-LNL
Legnaro (Padova), Italy

M. BALLAN
INFN-LNL
Legnaro (Padova), Italy

A. BOSCHI
Department of Chemical, Pharmaceutical and Agricultural Sciences, University of Ferrara and INFN-FE
Ferrara, Italy

S. CISTERNINO
INFN-LNL and Engineering Department, University of Padova
Legnaro (Padova) and Padova, Italy

S. CORRADETTI
INFN-LNL
Legnaro (Padova), Italy

L. DE DOMINICIS
INFN-LNL and Physics and Astronomy Department, University of Padova
Legnaro (Padova) and Padova, Italy

J. ESPOSITO
INFN-LNL
Legnaro (Padova), Italy

E. FIORETTO
INFN-LNL
Legnaro (Padova), Italy

M. MANZOLARO
INFN-LNL
Legnaro (Padova), Italy

P. MARTINI
Department of Environmental and Prevention Sciences, University of Ferrara and INFN-FE
Ferrara, Italy

A. MONETTI
INFN-LNL
Legnaro (Padova), Italy

L. MORSELLI
INFN-LNL and Physics and Earth Science Department, University of Ferrara
Legnaro (Padova) and Ferrara, Italy

L. MOU
INFN-LNL and Physics and Earth Science Department, University of Ferrara
Legnaro (Padova) and Ferrara, Italy

D. SCARPA
INFN-LNL
Legnaro (Padova), Italy

G. SCIACCA
INFN-LNL and Engineering Department, University of Padova
Legnaro (Padova) and Padova, Italy

E. VETTORATO
INFN-LNL
Legnaro (Padova), Italy

Abstract

The cyclotron-based production of radionuclides for medicine is one of the research activities carried out in the framework of the SPES (Selective Production of Exotic Species) project at the Legnaro National Laboratories of the National Institute for Nuclear Physics (INFN-LNL). The heart of SPES is the 70 MeV proton-cyclotron with a dual-beam extraction, installed in 2015 in a new building equipped with ancillary laboratories currently under completion. The project aims at the construction of an advanced ISOL (Isotope Separation On-Line) facility to produce re-accelerated exotic ion beams for nuclear physics studies. The double-beam extraction of the cyclotron also allows to perform multidisciplinary activities, such as radionuclides production for medical applications and neutron-based research. This paper will mainly present the results obtained with the interdisciplinary projects LARAMED (LAboratory of RAdionuclides for MEDicine) and ISOL-pharm. The first one is based on the direct-activation method, and it includes the proton-based production of ^{99m}Tc, ^{67}Cu, $^{52/51}$Mn, ^{47}Sc and recently Tb-isotopes, from the nuclear cross section measurements to the preclinical studies. ISOL-pharm uses the ISOL technique for the development and the production of radioisotopes with high-specific activity, such as ^{111}Ag, going beyond the state-of-art in the field. A consolidated network of collaborations with national and international facilities, including universities and hospitals, characterizes the research activities on radionuclides production at the INFN-LNL.

1. INTRODUCTION

The SPES project at the INFN-LNL has an ambitious scientific program ranging from nuclear physics and astrophysics to interdisciplinary applications [1, 2]. The heart of SPES is the 70 MeV proton-cyclotron [3], capable of providing intense beams (up to 700 µA) also in the dual-extraction configuration. This characteristic will allow to perform not only state-of-the-art experiments with Radioactive Ion Beams (RIBs) [4] but also multidisciplinary research activities, such as radionuclides production for medical applications and neutron-based research. Figure 1 represents the main parts of the SPES project at the INFN-LNL.

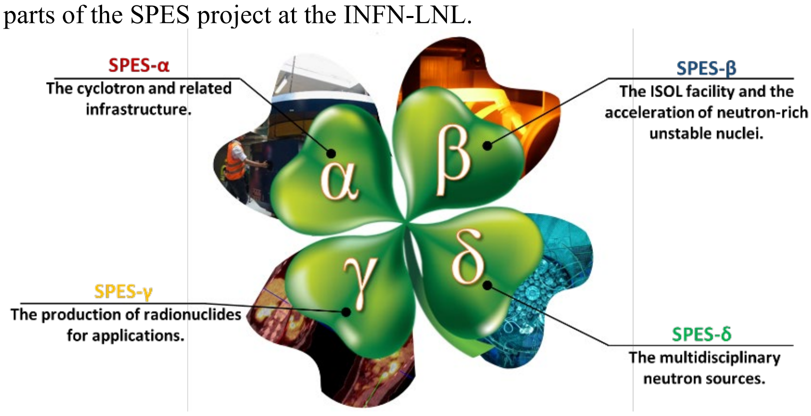

FIG. 1. The SPES-project phases.

