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 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 (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 (sst2). sst2 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 sst2 (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 sst2. 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 sst2 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 glucagon-like 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...
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


