European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:251–252
https://doi.org/10.1007/s00259-022-06033-y

EDITORIAL

Stanford University from across the Atlantic Ocean: an Italian Medical Student research experience

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Published online: 11 November 2022

"Research is formalized curiosity. It is poking and prying with a purpose" (Zora Neale Hurston). Progression is what brings us forward, what allows humanity to evolve and grow. Research is at the core of progression; it is the key to innovation and ultimately aims to overcome current boundaries and set the new standards of tomorrow. The interplay between clinical practice and fundamental research has always been crucial in the medical field. Recent technological advances, namely, artificial intelligence, machine learning, data science, and many others, are becoming an integral part of current research studies and the scientific community will soon be governed by the aforementioned analytical systems. In this picture, a Medical Doctor lacking strong scientific training is destined to encounter substantial difficulties not only in practicing research, but also in keeping pace with a world that is continuously evolving.

I am an Italian Medical Student currently attending the 5th year at Humanitas University in Milan and, 2 years ago, I was selected on merit for the Virgilio Program—excellence in research track, an innovative pre-graduate opportunity open to medical students who are interested in deepening their understanding of research methods and exploring the link between basic sciences and clinical research. The Program enables students to plan research internships choosing among a wide plethora of laboratories, with the opportunity to be mentored by a senior scientist. My Mentor, Professor Arturo Chiti, has guided me in these past years through the world of research; first, allowing me to attend his Laboratory of Advanced Imaging Analysis at Humanitas University in Milan, and then giving me the opportunity, together with Professor Andrei Iagaru, to experience a 2-month internship in the USA. During August and September of 2022, in fact, I attended the Research Labs and the Nuclear Medicine Clinic at Stanford University. I had the chance to work in the Radiology and Molecular Imaging Program in Dr. Beinat Lab, which focuses on developing novel imaging and treatment strategies to detect and better manage cancer.

During my internship, I was able to train and learn different laboratory techniques thanks to the teachings of researchers working at Stanford, so that I could apply these skills to the current experiments of the laboratory.

One of the projects I worked on investigates the imaging of brain tumor metabolism and studies how different cells in the brain tumor microenvironment utilize glucose. The Beinat research team published an article in 2021 summarizing the results of a mouse imaging study investigating [^{18}F]DASA-23 to monitor pyruvate kinase M2–induced glycolytic reprogramming in glioblastoma [1]. Pyruvate kinase M2 (PKM2) is an isoform of pyruvate kinase; it is a key enzyme in glycolysis, catalyzing the final step of the cascade and being involved in embryogenesis, tissue repair, and cancer [2]. [^{18}F]DASA-23 is a radiotracer formulated by the Beinat Laboratory and it is a PKM2 activator from the *N*,*N*′-diarylsulfonamide class of ligands that is combined with its preliminary in vitro characterization [3]. In this study, 4×10^5 U87 (human glioblastoma cell line) cells were implanted in the right hemisphere of the brains of 6- to 8-week-old nude mice and, subsequently, small-animal PET imaging scans were completed after a bolus of intravenous injection of 8 ± 0.9 MBq [^{18}F]DASA-23. The scans allowed clear visualization of aberrantly expressed PKM2 within the brain tumors. Twenty-one days after tumor implantation, the brains were removed, homogenized, and stained with antibodies for flow cytometry analysis, which revealed that PKM2 expression was almost exclusively found in U87 GFP–positive cancer cells [1]. Currently, the research team is focusing on further studies investigating the use of [^{18}F]DASA-23 in brain imaging and, as a visiting scholar, I was able to take part in the animal studies by imaging

This article is part of the Topical Collection on Editorial.

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mice models injected with the radiotracer and subsequently extracting and analyzing their brains.

I actively contributed to another project that focuses on the type I transmembrane protein B7H3 (CD276). B7H3 is part of the B7 superfamily of immune checkpoint molecules [4] and is encoded by a gene in chromosome 15q24 in humans [5]. This protein has several roles in immunity, among which it may inhibit NK-cell activation and have a pro-inflammatory role leading to cytokine release from monocytes and macrophages, as well as being involved in T-cell activation. Moreover, B7-H3 appears to promote tumorigenesis mainly via immunologic mechanisms [5]. B7-H3 was found to be overexpressed among several types of cancers, including bladder, breast, cervical, colorectal, esophageal, kidney, liver, lung, ovarian, pancreatic, prostate, endometrial, gastric, intrahepatic cholangiocarcinoma, glioma, squamous cell carcinoma, and melanoma [6]. Being a key molecule involved in tumorigenesis, it has quickly become an attractive target for cancer immunotherapy and several strategies are being investigated as, for instance, B7H3 blocking with monoclonal antibodies (mAbs), mAbs mediating cellular cytotoxicity, bispecific antibodies, and radioimmunotherapy with B7H3-specific mAbs as carriers to selectively target radioisotopes to tumors. [7] My role in this project was to select, together with the Lab team, certain cell lineages from human cancer and investigate the expression of B7H3 through western blot and flow cytometry.

Working on these projects, I got to learn and master many experimental techniques including mammalian cell culture, protein quantification, western blotting, tissue extraction and digestion, cell staining, and analysis of cells using flow cytometry.

During my time at Stanford, I was also given the opportunity to shadow Doctors in the Nuclear Medicine Clinic and witness how state-of-the-art technology is incorporated into the daily practice of medicine. I was allowed in the reading room where I learned how to efficiently analyze imaging studies and in the radiopharmacy where I observed the techniques employed for the formulation of radiotracers.

Being in close contact with such brilliant minds has truly inspired me and has given me the motivation to keep learning and train in a broad and cross-disciplinary manner to set the path to become a successful physician-scientist. Eager to leave my mark on every commitment by bringing it to its full potential, I hope to be part of a new generation of Medical Doctors who understand the new challenges of research practice and possess the competencies to be an integral part of the scientific community.

Declarations

Conflict of interest The author declares no competing interests.

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