Radionuclides are fundamental tools in several applications of nuclear physics, ranging from toxicological to environmental and industrial studies, but play a key role in nuclear medicine, by enabling imaging and treatment in tens of millions of procedures performed worldwide on a yearly basis. Given that the production of medical radionuclides is thus a crucial aspect, and the availability of emerging radionuclides fosters the development of innovative radiopharmaceuticals, the SPES project includes the "The production of radionuclides for applications" as its gamma phase (Figure 1) and the INFN-LNL Research Division contains the "Radioisotope Service for Medicine and Applied Physics" (RMFA) [5, 6]. The activities of the RMFA service include:

— Radionuclide production using direct activation method (LARAMED project) and ISOL technique (ISOLPHARM project), for research in medicine (e.g. new radiopharmaceuticals development) and in applied and interdisciplinary physics (e.g. radiobiology, environmental studies).
— Measurements of proton-induced nuclear cross sections for medical radionuclides production.
— Study, development, and optimization of radiochemical procedures aimed at the separation and purification of radionuclides, development of radiopharmaceuticals.

Since currently the laboratories and infrastructures of the SPES building devoted to these research activities are not yet operative, the SPES-γ research activities rely on a wide network of collaborations, internal and external the LNL, as outlined in the following sections. Figure 2 shows the planimetry of the SPES building at the underground level, where the cyclotron is in the centre and the LARAMED and ISOL-bunkers are indicated on the right and left side of the picture.

