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.

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Published online Jun. 29, 2023.
DOI: 10.2967/jnumed.123.266006

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.

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*)

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Published online Jun. 29, 2023.
DOI: 10.2967/jnumed.123.266028

Potential of ^{188}Re as an Alternative to ^{177}Lu and Dosimetric Consequences

TO THE EDITOR: We read with interest the article "PSMA-GCK01: A Generator-Based ^{99m}Tc/^{188}Re Theranostic Ligand for the Prostate-Specific Membrane Antigen" in *The Journal of Nuclear Medicine* (*1*). It is noteworthy that kidney accumulation of ^{188}Re-PSMA-GCK01 in LNCaP tumor–bearing mice was found to be 14 times higher than tumor uptake 1 h after injection and 9 times higher 2 h after injection (*1*).

It is worthwhile to investigate ^{188}Re as an alternative to ^{177}Lu, because accredited ^{177}Lu radiopharmaceuticals are available and the amount of ^{177}Lu is limited. Further alternatives such as ^{161}Tb (*2*) or ^{67}Cu (*3*) are moving into the focus of clinical research and could have even better therapeutic properties because of the coemission of Auger–Meitner electrons.

However, the kidney geometry in small animals is not representative for humans regarding geometry and pathlengths of the β-emission. Recently, Vargas et al. presented a method to understand the heterogeneity of absorbed doses in the kidneys of mice (*4*). In humans, the heterogeneity of absorbed doses in, for example, kidneys is crucial for the application of therapeutic radiopharmaceuticals (*5*). Hence, studies in pigs (single kidney weight, 125 g for pig vs. 150 g for human) may be required. Further, most patients currently receive radionuclide therapy as the last line of treatment after previous hormone and chemotherapy, so that bone marrow and kidney function may already be predamaged. This effect, too, can neither be simulated nor reproduced in animal experiments but requires clinical testing.

In our own efforts on ^{188}Re-PSMA derivatives, we found that biokinetics must be considered in terms of the physical half-life of the applied isotopes: at 17 h (^{188}Re) versus 6.6 d (^{177}Lu), the initial phase is more significant for ^{188}Re, and this is the phase with the greatest renal accumulation or excretion. Dosimetric calculations for ^{177}Lu-PSMA by Kurth et al. revealed kidney doses between 2.9 and 3.7 Gy, depending on the therapeutic cycle (*6*). On the basis of the effective half-lives for the kidneys that were reported, we calculated the biologic half-life for PSMA in the kidneys. We identified the expected effective half-life for ^{188}Re-PSMA by assuming a biodistribution identical to that for ^{177}Lu-PSMA and using the physical half-life for ^{188}Re. The calculated number of ^{188}Re decay in the kidneys was found to be approximately 66% lower than that of ^{177}Lu-PSMA decay. Nevertheless, the S value, S(kidney←kidney), for ^{188}Re is 5 times higher than that for ^{177}Lu. This means that the dose to the kidney is expected to be 1.7 times higher when using the same activity for ^{188}Re-PSMA as for ^{177}Lu-PSMA. The dose would be even higher when the initial kidney biokinetic is considered more accurately by assuming a linear accumulation within the first 2 h (*6*).

Furthermore, radiation biology must be considered, as higher activity levels must be used to achieve the same dose because of the shorter half-life of ^{188}Re. The authors used the same activity of ^{188}Re-PSMA and ^{177}Lu-PSMA (3.7 GBq) (*1*). Assuming an identical tumor uptake in a lesion with a mass of 10 g, the absorbed dose of ^{188}Re will be only 51% of the absorbed dose of ^{177}Lu. Hence, in therapeutic applications, the activity of ^{188}Re must be twice the activity of ^{177}Lu to achieve the same tumor dose. Furthermore, the various effective half-lives must be considered with respect to cellular repair mechanisms. The biologically effective dose is expected to be about 25% higher from ^{188}Re than from ^{177}Lu for equal absorbed doses. In conclusion, it is necessary to consider the dosimetric consequences carefully when replacing ^{177}Lu with ^{188}Re as mentioned above.

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Published online Aug. 3, 2023.
DOI: 10.2967/jnumed.123.265782

REPLY: In our recent publication about the preclinical development and clinical translation of ^{99m}Tc- and ^{188}Re-PSMA-GCK01, we consciously withheld the presentation of dosimetry estimates, despite having serial planar images of patients available (*1*). One reason is the