European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:942–946
https://doi.org/10.1007/s00259-023-06570-0

EDITORIAL

Theragnostic: radiopharmaceuticals and nuclear medicine as viewed through Hegel's eyes

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Published online: 20 December 2023

> "The true is the whole. But the whole is only the essence which is fulfilled through its development." Georg Wilhelm Friedrich Hegel, The Phenomenology of Spirit

Nuclear medicine, particularly positron emission tomography (PET), was born with an intrinsic "diversity" compared to traditional imaging methods. This diversity lies in the ability to observe function versus morphology, functional, metabolic, or receptorial imaging versus two-dimensional morphological imaging. Philosophically speaking, one could call it a decidedly "phenomenological" imaging (φαινόμενον, phainómenon, that which appears and λόγος, logos, study) which goes directly, molecularly, to what is functionally manifested. Inherent in it is the Husserlian concept of "intentionality."

The different branches of nuclear medicine have in common a truly original aspect, which characterizes it peculiarly: the use of molecules labelled with radioactive nuclides, the radiopharmaceuticals.

And it is precisely this beating heart, the radiopharmaceuticals, that has driven the development of Nuclear Medicine, particularly in diagnostics. But the "seed" of the therapeutic use of radiopharmaceuticals has been emerging since the 1950s when iodine-131 ([^{131}I]NaI) was the first radiopharmaceutical to be approved by the FDA (1951) and marketed by Abbot in 1953 for the diagnosis and therapy of thyroid pathology [1, 2].

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As written in a recent Editorial [3], we can consider radiopharmaceutical a "structured whole." The concept of "whole" referred to a radiopharmaceutical, even more to a modality that could combine within itself the diagnostic (διαγιγνώσκω, to recognize through) and the therapeutic capacity (θεραπευτικός, capable of curing) is an inherently revolutionary concept.

It does not exist in medicine, and the definition itself of "Medicinal Product" according to Directive 2001/83/EC:

1. Any substance or combination of substances that may be used in or administered to human beings with a view to either restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action, or to making a medical diagnosis;

distinguishes between therapeutic or diagnostic functions.

PET "explodes" with a radiopharmaceutical, [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), which has changed the world of medicine, becoming a reference method in cancer diagnosis and staging. It is indeed the progenitor of metabolic radiopharmaceuticals, those molecules that are the same or at least similar to "natural" molecules that enter the metabolism of the healthy subject or cancer patient. All the metabolic radiopharmaceuticals developed later on in oncology will have a predominantly diagnostic role.

But probably the greatness of [^{18}F]FDG lies in the relative "unspecificity" of its mechanism of action, i.e., in being a marker for the tissue uptake of glucose, which in turn is closely correlated with certain types of tissue metabolism. A ubiquitous mechanism and a radiopharmaceutical that can be a marker for most cancers: the concept of "whole" is already, to some extent, expressed.

In practice, this has not been the case, and the extensive development of radiopharmaceuticals for prostate cancer, where [^{18}F]FDG usually does not provide acceptable results, is an outstanding example.

Therefore, the search for new metabolic radiopharmaceuticals for the diagnosis and staging of tumors has turned to other, more specific metabolic patterns. Hence, radiopharmaceuticals of amino acidic metabolism, lipid metabolism, and cell proliferation, in a race towards "multiplicity," which, however, has yielded positive results: [^{11}C]choline and [^{18}F]-fluorocholine in the diagnosis and staging of prostate carcinoma are mentioned as examples.

However, [^{18}F]FDG still plays the role of the main radiopharmaceutical in PET diagnostics, accounting for about 80% of all patients studied.

So, why refer to the concept of the "one," of the "whole" as "truth"? This concept has dominated the whole of philosophical thought, from the Greeks, Pythagoras, Parmenides, and Plato, to the Renaissance, whose philosophy is permeated by the tension towards the One, in search of a unitary, organic, coherent knowledge that acts as a link between all the human knowledge and is able to bring multiplicity into unity, diversity into identity.

The search for the philosopher's stone is an example of this. We do not want to push the philosophical delirium as far as comparing today's radiochemists or radiopharmacists to alchemists; we would like to emphasize how the relationship between science and philosophy is always vivid.

Spinoza (1632–1677), aiming to recompose Cartesian dualism between *res cogitans* and *res extensa*, posits a single substance, God, as the foundation of his philosophical system. 'Deus sive Natura', the view that God and nature are mutually interchangeable, or that there is no distinction between the creator and the creation. According to Spinoza, it is absurd to postulate two substances as Descartes did: everything in nature originates from a single and infinite principle, namely God.

But this argument is still far from our interest in the One, the "whole," because, until the seventeenth century, the "Whole" was considered the origin of everything and perceived in this sense, while our interest lies in the concept of the "whole" as the point of arrival, the opposite of the origin, "the essence fulfilled through its development."

Georg Wilhelm Friedrich Hegel (1770–1831) messed up the cards to build a new philosophical system. With Hegel there is a reversal of the Neo-Platonic conception of the "whole," conceived no longer as origin but as an endpoint at the end of the philosophical dialectical path from multiplicity to unity. Here we recognize ourselves, in the thought that, through successive steps, eventually leads to a synthesis.

