

# What Is Theranostics?

Wolfgang A. Weber<sup>1</sup>, Henryk Barthel<sup>2</sup>, Frank Bengel<sup>3</sup>, Matthias Eiber<sup>1</sup>, Ken Herrmann<sup>4</sup>, and Michael Schäfers<sup>5</sup>

<sup>1</sup>Technical University of Munich, Munich, Germany; <sup>2</sup>Leipzig University, Leipzig, German; <sup>3</sup>Hannover Medical School, Hannover, Germany; <sup>4</sup>Universitätsklinikum Essen, Essen, Germany; and <sup>5</sup>University of Munster, Munster, Germany

The term *theranostics* has clearly become a buzzword. To a large extent, this is due to the success of prostate-specific membrane antigen (PSMA)-targeted radioligands. These ligands can be labeled with positron- or  $\gamma$ -emitting isotopes for imaging or with  $\beta$ - or  $\alpha$ -emitting isotopes for therapy. The diagnostic or therapeutic targeting ligands are otherwise identical or similar. PSMA-targeted imaging and therapy have rapidly become a new clinical standard for prostate cancer management during the last 10 y, and applications in other diseases are being investigated. Sessions at nuclear medicine meetings are now often separated between PSMA imaging and non-PSMA imaging, and several PSMA radioligands have been approved for imaging and therapy of prostate cancer or are in late-stage development. In the wake of these clinical successes, an impressive number of new biotech companies have been founded that aim to develop new theranostic agents.

But what exactly has made PSMA theranostics so successful? In this editorial, we try to answer this question and reflect on what may be necessary to repeat the success of PSMA theranostics in other areas of nuclear medicine. In doing so, we argue that the concept of theranostics should not be limited to oncology but may be equally or even more successful for nuclear medicine applications in neurology, cardiology, and inflammatory and infectious diseases.

As a starting point, we define theranostics as a combination of molecularly targeted imaging and therapy in which imaging provides actionable information that enables new or more effective therapies. This definition is much broader than the commonly used definition of theranostics as a combination of radionuclide imaging therapy that uses the same (a similar) targeting molecule or as a combination of imaging and therapy that both use the same molecular target, as exemplified by PSMA-based theranostics (1). Nevertheless, we believe it is still specific enough to differentiate theranostics from other common uses of medical imaging.

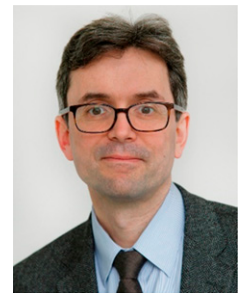
Most oncologic imaging for tumor staging in fact does not meet our definition of theranostic imaging. These imaging studies stratify patient populations better but do not improve outcomes, because they merely shift patients from one prognostic group to another. This stage migration was described by Feinstein et al. in 1985 (2) and called the Will Rogers phenomenon in honor of the humorist-philosopher Will Rogers. Will Rogers, who was born in Oklahoma in 1879, supposedly once said that “When the Okies left Oklahoma and moved to California, they raised the average intelligence levels in both states.” Will Rogers was referring to the exodus of the Okies to California during the Great Depression in the 1930s. Feinstein et al. observed

that new imaging technologies, at that time CT and bone scans, shifted many patients with lung cancer to a higher TNM stage because these new technologies found more metastases than clinical examination and planar radiographs. The outcome of the patients who were shifted to a higher stage was better than that of patients in the same stage as defined by the older imaging technologies. This led to an improved outcome in each of the stage groups without changing the outcome of the whole patient group. Similar effects of new imaging technology on stage-specific patient outcomes have been reported for many other cancer types and other diseases.

Although oncologic CT and <sup>18</sup>F-FDG PET/CT mostly upstage patients and thereby only limit therapeutic options (3), the results of PSMA PET/CT can lead to new therapeutic options. This is most obvious in patients with metastatic castration-resistant prostate cancer. In this setting, high PSMA radioligand uptake indicates that PSMA radioligand therapy is a therapeutic option. However, PSMA PET scans can also provide actionable information in another setting. PSMA PET is highly specific for the detection of lymph node metastases of prostate cancer and can detect metastases much earlier than CT or MRI. Patients with biochemical recurrence after prostatectomy now frequently undergo radiotherapy of lymph node metastases identified on PSMA PET. The information from PSMA PET in this setting is actionable because of the high specificity of PSMA PET and because of the availability of a therapy that is guided by the imaging results, that is, stereotactic radiotherapy (4). Because of the lower sensitivity and specificity of CT and MRI, this radiotherapy was not feasible before the introduction of PSMA PET. Thus, the combination of PSMA PET and external-beam radiotherapy is also an example of theranostics according to our definition. In addition to radiotherapy, salvage lymph node dissection for PSMA-positive lymph node metastases is also being explored (5).