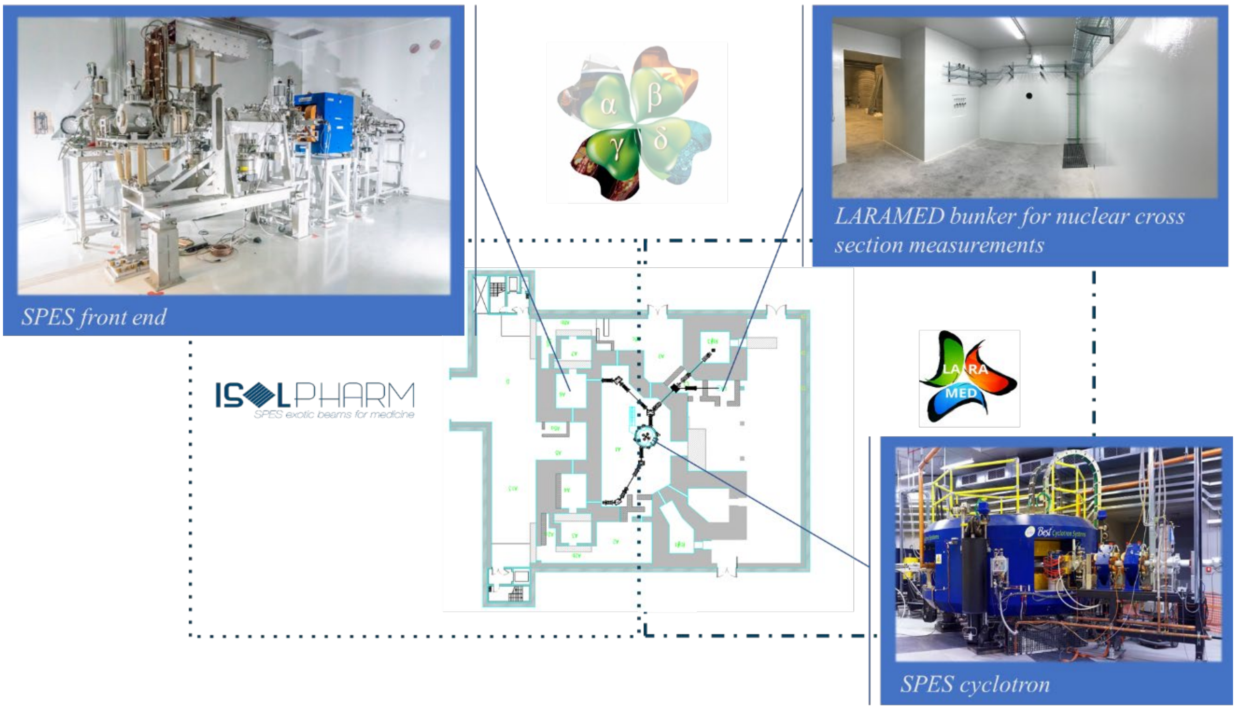

FIG. 2. The SPES building planimetry at the underground level.

Ultimately, the major objective of these research activities is to elect LNL as an internationally recognized hub (in collaboration with other research centres in Europe) aimed at the development of unexplored production methods for novel medical radionuclides, as well as to establish a production facility at LNL for a few relevant medical radionuclides to be distributed to hospitals and clinical departments, to support both preclinical/clinical ongoing research programs and for routine use in patients' treatment. Since only a few examples of this type of high-energy, high-current cyclotrons are currently operating around the world, it becomes plain the potential important role that the INFN-LNL could play in the global scenario, related to the production of unprecedented medical radionuclides. In fact, the LNL are participating as emerging infrastructure also at the European medical isotope programme PRISMAP [7], recently approved by the EU as H2020.

2. LARAMED

The LARAMED project, acronym for LAboratory of RAdioisotopes for MEDicine [8, 9] is funded by the Italian Ministry of University and Research (year 2014 and 2016) at the INFN-LNL. It has been conceived, since the beginning, to meet a double scope. The first one was to develop a more efficient production for well-established radionuclides already playing a key role in nuclear medicine (e.g. ^{99m}Tc) [10-13], while the other was to investigate yet unexplored production routes for novel radionuclides having potential interest in medicine, but still unavailable [14]. The latter may indeed summarize the most interesting aspect of this project, playing a key role in improving approaches in patients' treatment and clinical research purposes. Nonstandard radionuclides production is, indeed, a fundamental step to select new radiopharmaceuticals classes for both diagnostic and therapeutic applications [15].

As shown in Figure 3, the LARAMED research activity is envisaged to cover different topics, ranging from basic nuclear physics (experimental measurements of excitation functions) [16-20], to target technology (design and manufacturing of high-power targets for proton irradiation to produce important medical radionuclides, such as ^{99m}Tc, ^{64}Cu, ^{67}Cu, ^{47}Sc, ^{89}Zr, etc.) [21-25] and radiochemistry (development of highly automated separation/purification techniques and labelling studies of new biological carriers) [26-29]. The synergy between these skills resulted in high-level research on the cyclotron production of conventional and emerging radionuclides. Although LARAMED will be a public research facility, joint ventures with private companies interested in the already available and/or new radionuclides development programs is anyway foreseen.

