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Editorial

"Albumin Hitchhiking" with an Evans Blue Analog for Cancer Theranostics

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Abstract

Although ^{177}Lu-DOTA-TATE was recently approved in Europe for the treatment of certain neuroendocrine tumors, continued development and optimization has been ongoing to further improve the therapeutic efficacy of somatostatin receptor 2 targeted peptide receptor radionuclide therapy, as well as reducing the renal toxicity. In this work, the use of an Evans blue analog for "albumin hitchhiking" resulted in significant improvement in both the imaging performance and therapeutic efficacy of radiolabeled octreotate, as well as reducing the toxicity since much less radioactivity was used for therapy. Upon clinical translation, such "albumin hitchhiking" could make significant impact in the near future for cancer patient management.

Key words: somatostatin receptor 2 (SSTR2), peptide receptor radionuclide therapy (PRRT), octreotate (TATE), positron emission tomography (PET), theranostics, cancer, precision medicine

Precision medicine is the future for cancer patient management [1]. With the continued development of cancer diagnostic and therapeutic agents over the last several decades, many of these agents are already widely used in the clinic. One of the best examples is the targeting of somatostatin receptor 2 (SSTR2) with certain peptides for peptide receptor radionuclide therapy (PRRT) [2]. Two of the most commonly used peptides for PRRT are octreotide and octreotate (TATE), where TATE possesses higher binding affinity and selectivity towards SSTR2. In typical clinical practice, ^{68}Ga-labeled octreotide or TATE is used first for positron emission tomography (PET) imaging to confirm that the neuroendocrine tumors in patients express high levels of SSTR2, before a large therapeutic dose (or multiple doses) of ^{177}Lu-labeled TATE is administered for non-invasive and targeted cancer therapy.

Such SSTR2-targeted PRRT has been a shining example of cancer theranostics and precision medicine over the last decade. Currently, ^{177}Lu-DOTA-TATE (Brand name: Lutathera) has already been approved in Europe for "the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults" [3]. In the Unites States, this agent is not yet approved by the FDA, although it may happen in the near future. Some of the well-recognized limitations for ^{177}Lu-DOTA-TATE include the facts that: 1) the therapeutic efficacy is still limited, with modest complete response (CR) and partial response (PR) rate; 2) due to the fast renal clearance of the agent, there is significant renal toxicity associated with ^{177}Lu-DOTA-TATE [4]. Therefore, continued development and optimization has been ongoing to further improve the therapeutic

efficacy of SSTR2-targeted PRRT, as well as to reduce the undesirable toxicity.

In this issue of Theranostics, Chen and colleagues reported the use of an Evans blue analog (EB) for albumin hitchhiking to improve both the PET imaging performance and therapeutic efficacy of radiolabeled TATE in several animal tumor models, targeting SSTR2 [5]. Both the imaging and therapy results in these animal tumor models are very exciting, which could have significant clinical impact in the near future, once they are translated into the clinic.

Since human serum albumin is the most abundant protein in blood plasma (~ 50 mg/ml), it has been intensively investigated as a drug carrier for several decades. A large number of literature reports exist regarding the use of "albumin hitchhiking" to improve the pharmacokinetics of various imaging and/or therapeutic agents [6]. The agents that have been used for albumin binding include lipids, fatty acids, peptides, albumin binding motif, among many others, and many of these indeed led to significantly improved performance in vivo [6]. In this work [5], the researchers used an Evans blue analog (EB), which binds to albumin in a reversible manner, to improve the pharmacokinetics of TATE for neuroendocrine tumor imaging and therapy in several animal models. As for the radioisotope pair, the investigators used ^{86}Y (a PET isotope with a decay half-life of 14.7 h) and ^{90}Y (a beta-emitter with a decay half-life of 64.1 h and maximum energy of 2.28 MeV), which are from the same element. Hence, the imaging and therapy agents are the same chemical entity, truly embodying the notion of theranostics with exactly the same molecule. Such a perfectly matched theranostic pair will certainly facilitate clinical translation when compared to other theranostics agents that use radioisotopes from different elements (e.g. ^{68}Ga/^{177}Lu).

The chemical synthesis of the agent was quite straightforward, via a short linker that connects the three motifs: TATE (for SSTR2 binding), EB (for albumin hitchhiking), and DOTA (for ^{86}Y/^{90}Y labeling and PET/PRRT) (**Figure 1**). Various in vitro studies in multiple cell lines confirmed that such chemical conjugation did not significantly alter the SSTR2-binding affinity of TATE, or the albumin binding affinity of EB. Equally importantly, such modification did not significantly alter the internalization of TATE, which is critical for tumor uptake and PET imaging contrast, as well as the therapeutic efficacy of PRRT. A pleasant surprise in the experimental results is that although EB-TATE only exhibited about twice the circulation half-life when compared to that of TATE, the tumor uptake was much higher at about 4-fold. Even in a medium SSTR2-expressing model (i.e. HCT116/SSTR2), such a small molecule (i.e. ^{86}Y-EB-TATE) was able to accumulate in the tumor at ~30 %ID/g within 24 h post-injection, outperforming many radiolabeled monoclonal antibodies in the literature [7-9]. In the model that expresses high level of SSTR2, the AR42J model, tumor uptake of ^{86}Y-EB-TATE was about 60 %ID/g, which is an extremely impressive number!