It is important to note here that the effectiveness of these local therapies in the setting of biochemical recurrence still needs to be proven by prospective clinical trials, but nevertheless, we would argue that one important reason for the success of PSMA PET imaging has been that it has enabled these new therapeutic options.

Our definition of theranostics is not limited to oncologic imaging and therapy. Another area of theranostics is the combination of  $\beta$ -amyloid imaging and antibody therapy. The amyloid antibody lecanemab has recently been approved by the Food and Drug



Wolfgang A. Weber

Administration, and some health insurances have already begun to reimburse lecanemab therapy (6). Before a patient can be treated with lecanemab, the presence of amyloid in the brain has to be determined. In most of the clinical studies of lecanemab, the presence of amyloid has been determined by amyloid PET. Thus, the results of the amyloid PET scan provide actionable information that results in a new therapy. Amyloid PET scans have so far been used relatively infrequently as purely diagnostic tools, but their use will now in all likelihood increase.

In addition to these 2 concrete examples of theranostics in a broader sense, there are several other such approaches in clinical use or development. In the fields of immunology and fibrosis, various novel radiopharmaceuticals for imaging are emerging in parallel to various targeted immunomodulatory or antifibrotic therapies. In the field of amyloidosis, novel, highly specific disease-modifying therapies are emphasizing the increasing need for companion diagnostic (imaging) biomarkers. Another example is dopamine transporter imaging and dopaminergic therapeutics in Parkinsonian syndromes. Moreover, under development are novel bacteria-selective radioligands that would enable differentiating sterile inflammation from infections. However, such approaches would also offer theranostic imaging characterizing individual bacterial strains to initiate specific and targeted antibiotic treatment and surgical resections. In oncology,  $^{18}\text{F}$ -fluoroestradiol has been Food and Drug Administration–approved for imaging of estrogen receptors and may be used to select patients for estrogen receptor–targeted therapies. Several clinical studies have suggested that imaging of human epidermal growth factor receptor 2 with radiolabeled antibodies may be superior to the analysis of expression of this receptor on biopsies for selecting patients for therapies directed toward it. Preclinically, imaging with  $^{18}\text{F}$ -labeled fibroblast activation protein inhibitor 74 has been used to image expression of fibroblast activation protein before chimeric antigen receptor T-cell therapy directed toward it.

We believe that it is more than semantics to call these approaches theranostic. Linking molecular imaging closely to a specific therapy provides a clear path to regulatory approval as a companion diagnostic. Once approved, it becomes significantly easier to run clinical trials of off-label uses in other indications.

In conclusion, theranostics is much more than switching of diagnostic and therapeutic isotopes. In fact, the concept of theranostics can and should be applied to imaging applications outside radioligand therapies and nuclear oncology. The therapeutic part of a theranostic pair does not have to be a radionuclide therapy but can be external-beam radiotherapy, surgery, medical therapy, or cellular therapy. Nevertheless, the underlying principle remains that the molecular imaging part of the theranostic pair provides actionable information. Obtaining this information requires that the results of the imaging study be highly specific and allow for clinical decision making. Following these principles may accelerate the regulatory approval of new molecular agents and broaden the use of molecular imaging in the clinic.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Langbein T, Weber WA, Eiber M. Future of theranostics: an outlook on precision oncology in nuclear medicine. *J Nucl Med*. 2019;60(suppl 2):13S–19S.
2. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312:1604–1608.
3. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009;361:32–39.
4. Bukavina L, Luckenbaugh AN, Hofman MS, et al. Incorporating prostate-specific membrane antigen positron emission tomography in management decisions for men with newly diagnosed or biochemically recurrent prostate cancer. *Eur Urol*. November 17, 2022 [Epub ahead of print].
5. Horn T, Krönke M, Rauscher I, et al. Single lesion on prostate-specific membrane antigen–ligand positron emission tomography and low prostate-specific antigen are prognostic factors for a favorable biochemical response to prostate-specific membrane antigen–targeted radioguided surgery in recurrent prostate cancer. *Eur Urol*. 2019;76:517–523.
6. US VA to cover Eisai, Biogen Alzheimer’s treatment Leqembi. Reuters website. <https://www.reuters.com/world/us/us-veterans-health-administration-providing-coverage-eisais-alzheimers-treatment-2023-03-13/>. Updated March 14, 2023. Accessed March 29, 2023.