After Hegelian thought, a leading school of psychology that emerged in the early decades of the twentieth century in Austria and in Germany, the Gestalt, emphasized that organisms perceive entire patterns or configurations, not merely individual components. The view is sometimes summarized using the adage, "the whole is more than the sum of its parts"; every perception presents itself to experience as a whole, as a definitive structure having its form and not as a juxtaposition of elementary units.

The history of radiopharmaceuticals has evolved along a seemingly random line of thought, following various "novelties" from the radiochemical world, but primarily by the "motionless engine" driving their development: to address unmet clinical needs in oncology.

The breakthrough of gallium-68, a positron emitter radionuclide obtained by a generator, has led to a new concept of radioligands in oncology. Instead of the tendency to identify specific radioligands for peculiar metabolic patterns, a shift in the "vision": from metabolic to receptorial radiopharmaceuticals, specific for tumor-expressed receptors. The design of a PET radioligand that should bind a metal using a bifunctional chelator has resulted in an original molecular architecture: no longer a "pseudo-natural" molecule, but a structure consisting of a biological effector (receptor agonist or antagonist), a linker/spacer that enables it to link to a chelator that coordinates the metal. It was precisely this structure that allowed the optimization of the performance of the radioligand in terms of affinity, internalization, kinetic inertness, and thermodynamic stability.

We are now at the turning point of "unifying" thought to the possibility of extending the architectural structure of the radioligand beyond gallium-68 toward the use of the so-called "trivalent ions" yttrium-90, lutetium-177, beta-emitters, or actinium-225, an alpha-emitter, for radioligand therapy (RLT). As reported by Duatti [4], the terminology "trivalent ion," widely used to refer to a cation with a net charge + 3, is not consistent with the standard definition of "valence" [5] anyway it is extensively used in the radiopharmaceutical community.

The development of ^{68} Ga-somatostatin analogues represents the gold standard imaging modality for neuroendocrine tumors (NET), replacing almost completely ^{111}In-derivatives [6]. And the theragnostic pairs ^{90}Y-octreotide ([^{90}Y]Y-DOTA-Tyr^3-octreotide) and ^{177}Lu-octreotate ([^{177}Lu]Lu-DOTA-Tyr^{3}Thr^8-octreotide) are widely used as theragnostic radiopharmaceuticals [7].

The clinical introduction of a new class of small-molecule prostate-specific membrane antigen (PSMA) inhibitor radiopharmaceuticals, just 40 years after the clinical introduction of [^{18}F]FDG, represented the dawn of a new era in nuclear medicine. These ligands play a pivotal role in the diagnosis, staging, and therapy of prostate cancer. Kopka et al. [8] reported on the importance of what we have learned during the development of this new class of radiopharmaceuticals.

Developments in theragnostic pairs of radionuclide production represent an important step to "unifying thought." To reach the goal of theragnostic, new radionuclides with optimum decay characteristics and chemical properties are essential.

Six pairs of radionuclides have been considered, each consisting of a positron emitter and a β^- emitter, namely $^{44}Sc/^{47}Sc$, $^{64}Cu/^{67}Cu$, $^{83}Sr/^{89}Sr$, $^{86}Y/^{90}Y$, $^{124}I/^{131}I$, and ^{152} Tb/^{161} Tb.

Theragnostic pairs give the opportunity to measure uptake kinetics via PET imaging, allowing an accurate dosimetric calculation leading to a correct quantification of therapy.

The clinical introduction of molecular theragnostic pair is rapidly changing the approach to some oncological conditions, introducing the simple concept of "see what you treat and treat what you see," i.e., making it possible to image tumor cells and target the same cells with the same cytotoxic (highly energetic, radioactive) compound, sparing healthy surrounding tissues.

However, it is worth reminding that biological mechanisms are always much more complex than a schematic, theoretical reconstruction of the "truth." Clinical applications need a pragmatic-practical and simple approach. The theoretical concept on which theragnostic relies has been proven effective in the "battlefield" of clinical applications, especially prostate cancer and neuroendocrine neoplasia.

This pragmatistic approach includes the concept of "truth" as a projection of an application in the future, not because it is comparable with past experiences. The future that theragnostics, as a "whole," carries within itself. Hence, the connection from a theoretical to a pragmatic, projectual aspect.

A relevant step forward which opened the way to a theragnostic approach was the possibility to precisely image and quantify in vivo and non-invasively with PET the presence of antigen expression in the whole body. This opportunity made available so many information regarding the "whole" disease (and not only bioptic or partial surgical specimens) based on the presence and the quantification of the expression of one antigen. For the first time, much information has been made available for clinicians, diagnostic, prognostic, and predictive information regarding the response to a specific treatment. Finally and more importantly the use of that specific antigen as a target for a directed therapy. This last opportunity opened the way to the theragnostic approach: labelling high energy emitters to already in-use diagnostic molecules targeting antigens overexpressed in oncological tissues.

