Citius, Altius, Fortius: An Olympian Dream for Theranostics

Rodney J. Hicks, FRACP, FAAHMS

Peter MaCallum Cancer Centre, Melbourne, Australia

We have recently witnessed the heroic efforts of athletes from around the world striving to achieve the Olympic motto—Faster, Higher, Stronger. This could equally be the catch-cry of radiochemists who seek to make tracers with faster synthesis times, higher yields, and stronger binding affinity to the target of choice. Rapid synthesis is particularly important for short-lived radionuclides such as ^{68}Ga, and high yields are necessary to make tracers commercially viable. However, especially for agents that might become the diagnostic pair for a therapeutic agent, stronger binding to cellular targets is the ultimate goal. Radiochemistry is generally a team sport, with many important players. Most successful teams in the development of novel tracers have included a multidisciplinary team of biologists, pathologists, preclinical imaging scientists, chemists, and clinicians. Jean-Claude Reubi, Helmut Mäcke, and colleagues represent one of the eminent teams in receptor-based molecular imaging. In this edition of *The Journal of Nuclear Medicine,* this team describes the potential extension of

See page 300

peptide receptor radionuclide therapy (PRRT) targeting the somatostatin receptor (SSTR) beyond neuroendocrine tumor (NET) into a range of other malignancies (*1*).

The therapeutic use of radiolabeled somatostatin analogs is now well established in many parts of the world (*2*). This represents the culmination of an approach pioneered a quarter of a century ago by another extremely important team in this field, the Erasmus Medical Center in The Netherlands (*3*). As a result of recent Food and Drug Administration approval of ^{68}Ga-DOTA-octreotate (NETSpot), which has a diagnostic capability superior to conventional imaging modalities (*4*) and significant impact on patient treatment planning (*5*), and the recent presentation of encouraging results of the NETTER-1 trial using ^{177}Lu-DOTA-octreotate (Lutathera) (*6*), the theranostic approach in NET will also likely become more widely available in the United States.

The key prerequisite for the selection of patients for PRRT, or indeed any radionuclide therapy, is the presence of sufficient uptake at all active sites of disease to deliver adequate radiation to achieve therapeutic goals of symptom or disease control (*7*). For patients with NET, this decision is currently based on imaging with agents that have high affinity for the subtype 2 of the SSTR (sst_2). sst_2 is usually highly expressed in well and moderately differentiated NET of the lung, pancreas, and intestinal tract (*8*). There is also increasing evidence supporting the utility of such agents in staging metastatic pheochromocytoma and paraganglioma, especially those related to mutations in the succinate dehydrogenase subunit B gene (*9*).

Although several malignancies, including breast and prostate cancer and Hodgkin lymphoma, have long been known to also express sst_2 (*8,10*), in clinical practice the intensity of uptake of available SSTR ligands is often too low to consider PRRT. Nevertheless, motivated by the success of the theranostic paradigm in NET, the nuclear medicine community has been actively seeking means to facilitate radionuclide therapy for such tumors.

One approach has been an attempt to increase the affinity of the peptide for the sst_2. Receptor binding affinity and autoradiographic studies have emphasized the impact of both the radionuclide and the chelating agent (*11*) on tumor uptake of the peptide. Indeed, altering a chelating agent can fundamentally change a peptide from being an agonist to an antagonist (*12*). Although it is somewhat counterintuitive, it appears that antagonists of receptors, which are generally poorly internalized (*13*), typically provide much higher tumor–to–normal-tissue uptake ratios than agonists (*14,15*). This is evidently because they bind a higher proportion of available receptors (*16*). Preclinical studies have supported the theranostic potential of SSTR antagonists (*17*), and preliminary clinical trials have also demonstrated the feasibility of using antagonists for imaging and PRRT (*18,19*).

The current paper by Reubi et al. (*1*) provides further impetus for the evaluation of SSTR antagonists in diseases other than NET. When in vitro receptor autoradiography of ^{125}I agonists versus antagonists was used, 12 of 13 breast cancers, all 12 renal cell carcinomas, and 5 of 5 medullary thyroid cancers demonstrated high binding of the antagonist, whereas only low binding of the agonist was apparent in most cases. Other cancers, including prostate and colon cancers, seemed less promising prospects for imaging or therapy with sst_2 antagonists.

Because cancers can express a range of receptors, development of additional antagonists may further expand theranostic options. Antagonists have been described for imaging other cellular targets including glucagonlike peptide-1 (*20,21*), neurotensin (*22*), and gastrin-releasing peptide (*23,24*). As yet these agents remain primarily the focus of preclinical studies, but some are entering early clinical trials.

For clinicians, faster diagnosis, higher accuracy, and stronger evidence of therapeutic effectiveness are the goal. Citius, Altius, Fortius! We are indebted to the pioneers of theranostics for showing us the way to truly targeted therapies. The vision of Saul Hertz, Sam

Received Sep. 8, 2016; revision accepted Sep. 8, 2016.
For correspondence or reprints contact: Rodney J. Hicks, Peter MacCallum Cancer Centre, 12 Cathedral Place, East Melbourne, Victoria 3002, Australia
E-mail: rod.hicks@petermac.org
Published online Oct. 6, 2016.

DOI: 10.2967/jnumed.116.182188

Seidlin, Robley Evans, and others to bring radioiodine therapy into the clinic 75 y ago (*25–27*) serves as an inspiration to those facing the Olympian challenges of cancer. Teams such as those of Reubi continue to carry a torch that shows us the way.

