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How to Get Radiolabeled PSMA Diagnostic and Therapeutic Agents Approved

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The theranostic combination of ^{68}Ga diagnostic with ^{90}Y and ^{177}Lu therapeutic labeled somatostatin ligands has been shown to be a remarkably accurate and effective way to characterize and treat neuroendocrine tumors. FDA approval of such agents is imminent and is expected to occur within the next year.

A similar combination of ^{68}Ga and ^{177}Lu agents has now been demonstrated for diagnosis and therapy of prostate cancer with small molecule PSMA targeted ligands. Initial results are extraordinarily promising. The development and approval of these agents is being slowed significantly by the large expense needed to fund the necessary clinical trials and by the fragmentation of the current efforts, since there are several different competing compounds. Furthermore the most commonly studied ^{68}Ga labeled compound appears to be unpatented and so is not supported by any large company that might have the resources to be able to conduct the necessary trials and bring the agent to approval.

This situation is very frustrating for our patients, who are well aware of these highly promising agents and are anxiously awaiting their wider availability, and for the entire nuclear medicine community who would like to assess and treat these patients more effectively. In a recent editorial by authors from the Netherlands and Germany, they "call upon the nuclear medicine community not to waste this unique opportunity to greatly enlarge the role of nuclear medicine by the practice of the same petty rivalry that in the past could be seen so often" [1].

In the last few years most, if not all, of the large radiopharmaceutical companies have withdrawn from the market because the large financial investment cannot be justified by expected return. This has left several smaller, more tightly focused, medium and small size companies who are trying to bring new agents to approval. However, the large financial requirement and the onerous path to approval have slowed or stopped their efforts. A likely exception is in the case of a definite diagnostic-therapeutic pair, such as ^{68}Ga and ^{177}Lu DOTATATE, which are likely to be approved relatively soon.

Three different types of "industry" are interested in seeing more radiopharmaceuticals approved, such as the PSMA-directed ligands. These include PET-CT and PET-MRI manufacturers, since there is a real possibility that demand for new scanners will increase; the second are the large radiopharmacy companies, since collaboration with academia would likely both accelerate the approval process and save money; and third are smaller radiopharmacy companies, who may be unable to raise the resources to complete all the requirements for an NDA unless they have some help.

There are several approaches that are being explored or that need to be explored to address this problem. The first is simply finding more money. It is possible that a broadly organized effort by a collaboration between academia and industry could successfully approach one of the large healthcare-directed or patient advocacy foundations to help fund a joint effort to bring a theranostic pair to approval. The motivation for industry is that the collaborative process would be much faster and the effort in designing and conducting the trial(s) would be distributed, with considerable assistance from academia and the cost and

risk would be significantly lower. The obvious motivation for academia is that the agents would become available years sooner than if the current fragmented approach continues.

Another approach is for academia to do it without industrial support. This is already underway through efforts of the Gallium Users Group, which is part of the Clinical Trials Network (CTN) of SNMMI. Several academic sites are working together to begin coordinated clinical trials with ^{68}Ga PSMA HBED-CC, an unpatented agent. Trials with a therapeutic agent would follow as soon as feasible. The goal is to design a multicenter clinical trial with identical inclusion and exclusion criteria for at least a fraction of the subjects at all the sites, along with a standardized imaging protocol and standardized radiopharmaceutical preparation, so that the data from all the sites can be harmonized and be brought together for an NDA. The studies are initially being funded locally or through cost-recovery INDs. Funding will also be sought from one or more philanthropic organizations, as well as from industry. Eventually it is likely that a commercial partner will be found, who will be capable of packaging and distributing the agent. Even though the agent is unpatented, the relatively low investment should justify the modest cost of organizing the data and submitting the NDA to the FDA, especially since the academic partners will be willing and eager to help.

For both of these possible plans it is essential to arrange for a detailed discussion with the FDA to explicitly define exactly what is needed to bring these agents to approval. For the first plan, we need to organize a preliminary discussion between interested companies and representatives from academia to explore the feasibility of a collaborative approach. For

the second plan, we need to gather representatives from several academic sites to jointly plan and agree on a collaborative path forward. This is already underway with the Gallium Users Group of the CTN.

Either with primary industry or CTN leadership, it is important to move forward rapidly, since it is clear that the PSMA-directed ligands are likely to revolutionize the approach to the diagnosis and treatment of metastatic prostate cancer and help thousands of prostate cancer patients.

Reference

1. Mottaghy FM, Behrendt FF, Verburg FA. ^{68}Ga-PSMA-HBED-CC PET/CT: where molecular imaging has an edge over morphological imaging.
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