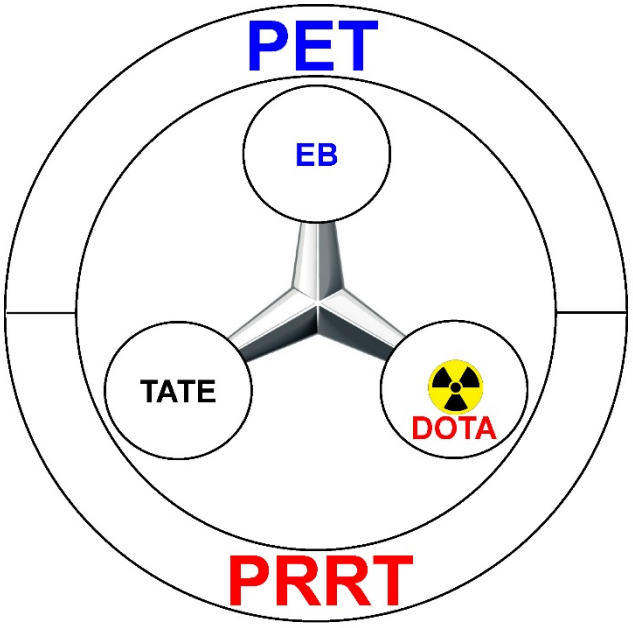

Figure 1. Schematic representation of ^{86}Y/^{90}Y-EB-TATE for positron emission tomography (PET) and peptide receptor radionuclide therapy (PRRT).

Absolute tumor uptake of the radiopharmaceutical is only part of the story. According to the area under the curve (AUC) calculation, ^{86}Y-EB-TATE had ~6-fold higher tumor exposure to the radioisotope than ^{86}Y-TATE. Since it is almost impossible to measure the absolute biodistribution of ^{90}Y-EB-TATE over time, hence it is very challenging to calculate the tumor radiation dose when ^{90}Y is used, the difference in tumor radiation dose between the two agents (i.e. ^{90}Y-EB-TATE vs. ^{90}Y-TATE) could be much higher than the numbers calculated for ^{86}Y, since ^{90}Y has a much longer decay half-life. The decline in tumor radioactivity at late time points from mice injected with ^{86}Y-EB-TATE was mostly due to radioactive decay, rather than biological clearance of the agent from the tumor.

With such high tumor uptake and persistent retention of ^{86}Y/^{90}Y-EB-TATE radioactivity in the tumor, it is of no surprise that the therapeutic effect was also very promising and long lasting. More importantly, the radioactivity dose administered was much lower than other studies reported in the literature. 0.2 mCi (i.e. 7.4 MBq) of ^{90}Y-EB-TATE was able to achieve an almost 100% survival rate for at

least 180 days in mice bearing either the HCT116/SSTR2 or AR42J tumors. Based on dosimetry estimations, the investigators concluded that treatment of a mouse with an average weight of 27 g with 7.4 MBq of ^{90}Y-EB-TATE is equivalent to the treatment of a 60 kg patient with 1.3 GBq of radioactivity, which is more than 10 times lower than the cumulative ~30 GBq of radioactivity used in the clinic for ^{177}Lu-DOTA-TATE [3]. Since a much lower amount of radioactivity is used for the investigated therapeutic applications, the potential (renal) toxicity of such treatment was also expected to be much lower. Indeed, histopathological staining of major organs and blood analysis showed no obvious difference between the treated groups and control mice.

Such exciting preclinical results clearly warrant clinical translation. According to personal communications with the investigators, clinical translation and investigation of this agent is currently ongoing in China. Furthermore, unpublished results by the investigators comparing ^{177}Lu-EB-TATE and Lutathera were also quite encouraging, which further increased the potential clinical impact and future broad applications of this strategy of EB-based albumin hitchhiking. Based on clinicaltrials.gov, a Phase I trial of ^{177}Lu-EB-TATE in patients with advanced metastatic neuroendocrine tumors is already ongoing in China (https://clinicaltrials.gov/show/NCT03308682). We look forward to the exciting clinical results in the near future.

Although this report is an excellent example of using EB to improve the pharmacokinetics of imaging/therapeutic agents, such albumin hitchhiking with EB is by no means limited to TATE. Over the last several years, the Chen group has published a large number of studies using EB to improve the performance of various agents [6, 10-15], which makes such EB-based albumin hitchhiking a generally applicable platform technology. Not only can this strategy be employed in oncologic applications, but it can also be utilized to improve the therapeutic efficacy of various agents in other diseases such as diabetes [12]. With continued development and application across many biomedical areas, as well as future clinical translation, this strategy holds tremendous promise as a platform technology for the new era of precision medicine and theranostics, not only in cancer patient management, but also in various other devastating diseases.

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