REFERENCES

1. Reubi JC, Waser B, Mäcke H, Rivier J. Highly increased 125I-JR11 antagonist binding in vitro reveals novel indications for sst2 targeting in human cancers. *J Nucl Med.* 2017;58:300–306.
2. Kwekkeboom DJ, de Herder WW, van Eijck CH, et al. Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med.* 2010;40:78–88.
3. Lamberts SW, Bakker WH, Reubi JC, Krenning EP. Somatostatin-receptor imaging in the localization of endocrine tumors. *N Engl J Med.* 1990;323:1246–1249.
4. Deppen SA, Blume J, Bobbey AJ, et al. ^{68}Ga-DOTATATE compared with ^{111}In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med.* 2016;57:872–878.
5. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol.* 2012;56:40–47.
6. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-dotatate. *J Clin Oncol.* 2016;34(suppl 4S):194.
7. Hicks RJ. Use of molecular targeted agents for the diagnosis, staging and therapy of neuroendocrine malignancy. *Cancer Imaging.* 2010;10(spec no. A):S83–S91.
8. Reubi JC, Schaer JC, Waser B, Mengod G. Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using in situ hybridization. *Cancer Res.* 1994;54:3455–3459.
9. Janssen I, Blanchet EM, Adams K, et al. Superiority of [^{68}Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. *Clin Cancer Res.* 2015;21:3888–3895.
10. Reubi JC, Waser B, Schaer JC, Markwalder R. Somatostatin receptors in human prostate and prostate cancer. *J Clin Endocrinol Metab.* 1995;80:2806–2814.
11. Fani M, Del Pozzo L, Abiraj K, et al. PET of somatostatin receptor-positive tumors using ^{64}Cu- and ^{68}Ga-somatostatin antagonists: the chelate makes the difference. *J Nucl Med.* 2011;52:1110–1118.
12. Reubi JC, Erchegyi J, Cescato R, Waser B, Rivier JE. Switch from antagonist to agonist after addition of a DOTA chelator to a somatostatin analog. *Eur J Nucl Med Mol Imaging.* 2010;37:1551–1558.
13. Waser B, Cescato R, Tamma ML, Maecke HR, Reubi JC. Absence of somatostatin SST_2 receptor internalization in vivo after intravenous SOM230 application in the AR42J animal tumor model. *Eur J Pharmacol.* 2010;644:257–262.
14. Ginj M, Zhang H, Waser B, et al. Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. *Proc Natl Acad Sci USA.* 2006;103:16436–16441.
15. Wang X, Fani M, Schulz S, Rivier J, Reubi JC, Maecke HR. Comprehensive evaluation of a somatostatin-based radiolabelled antagonist for diagnostic imaging and radionuclide therapy. *Eur J Nucl Med Mol Imaging.* 2012;39:1876–1885.
16. Cescato R, Waser B, Fani M, Reubi JC. Evaluation of ^{177}Lu-DOTA-sst2 antagonist versus ^{177}Lu-DOTA-sst2 agonist binding in human cancers in vitro. *J Nucl Med.* 2011;52:1886–1890.
17. Dalm SU, Nonnekens J, Doeswijk GN, et al. Comparison of the therapeutic response to treatment with a ^{177}Lu-labeled somatostatin receptor agonist and antagonist in preclinical models. *J Nucl Med.* 2016;57:260–265.
18. Wild D, Fani M, Behe M, et al. First clinical evidence that imaging with somatostatin receptor antagonists is feasible. *J Nucl Med.* 2011;52:1412–1417.
19. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. *J Nucl Med.* 2014;55:1248–1252.
20. Waser B, Reubi JC. Radiolabelled GLP-1 receptor antagonist binds to GLP-1 receptor-expressing human tissues. *Eur J Nucl Med Mol Imaging.* 2014;41:1166–1171.
21. Rylova SN, Waser B, Del Pozzo L, et al. Approaches to improve the pharmacokinetics of radiolabeled glucagon-like peptide-1 receptor ligands using antagonistic tracers. *J Nucl Med.* 2016;57:1282–1288.
22. Schulz J, Rohracker M, Stiebler M, et al. Comparative evaluation of the biodistribution profiles of a series of nonpeptidic neurotensin receptor-1 antagonists reveals a promising candidate for theranostic applications. *J Nucl Med.* 2016;57:1120–1123.
23. Gourni E, Del Pozzo L, Kheirallah E, et al. Copper-64 labeled macrobicyclic sarcophagine coupled to a GRP receptor antagonist shows great promise for PET imaging of prostate cancer. *Mol Pharm.* 2015;12:2781–2790.
24. Maina T, Bergsma H, Kulkarni HR, et al. Preclinical and first clinical experience with the gastrin-releasing peptide receptor-antagonist [^{68}Ga]SB3 and PET/CT. *Eur J Nucl Med Mol Imaging.* 2016;43:964–973.
25. Chapman EM, Evans RD. The treatment of hyperthyroidism with radioactive iodine. *J Am Med Assoc.* 1946;131:86–91.
26. Hertz S, Roberts A. Radioactive iodine in the study of thyroid physiology; the use of radioactive iodine therapy in hyperthyroidism. *J Am Med Assoc.* 1946;131:81–86.
27. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. *J Am Med Assoc.* 1946;132:838–847.