

Not All Gatekeepers Are Theranostics

TO THE EDITOR: Sometimes we need to challenge the views of colleagues and friends, especially when their thinking has the effect of muddying the waters rather than providing greater insight and clarity. I believe this to be the case with the opinion piece by Weber et al. in the May 2023 issue of the journal (1).

The authors seek to redefine the term *theranostic*. They assert that this is any molecular imaging probe that provides actionable information for any subsequent therapeutic. This includes medical therapies, radiation therapy, surgery, or cell therapies.

I believe that, in doing so, they are losing the very essence of what a theranostic is.

I agree with the authors that the therapeutic component of a theranostic pair need not be a radionuclide therapy, but I contend that it must be the same (or a very similar) molecule or moiety. It could be carrying a toxic therapeutic or it may be an antibody that targets a protein (e.g., amyloid in the brain), but it has to be the same targeting moiety.

What the authors of this article are referring to as a theranostic imaging probe when used with a range of other therapies is more accurately described by the term *gatekeeper* or *companion diagnostic*. The imaging study validates the use of a certain therapeutic approach: this is not theranostics but simply a good use of medical imaging. The authors surely would not contend that a ventilation–perfusion lung scan demonstrating a pulmonary embolism that was subsequently treated with anticoagulation was a theranostic approach.

Definitions are important and help us to describe and conceptualize the strategy chosen to diagnose and treat diseases. Seeking to dilute the definition of a theranostic in the way the authors have done will have the effect of confusing the basis of the concept and will be unhelpful. The theranostic approach is an extremely powerful one and should be a major focus of future developments in molecular imaging and therapy. We need to keep the concepts clear and appreciate the differences between gatekeeper and theranostic approaches. They are both very important, but they are not the same. Not all gatekeepers are theranostics.

REFERENCE

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REPLY: We very much would like to thank Dr. Bailey for his valuable comments, which give us the opportunity to further explain our definition of theranostics.

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Dr. Bailey writes that a meaningful definition of theranostics requires that the targeting moiety be the same or very similar for the imaging agent and the therapeutic agent. We are not sure if this is a reasonable requirement. For example, amyloid imaging agents are small molecules, whereas the therapeutics are full-size antibodies. Nevertheless, the identical molecular target is addressed, and the use of amyloid PET imaging to select patients for amyloid antibody therapy seems to be a perfect example of a theranostic approach. Conversely, minor chemical changes in a peptide can fundamentally alter its binding affinities. For example, somatostatin receptor antagonists are highly sensitive to N-terminal modifications of the peptide chain. As a consequence, the somatostatin receptor antagonist DOTA-JR11 has a more than 10-fold lower binding affinity when labeled with ^{68}Ga than when labeled with ^{177}Lu (1). Consequently, the combination of ^{68}Ga -DOTA-JR11/ ^{177}Lu -DOTA-JR11 is not an ideal theranostic pair (2). A better companion diagnostic for ^{177}Lu -DOTA-JR11 is ^{68}Ga -NODAGA-JR11, that is, a compound that is chemically less similar to ^{177}Lu -DOTA-JR11 than is ^{68}Ga -DOTA-JR11 (3).

Because similar molecules may be poor theranostic pairs and very different molecules may be excellent theranostic pairs, we do not think that the definition of theranostic agents should require that the imaging agent and the therapeutic agent be identical or very similar. A better definition may be that the imaging agent and the diagnostic agent have an identical target.

One can have different opinions on the question of whether the definition of theranostic imaging should be made even wider. We have argued in our article that the definition should be broad, especially for the development of new imaging agents. Imaging agents that are companion diagnostics for a specific therapy have a clear path for regulatory approval and reimbursement because they have an obvious impact on patient management. Whether one should use the term *theranostic* or *companion diagnostic* for this use of imaging can be debated. We would prefer *theranostic* because the term *companion diagnostic* is already broadly used for blood- or tissue-based biomarkers.

However, we would caution on use of the term *gatekeeper* to refer to theranostics or companion diagnostics. In fact, we believe that a theranostic imaging agent is the opposite of a gatekeeper—which limits therapeutic options—but rather is a facilitator that creates new opportunities to treat patients. In other words, no theranostic is a gatekeeper. We of course realize that this is often a matter of perspective: a theranostic agent that images the expression of a target for radiopharmaceutical therapy can be seen as a test that facilitates this therapy or as a gatekeeper that prevents an ineffective therapy in a patient who does not express the target. However, in other instances theranostic imaging clearly enables new therapies, for example, by detecting the site of recurrence in a patient with an elevated tumor marker. Therefore, we believe that theranostic imaging should be viewed as a facilitator, not a gatekeeper.

In conclusion, we appreciate the opportunity to further clarify our definition of theranostics and would maintain that theranostics is “a combination of imaging and therapy in which imaging provides actionable information that enables new or more effective therapies.” (4)

REFERENCES

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