Newsletter Interview

NUCLEAR PHYSICS AND MEDICINE: THE CHALLENGE OF SPES AT LEGNARO NATIONAL LABORATORIES

Interview with Faïçal Azaïez, Director of INFN Legnaro National Laboratories

Particle accelerators, radiation detectors, technology transfer activities: the complex machine of INFN Legnaro National Laboratories addresses challenges in various fields ranging from nuclear physics and astrophysics to interdisciplinary research, and is entrusted, as of 2023, to Faïçal Azaïez. Former Director of the Institute for Nuclear Physics of Orsay in France and the iThemba Laboratory for Accelerator Based Science in South Africa, Azaïez has very clear goals for Legnaro's direction: to make these national Laboratories a world reference for science and technology. We met with him to hear about the present, but more importantly, the future of this center for low-energy nuclear physics.

You have been appointed Director of Legnaro National Laboratories (LNL) in 2023. How was your first year as Director? Did it meet your expectations?
It has gone far beyond that! I have never found such a positive and collaborative work environment as the one I found at INFN and LNL. Then, from the perspective of my assignment and the work to be done, I had a pretty clear idea of what to expect. You have to imagine nuclear physics as a family, where all the members know each other. And I am not only part of this family as a nuclear physicist, but I have also had many opportunities for direct exchange with INFN over the years. When I was director of the Institute of Nuclear Physics of Orsay in Paris, I interacted a lot with the INFN National Laboratories of the South and of Legnaro. And while I was in charge of the South African iThemba Laboratory, consisting of two facilities, Cape Town and Johannesburg, I signed a Memorandum of Understanding with INFN. In addition, I have been a member of many scientific committees that evaluate the activities of nuclear physics laboratories, and of the NuPECC (Nuclear Physics European Collaboration Committee) organisation, a committee that coordinates all the national nuclear and hadron physics laboratories in Europe; so my knowledge of INFN, and Legnaro in particular, is very solid. When I was appointed Director, I already knew that the main challenges of Legnaro National Laboratories were related to an ambitious project, SPES (Selective Production of Exotic Species), which was conceived about fifteen years earlier.

What is SPES? What are its objectives?
Nuclear physics has one primary goal: to describe this correlated collection of neutrons and protons that we call nucleus. There are hundreds of nuclei and thousands of isotopes, since each nucleus can maintain a fixed

number of protons but vary in the number of neutrons, forming different configurations known as isotopes. To understand and describe these nuclei, we develop theories that aim to determine the mass of a nucleus and the lifetimes and internal structure of its isotopes. However, this is an incredibly challenging task that nuclear physicists have been grappling with for many decades without reaching a comprehensive solution. The difficulty arises from one of the four fundamental forces: the strong interaction. This force is responsible for binding protons and neutrons together. It is a central topic to hadron physics, and at the same time it plays a crucial role in nuclear physics, such as in the experiments conducted at ALICE (CERN) or at the Jefferson Lab, all with the shared goal of describing nuclei and isotopes. Why is achieving this understanding so important, though? Because it holds the key to unraveling how elements are created in the universe. It explains how, following the Big Bang, protons and neutrons formed and combined to give rise to the elements we observe today, such as carbon-12, a stable isotope. Why not carbon-11 or carbon-13? Because only the stable configuration "live" forever, the unstable ones decay over time depending on their intrinsic properties. Understanding the formation of elements, that are chemical elements, reveals much about our own existence. For example, carbon, which we are also made of, is created through the fusion of three helium nuclei (alpha particles) simultaneously. This process occurred early in the life cycles of stars, which is why we are often described as being made of "stardust." By uncovering how elements were created, we gain deeper insight into the universe's evolution and, ultimately, ourselves. With this goal in mind, SPES will produce unstable nuclei and study their properties to integrate them into theoretical models. The production of these unstable nuclei is accomplished through the use of radioactive ion beams, a method also employed in Japan, the US, Canada, France, Germany, and Finland. Before the 21st century, research in nuclear physics relied on using accelerated stable ions. However, it soon became evident that this method restricted access to the exotic and highly unstable nuclei formed in stars. As a result, researchers shifted their focus to production and usage of rare, unstable isotopes, that bring us closer to understanding the conditions present at the very first moments of the universe's creation.

The objectives are really challenging: which is the strategy that you, as Director, have worked out?

Let's take a step back to when I first came to Legnaro. SPES, but also other projects based on the same technology, were rather behind schedule, and for me the challenge was to develop a strategy to move efficiently and expeditiously towards the completion of SPES, while continuing to strengthen and upgrade the Laboratories, and to maximise their scientific production, both basic and applied, using the existing and new stable ion beams. INFN has always believed in SPES project and supported it excellently. Therefore, it was mainly a task of implementing work organisation and identifying and assigning personnel, drawing from within the laboratories, both scientific and technological expertise. To accomplish this, I implemented a very simple strategy, the same one you adopt when you go grocery shopping: you make a list before entering the supermarket, so as not to waste energy and to optimise time and money. In the same way, we have defined a list of steps in time with their detailed description, in order to reach the goal in a phased approach. Having a limited number of researchers and technical staff, we need them to follow a well-defined line of actions, along which they can move efficiently, without dispersion and in a timely manner. We cannot afford to have many groups advancing in parallel and in different parts of the project. We rather concentrated human resources to work and deliver the project phase by phase: once the first one is completed, everyone moves on to the second, and so on, until the fifth and final one. With this strategy phase 1 was completed in six months, and now also phase 2 is almost complete. Phase 2 was divided into two sub-phases, of which phase 2A, the "proof of concept", led to the achievement of the most important and challenging goal of the project: the first

