Commentary on "Radioactive Iodine: A Living History"

TO THE EDITOR: An article was recently published in *Thyroid* to commemorate the discovery and use of radioiodine for the management of patients with thyroid disease (*1*). Although "Radioactive Iodine: A Living History" is overall an excellent review, there are some errors of fact in the historical record that we would like to correct. The reason for these errors is unclear, as is the reason the editors of the journal did not feel the need to correct them or provide an erratum. When selling great art, it is important to know the provenance of that art. Ideally, you want a paper trail from the artist to the present owner. In medicine, that provenance is normally provided by a series of published papers available on search engines such as PubMed. However, the attestation of a particular idea may not be fully provided in scientific papers alone. Thus, to identify the provenance of radioiodine and ensure the correct attestation of ideas, it may be necessary to look at sources other than just published papers. We now have access to primary-source verification. In the case of the discovery and development of radioiodine in thyroid disease by Saul Hertz, one must look at Hertz's correspondence with other important players, such as Karl Compton, James Means, and the Markle Foundation. Fortunately, Hertz's daughter has already done much of this work, which was published in an article in the *World Journal of Nuclear Medicine* (*2*). However, when the primary-source data are consulted, it is evident that the article contains several factual errors, particularly in the attestation of the genesis and implementation of the use of radioiodine. In this letter, we aim to identify and correct these errors.

The first use of ^{131}I to treat hyperthyroidism (Graves disease) was on March 31, 1941, not in January 1941. In honor of this first radioiodine therapy, we now celebrate Saul Hertz World Theranostics Day on March 31 (*2*).

On Nov. 12, 1936, Karl Compton, president of the Massachusetts Institute of Technology, presented a guest lecture entitled, "What Physics Can Do for Biology and Medicine," as part of a weekly luncheon lecture series at the Massachusetts General Hospital. At the end of the lecture, Saul Hertz solely conceived and spontaneously asked the seminal question "Could iodine be made radioactive artificially?" Compton was uncertain and said he would look into it. He wrote to Hertz on December 15, 1936, apologizing for the delayed response and replying that "Iodine can be made artificially radioactive." In fact, Enrico Fermi had produced ^{128}I in 1934. Letters between Hertz and Compton make it clear that the idea of using radioactive isotopes to study metabolism came from Hertz (*2–5*). The fact that it was solely Hertz who conceived and asked the question was confirmed by James Means, chief of medicine at the Massachusetts General Hospital, in a letter to the Markle Foundation (Fig. 3 in (*3*)) in which he stated " … when it became apparent that there might be radioactive isotopes of iodine, it at once occurred to Hertz that we might make use of them to solve a problem we were already working on."

The summary at the beginning of the article in *Thyroid* states, "In 1936, Karl Compton … in a lecture attended by Massachusetts General Hospital physicians, suggested that artificially radioactive isotopes might be useful for studying metabolism." (*1*). On page 2, it is stated that Robley Evans suggested discussing "artificially radioactive isotopes" and their potential for studying metabolism. We think it highly unlikely that either Evans or Compton, who were physicists, made that suggestion. This idea actually was conceived by Hertz.

The *Thyroid* article erroneously states, "Hertz and Evans demonstrated uptake of iodine in rabbit thyroids … " (*1*). However, the evidence supports that it was Hertz and Roberts who demonstrated uptake of iodine in rabbit thyroids (*4*,*5*). Actually, Evans, who was chief of medical physics at the Massachusetts Institute of Technology, never participated in any of the studies, according to a letter by Arthur Roberts to John Stanbury in 1991 (*6*). However, Evans demanded credit (i.e., as a coauthor) because of his supervisory position.

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[^{18}F]FDG and Lymphomas: Still a Winning Golden Couple in the Era of FAPI-Based Radiotracers

TO THE EDITOR: We were greatly intrigued by the article titled "Fibroblast Activation Protein and Glycolysis in Lymphoma Diagnosis: Comparison of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT" by Chen et al. in *The Journal of Nuclear Medicine* (*1*). This article highlights the distinctive and well-established role of [^{18}F]FDG PET/CT in the management of lymphoma patients for determining disease extent, prognosis, and treatment response as exemplified by the Deauville score. In lymphoma patients, the superiority of [^{18}F]FDG over fibroblast activation protein inhibitor (FAPI)–based tracers, a new class of radiopharmaceuticals that have otherwise shown higher diagnostic performance than [^{18}F]FDG in various oncologic settings (*2*), raises important questions.

The paper's results are thought-provoking, particularly considering the crucial role of the tumor microenvironment in lymphoma survival and growth (*3*). Notably, there has already been significant uptake of FAPI-based agents targeting the tumor microenvironment in lymphoma (*4*). In the study by Chen et al. (*1*), immunohistochemistry analysis revealed significantly lower fibroblast activation protein expression cell densities than hexokinase 2 and glucose transporter 1 in most lymphoma subtypes ($P < 0.001$).