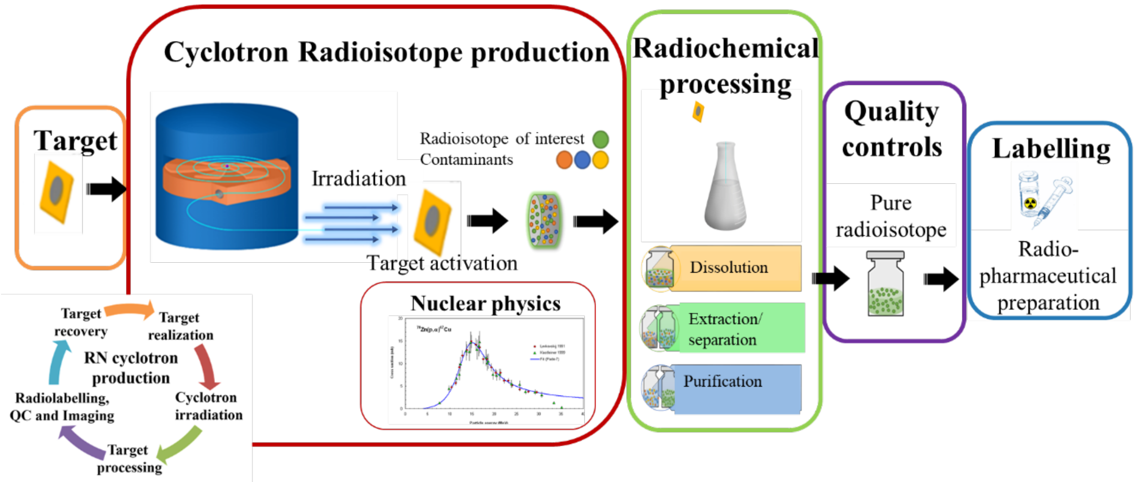

FIG. 3. The medical radionuclide production scheme exploiting the direct activation method.

Regarding the LARAMED facility in the SPES building, it includes:

— The *RILAB Bunkers* (RI#3 and A9c), the first dedicated to irradiation of high power (i.e. up to ~ 10 kW) solid targets and the second dedicated to nuclear cross-sections measurements with low-intensity proton-beams (i.e. up to 100 nA).
— The *RIFAC Bunkers* (RI#1 and RI#2), where two additional beamlines are foreseen to be installed in further years and used to produce massive amounts of radioisotopes, in collaboration with a private partner, to hospitals and clinical departments, for both routine and clinical research purposes.
— The *RILAB Radiochemistry laboratory*, covering all the radiochemical processing aspects and designed to carry out R&D activities on radioisotope production, separation/purification, up to perform all the requested quality control procedures.
— The *RILAB Target-preparation laboratory* where all the new/alternative cold-chemistry technologies devoted to target manufacturing are under development by the LARAMED research group.

In Figure 4 a schematic layout of the building upper floor is shown, along with the area reserved for the future installation of Radiochemistry laboratory for radioisotope/ radiopharmaceutical production dedicated to future RIFAC activities.

FIG. 4. The LARAMED laboratories planimetry at the upper floor of the SPES building.

The LARAMED research activities started 10 years ago with the following projects:

— APOTEMA and TECHN-OSP (INFN-CSN5 funded, 2012-2017), dedicated to the direct ^{99m}Tc production using isotopically enriched ^{100}Mo targets at medical cyclotrons; the results have been also presented in the IAEA CRP focused on “Alternative, non HEU-based, ^{99m}Tc/^{99}Mo supply” (2011-2015).
— COME (INFN-CSN3 funded, 2016), dedicated to the first measurements of the ^{70}Zn(p,x)^{67,64}Cu nuclear reactions above 35 MeV and the ground of the INFN patent on ^{67}Cu multi-layers target [25].
— PASTA (INFN-CSN5 funded, 2017-2018), dedicated to the nuclear cross section measurements for ^{47}Sc production, whose results have been also presented in the IAEA CRP focused on “Radiopharmaceuticals labelled with new emerging radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc)” [15].
— E_PLATE (INFN-CSN5 funded, 2018-2019), dedicated to thin target manufacturing exploiting the High Intensity Vibrational Powder Plating (HIVIPP) technique.
— METRICS (INFN-CSN5 funded, 2018-2021), dedicated to $^{51/52}$Mn accelerator-based production and to the development of innovative radiopharmaceuticals for PET/MRI dual-imaging purposes.
— INTEFF_TOTEM (INFN-CNTT funded, 2021-2022), dedicated to the further development of the INFN patents on targetry for the production on medical radionuclides [24, 25].
— REMIX (INFN-CSN5 funded, 2021-2023), dedicated to the measurements of the ^{49,50}Ti(p,x)^{47}Sc nuclear reactions (exploiting the thin targets developed with the HIVIPP technique) and Tb-radionuclides production (^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb).

The wide national and international network of collaborations allowed the LARAMED team to enlarge the research topics to nuclear modeling, imaging, dosimetry, etc. [20, 12, 30-32]. The LARAMED network includes the ARRONAX facility (Nantes, France), the Universities of Ferrara, Milano, Padova, Pavia and the Wisconsin University, the CNR in Milano, the LENA laboratory, the Istituto Oncologico Veneto (IOV, Padova, Italy), the Sacro Cuore Don Calabria (Negrar, Verona, Italy) and the Sant’Orsola (Bologna, Italy) hospitals.