radioactive ion beam produced by SPES. What we did was sending a proton beam on a silicon carbide target to trigger an interaction from which other particles than the incoming beam are originated, i.e. many different ions of various isotopes. From there, this secondary ion beam was extracted and transported to an experimental station set up outside the irradiation bunker, where the ions produced were measured and identified. Now, this whole system – the target, the transport and the identification – has been finalised, and we have already entered phase 2B, a phase in which we will transport this short-lived ion beam from a point close to the production target to very complex beamlines for future users. Phase 2 is scheduled for completion in March 2025, then we will proceed with phase 3, phase 4 and phase 5.

Is there a phase that concerns you more than the others?

Yes, phase 4, which is also the closest to my heart. It consists in the production of radioisotopes for medical purposes, more specifically for diagnosis and treatment of cancer, and it is the phase with the most immediate impact for society. The others, related to basic research, require scientists to join forces to prepare and perform a long series of experiments, whereas phase 4 could have tangible results in a short time. Presently, we don't have the necessary infrastructure yet and we are in the process of the design and procurement of the components, that will take some time to be completed. As well as it will take time to comply with the administrative paperwork for the issuing of licences and authorisations that are mandatory for this type of irradiation facilities. To produce isotopes that are useful for medicine, and more specifically for cancer diagnosis and therapy, we have to irradiate targets. These targets must then undergo many chemical processes to extract, from several other produced isotopes, only those useful for our purposes. We do not have, for the time being, the capability to process targets in house. So, what we would like to do is to supply the radiopharmaceutical companies with raw material, namely the targets irradiated at our SPES facility, with the aim of speeding up the research and therefore getting new procedures and treatments into the healthcare system.

Let's delve into these radioisotopes for medical purposes: how do they work?
The radioisotopes we are aiming to develop and supply to the medical sector are truly innovative, like for instance those called *theranostic* – from *tera* for therapy and *nostic* for diagnostics – which will be used for diagnostics and therapy at the same time. During phase 4 of the SPES project, we must therefore find, among all the isotopes we produce, those with theranostic potential, and then identify the best among them. Once we have identified those relevant for medical usage, either for diagnostics, or therapy, or both, we have to study how to produce them in the most efficient way (i.e. by obtaining the largest number of isotopes in the shortest time), and then transfer these radioisotopes to industry. But where do we start? From the unstable nuclei. These have many ways to decay: they can emit an alpha particle, a beta particle – which is an electron or positron (a positively charged electron) – and a gamma radiation. When they emit gammas or positrons, they can be used for medical diagnostics. How? Certainly not by injecting these radioisotopes into the body as they are, because they would spread everywhere, making it impossible to gather useful information. But if we manage to isolate them and give them to a molecular biologist, he or she could attach them to a molecule (generally called label or carrier) that will carry them to the desired organ inside the body. That way we ensure the radioisotopes target specific areas, where their decay and hence the emission of radiation occurs. Then, if the radioisotope decays by positron emission, a pair of gamma-rays of equal energy and opposed direction is produced by interaction of the emitted positron and electrons that are in the atoms of our body; and by identifying the exact locations where the two gamma rays are detected, one can create highly precise images

or PET (Positron Emission Tomography) scans of the region where the radioisotopes were in the body, and thus observe the areas with abnormal activity, which might indicate cancer. But if the isotope emits only gamma rays (and not positrons), the process is slightly more complex. In such cases, collimators put in different directions are used to deduce the direction, location and size of the region of the body where the radioisotopes were. So, this is how positrons and gammas are used for medical diagnostics. At the same time, some isotopes do not just emit positrons or gammas, they also emit alpha particles or low energy electrons, that are used for therapy. Alpha particles travel inside the body within a very short distance, meaning they can kill a targeted cancer cell without harming the surrounding healthy cells. Electrons travel farther and hence can kill both the targeted cancer cell and some healthy cells nearby. In both cases, the energy of the emitted radiation destroys cells, which makes them useful for cancer treatment.
To summarise, isotopes with these properties can perform both diagnostics (via positrons or gamma rays) and therapy (via alpha particles or electrons), as we said *theranostic*. Our role is to identify which ones have these characteristics, and to see how to produce them, how to separate them from other produced radioisotopes, and then, in collaboration with molecular biologists, how to transform them into radiopharmaceuticals by attaching them to the right molecule. At this stage, we move from radioisotopes to radiopharmaceuticals, which as such need to be taken by radiologists and practitioners for clinical trial and validation as such.

One final question: what is your wish for the future of the Laboratories and for you as Director?
My wish is to help completing SPES project, because the success of SPES will really breathe new life into the Laboratories. It will attract researchers from the rest of Italy and worldwide, and it will mark the beginning of a new exciting chapter. For me, as Director and as a nuclear physicist, it would be a great professional satisfaction to participate in this important achievement, and I will do everything necessary to see it through to completion at the earliest.