The results achieved by extensive clinical applications of this theragnostic approach are evidenced by two large randomized clinical trials in NET, NETTER [9], and NETTER 1[10]. For prostate cancer, randomized trials, like the VISION trial [11], led to the approval of PSMA radioligand therapy by the leading regulatory boards like the FDA in March 2022, followed by EMA in October 2022 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer, https://www.ema.europa.eu/en/medicines/human/EPAR/pluvicto).

Diagnostics and therapy have reached "the whole," theragnostics, and the name itself aims to emphasize, even etymologically, this concept. The synthesis, "the whole," came after walking a long path; it was not the origin anymore, but only "the essence fulfilled through its development," the outcome of the development.

A further conceptual step tending towards the search for the "whole," towards radiopharmaceuticals that could overcome the limits of the [^{18}F]FDG, was the discovery of fibroblast activation protein inhibitor (FAPI). This breakthrough required a "Copernican revolution": from targeting tumor cells to targeting the tumor stroma or the tumor microenvironment; with some imagination, we can extend this concept to "from the individual to the universal."

Cancers develop in complex environments composed of tumor cells and the surrounding stroma; however, diagnostic and therapeutic paradigms have predominantly targeted only tumor cells. In recent years, the tumor microenvironment has gained growing attention in the context of universal diagnostic and therapeutic strategies in oncology [12, 13].

The tumor microenvironment appears to provide mechanical and nutritional support to malignant cells and to be involved in tumor progression, invasion, metastasis, immunosurveillance, and drug resistance [13, 14]. Cancer-associated fibroblasts (CAFs) represent the widest sub-population in the tumor microenvironment with increased expression of peculiar markers, among them fibroblast activation protein (FAP). FAP can degrade proteins of the extracellular matrix (ECM) and promote matrix remodelling. CAFs are present in numerous tumors, especially in cancers with strong desmoplastic reactions; consequently, FAP expression is present in more than 90% of epithelial tumors.

Gallium-68 enzyme inhibitors of FAP with optimal characteristics in terms of affinity and internalization have been proposed [15], along with molecules with a marked improvement in tumor-to-background ratios (TBR) and higher image contrast [16]. An overview of several studies reveals superior performance for FAPI PET if compared with FDG, especially in desmoplastic tumors [17, 18].

As a pan-cancer target with an excellent TBR, FAP is considered an attractive target for radionuclide therapy; at the same time, the presence of macrocyclic chelators allows the labelling of FAPI inhibitors with therapeutic radionuclides. The initial theragnostic application of FAPI radiopharmaceuticals was with [^{90}Y]FAPI-04 [15]. Although more evidence is needed, FAPI inhibitors are a hot topic. Several results in labelling these ligands with yttrium-90, lutetium-177, samarium-153, and actinium-225 suggest a potential of FAP tracers for a future theragnostic application [19].

Probably, we are only scratching the surface of the potential of theragnostic; the lesson from theragnostic in neuroendocrine tumors and prostate cancer shows that we are on the right track. The seeds of wholeness are in radiopharmaceuticals that are increasingly on the way to identifying more universal structures and targets.

The success story of theragnostic agents originates in academic nuclear medicine. We should protect the academic development of theragnostic agents and radiopharmacies of the nuclear medicine departments. We should enable patient care at sustainable prices as well. The educational landscape should also aim at the "whole," providing appropriate training "that encompass diagnostic and therapeutic nuclear medicine procedures, patient management, appropriate use of diagnostic and therapeutic procedures and interventions, and also research and the regulatory principles of drug development" [20]. This concept is also supported by recent surveys [21, 22].

Thus, we would like to believe that Hegel would have viewed the theragnostic as a whole, encompassing within itself a meaning of "true." The truth is only the whole, the parts are only abstractions of the whole. The various sciences cannot consider the whole since they are abstractions, part of the whole. The conclusive point is the science, the philosophy, which contains within itself the totality of the whole. And it is precisely a philosophical approach that has enabled us to consider theragnostics as a whole.

After the enormous and complex philosophical system of Hegel, defined by some of his interpreters as "the last philosopher," the so-called "negative thought" was triggered. Theodor Adorno overturns Hegelian thought, affirming that the whole is false, the sharpest controversy between contemporary and Hegelian thought.

Contemporary philosophy, following the tragic historical events represented by the dictatorships and totalitarianism of both the nazi-fascist and communist kind, has become somewhat allergic to Hegelian concept and has kept its distance, preferring to define itself as "weak thought" or putting itself in a subordinate position in comparison to other disciplines. Postmodernism has declared the end of ideologies such as the Enlightenment, Idealism, and Marxism, that more crucial than sterile striving towards objectivity is the concept of solidarity and has condemned truth and knowledge as a form of power and violence. There are no facts, only interpretations, wrote Nietzsche at the height of the nihilist season. However, this choice may appear as a definitive abdication of philosophy from its historical duty 2500 years after its birth.

Declarations

Ethics approval Institutional Review Board approval was not required because the paper is an Editorial.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

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