3. ISOLPHARM

The general scheme of the ISOLPHARM method [33, 34] is shown in Fig. 5: a production target is hit by protons coming from the SPES cyclotron. Different nuclear reactions activate the generation of several different radioisotopes. Mainly neutron-rich β^- emitters are produced, due to the fact that at SPES and in general in ISOL facilities, uranium carbide is used as a fissile target material. Inside the so-called front-end (shown in Fig. 2), the target is kept at high temperature (more than 2000 °C) in high vacuum, so that the isotopes can escape from it towards an ion source, where they are ionized (1^+) by means of one of the three available ionization techniques (surface, laser, or plasma). After ionization, the charged radioisotopes are accelerated by means of a 40 kV potential, forming a radioactive ion beam. The following step, mass separation, is crucial for the purposes of ISOLPHARM. This stage allows to have an isobaric beam, removing all isotopic contaminants of the desired element, which are not otherwise chemically removable. These processes represent the scheme of operation of ISOL facilities (top part of Fig. 5) to perform nuclear physics studies by providing radioactive ion beam to experimental users. The new approach introduced by ISOLPHARM is the collection of radioisotopes on a secondary target (ion collection stage). This collector can then be dissolved and chemically purified to eliminate isobaric contaminants. The obtained product can be subsequently used for radiolabeling of specific molecules. These can be delivered to universities or external research centers for preclinical studies (bottom part of Fig. 5).

The key aspects to be underlined for ISOLPHARM are:

- The presence of a strong collaboration between several INFN laboratories and sections and several university departments.
- The production of radionuclides with high specific activity by means of the ISOL technique.
- The INFN patent which proves the innovation and excellence of the project [35].
- The low environmental and social impact, since nuclear reactors are not used for the provision of the radionuclides.

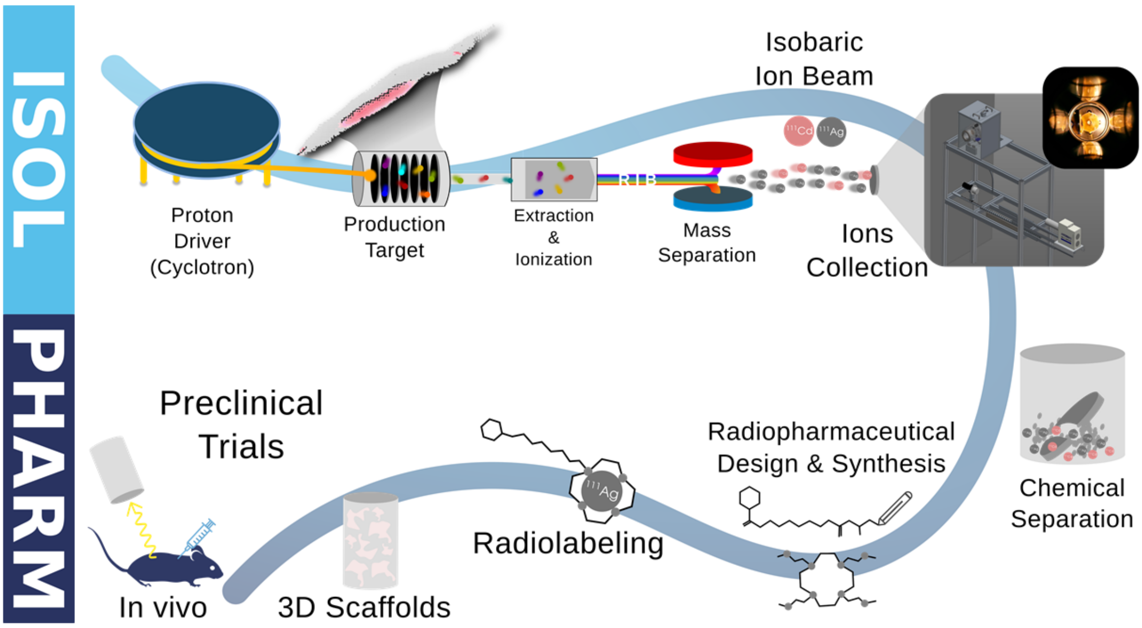

FIG. 5. The ISOLPHARM method.