Although [^{18}F]FDG PET/CT plays a pivotal role in lymphoma management, a gray zone exists in which its diagnostic performance declines, notably in cases of indolent lymphomas or those with low [^{18}F]FDG avidity. It is intriguing to explore whether a FAPI-based radiotracer could complement or serve as an alternative to [^{18}F]FDG for these specific lymphoma subtypes. However, Chen et al. (*1*) did not thoroughly address this aspect, mainly because of the limited number of patients with indolent or low-avidity lymphomas. Additionally, their patient population is highly heterogeneous, encompassing various histopathologic patterns and clinical settings for the examinations. To address this limitation, a prospective study with a homogeneous group of patients and a well-defined study design would be desirable.

Another crucial consideration is the evolving landscape of lymphoma treatment. The current standard of care is chemoimmunotherapy, with salvage high-dose chemotherapy and autologous stem cell transplantation serving as the second-line treatments for patients with relapsed or refractory lymphomas (*5*). However, only a few patients achieve a cure with this intensive approach, and its applicability is restricted by comorbidities and advanced age (*6*). Recent advancements in immunotherapy involve CD19 chimeric antigen receptor T cells, which are autologous T cells genetically reengineered and approved for the treatment of relapsed or refractory aggressive B-cell lymphomas (*7*). Nonetheless, despite the high efficacy of chimeric antigen receptor T-cell therapy, a significant number of patients do not respond or experience relapses (*8*). In this context, FAPI-based radiotracers could be explored in a theranostic context, addressing the molecular target with appropriately radiolabeled agents, similar to current practices in the treatment of neuroendocrine tumors and prostate cancer. However, the role of the FAPI agent in refractory lymphoma patients still remains unexplored.

In conclusion, there is still much to discover regarding the role of FAPI-based radiotracers in hematology. We eagerly await the availability of commercially accessible radiopharmaceuticals to explore the advantages and potential limitations of this class of agents in various clinical settings, laying the foundation for innovative cancer monitoring strategies.

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REPLY: We thank Dr. Guglielmo and Dr. Evangelista for the great summary and thoughtful comments regarding our paper (*1*). We agree that there is still much to discover regarding the role of fibroblast activation protein (FAP) inhibitor (FAPI)–based radiotracers in hematology—for example, the relationship between FAPI avidity and prognosis and the correlation of heterogeneous and relapsed or refractory lymphomas.

Several recent studies have revealed the distribution of fibrosis in nodular sclerosis Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma (*2–4*). We accidentally found that primary gastric lymphoma could accumulate ^{68}Ga-labeled FAPI, which highlighted that ^{68}Ga-FAPI is not cancer-specific (*5*). Most aggressive lymphomas were FAPI-avid, whereas indolent non-Hodgkin lymphoma lesions showed weak FAP staining and mild to moderate ^{68}Ga-FAPI uptake (*6*). These results are partially consistent with the result of Tataroglu et al., which provided quantitative information about the amount of fibrosis in lymphoma lesions (*2*). The focus is now to determine which is the superior method, ^{68}Ga-FAPI PET/CT or ^{18}F-labeled FDG PET/CT in indolent lymphoma. Compared with FAP expression in stromal cells, glycolytic markers with high cell density were overexpressed in tumors and the tumor microenvironment, resulting in higher rates of detecting lymphoma lesions. However, our result was not very convincing because of the limited number and heterogeneity of patient population, especially the indolent type.

The ability to detect fibrosis before and after treatment with ^{68}Ga-FAPI PET/CT could be the basis for planning prospective studies compared with treatment with ^{18}F-FDG PET/CT. A prospective study showed that the presence of tumor sclerosis was significantly associated with poor overall survival of patients with advanced-stage nodal follicular lymphoma (*7*). As Dr. Guglielmo and Dr. Evangelista suggested, a large-scale, well-defined, prospective study should be designed in a homogeneous group to explore the potential role of ^{68}Ga-FAPI PET/CT and the relationship between PET performance, heterogeneity, and prognostic value before and after treatment.

Malignancy theranostics is a novel approach that combines diagnostic imaging and radionuclide therapy. Only a few proof-of-concept studies have been published for FAP-targeted radioligand therapies, radiolabeled with ^{131}I, ^{90}Y, and ^{177}Lu, which showed mixed responses (*8–10*). It is valuable to explore the role of FAP-targeted radionuclide therapy in refractory lymphoma patients, especially in aggressive lymphomas. Also, combination therapies of FAP-targeted radionuclide therapy and immunotherapy could be explored in relapsed or refractory aggressive non-Hodgkin lymphoma.