In the framework of ISOLPHARM, a two-year experiment collaboration project named ISOLPHARM_Ag was financially supported by INFN CSN5 (Commissione Scientifica Nazionale 5) for the years 2018/2019 [36]. Such project aimed at studying and demonstrating as a proof of principle the production and use of the promising ^{111}Ag, an isotope which is produced in huge quantities in the SPES uranium carbide target. Its possible use was investigated both relatively to its ISOL production and to its possible application as a radiopharmaceutical precursor, with both computational and experimental investigations. Computational studies were focused on the development of Monte Carlo codes able to estimate the production and release of ^{111}Ag from the primary target. Such codes were computing intensive, and they were executed with the support of a cloud infrastructure in the CloudVeneto environment. The experimental studies involved: ionization and transport of silver (that will be tested at the SPES Front End using the SPES Plasma Ion Source) [37]; the chemistry studies to develop and characterize silver complexes [38]; the biological studies on such molecules, to evaluate the interaction of the synthesized complexes with cellular targets [39].

Following the good results obtained in the ISOLPHARM_Ag experiment, a new experiment started in the framework of CSN5, ISOLPHARM_EIRA (2020-2022), in which all the ISOLPHARM collaboration activities are now focused. The ISOLPHARM_EIRA experiment has three main goals, based on the application of the ISOLPHARM method to the production of ^{111}Ag radionuclides as radiopharmaceuticals precursors:

- Physics: production of ^{111}Ag, spectroscopy studies, laser ionization of Ag (Task 1).
- Radiochemistry: synthesis and characterization of chelators, linkers, targeting agents and purification of isotopes (Task 2).
- Biology: biological characterization on cells, scaffold production and 3D cell cultures, in vitro and in vivo studies (Task 3).

The main aim of Task 1 is the production of an appropriate amount of ^{111}Ag to be used in the Task 2 for the radiolabeling of the prepared radiopharmaceutical [40]. ^{111}Ag is produced by means of the traditional technique of neutron capture reaction on enriched ^{110}Pd. The irradiation is performed at the TRIGA Mark II nuclear reactor of the LENA (acronym for "Laboratorio Energia Nucleare Applicata") laboratory of the Pavia University. Several activities are ongoing:

- Production of ^{111}Ag in nuclear reactor, including the design and construction of a semi-automatic device for the extraction and handling of the irradiated samples.
- Spectroscopic studies for the isotopic characterization of the irradiated samples.
- Studies for the laser photoionization of natural Ag.

The final goal of Task 2 is to prepare and characterize the radiopharmaceutical to be used by Task 3, after having achieved the radionuclide produced by Task 1 [41]. Several activities are ongoing:

- Development of purification methods for Ag from Pd and recovery of Pd.
- Development and characterization of chelators for Ag and Cu.
- Synthesis and characterization of fluorescent targeting vectors.

The activities of Task 3 are mainly aimed at the a) preliminary screen and identify via standard fluorescent assays the optimal macromolecules for the b) subsequent more relevant in-vivo test that will be conducted with radiolabeled compounds [42]. Several activities are ongoing:

- Selection of cell lines for in vitro studies.
- In-vitro and in-vivo study of targeting vectors.
- In-vitro studies of targeting vectors with fluorescent targeting agents.
- Design of suitable 3D scaffold for in vitro tissue mimicking.
- In-vitro uptake studies (3D scaffolds) with fluorescent compounds.
- Biodistribution and in vivo imaging.

4. CONCLUSIONS

The SPES-γ will exploit the 70 MeV proton cyclotron to produce radionuclides of medical interest with the direct activation (LARAMED project) and the ISOL technique (ISOLPHARM project). Waiting for the completion of the SPES facility, both projects have a wide national and international network of collaborations to perform multidisciplinary research activities, ranging from nuclear physics to radiochemistry, from material science and targetry to engineering and radiopharmacy. A young team of researchers is involved, and the activities are coordinated by the recent "Radioisotope Service for Medicine and Applied Physics" (RMFA) in the Research Division at the INFN-LNL. The European PRISMAP consortium identifies the INFN-LNL as emerging infrastructure, a unique lab where the potential impact of both production techniques can be studied.

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