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PSMA-Targeted Therapeutics: A Tale About Law and Economics

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Without any doubt, the breakthrough of prostate-specific membrane antigen (PSMA) targeting radiopharmaceuticals has stirred up nuclear medicine and radiopharmaceutical research, and ultimately boosted industrial engagement in the entire field. The first-in-human application of the ^{68}Ga-labeled PET tracer ^{68}Ga-PSMA-11 in 2011 (hence its present name; initially referred to as ^{68}Ga-HBED-PSMA) (1) galvanized the community and led to a fierce race towards the matching ^{177}Lu therapeutics. To the best of our knowledge, this games' first goal was scored by ^{177}Lu-PSMA I&T, being the first radiometal-based PSMA ligand which was successfully applied for therapy of metastatic castration-resistant prostate carcinoma (mCRPC) (2). Shortly thereafter, one novel compound after another appeared, aiming primarily at therapeutic (e.g., ^{177}Lu-PSMA-617) (3) and purely imaging applications (e.g., ^{18}F-PSMA-1001) (4). Interestingly, the commercial interest also led to unexpected 'short squeezes' in some supply chains. For example, PSMA-617 became widely unavailable one fine day as as result of a change in ownership of the patent rights, leaving many clinical radiopharmacies at odds how to settle their respective requirements.

At this point, it is interesting to note that no patents were filed for PSMA-11 and PSMA I&T, most likely because the tremendous commercial success of this class of radiopharmaceuticals was not foreseeable at that time. As a result, PSMA-11 was widely used and became a global de-facto standard for PSMA-PET in an incredibly short time. Because it is sold by numerous manufacturers worldwide and available as a labeling kit, it is still one of the most frequently used PSMA tracers, despite other agents might arguably be more potent. In principle, the same used to be true for PSMA I&T. For quite a time, many departments were relying on it for their clinical routine. However, the market situation for this compound also took an interesting turn when a fairly old chelator patent entered the stage.

PSMA I&T features a particular flavor of DOTA as chelator moiety (5), namely, a tetraazacyclo**do**decane with **t**hree **a**cetic acid and one **g**lutaric **a**cid side arm—hence its acronym DOTAGA (6). This bifunctional chelator structure was developed more than 20 years ago by Helmut Mäcke and coworkers and filed for patent on May 11th, 2001 (7). The patent slumbered for quite a while but eventually was licensed from Basel university by CheMatech, a company who co-developed and marketed DOTAGA anhydride (8), a valuable building block for making DOTAGA-functionalized

compounds. By February 2019, parts of the same patent, covering the use of DOTAGA in all its conjugates, allegedly were sub-licensed to another player in the field in order to gain property rights for PSMA I&T (9). As a countermove, others have announced that any applicable license fees for PSMA I&T, made from a stock of DOTAGA anhydride purchased from CheMatech before February 2019, have inherently been settled by originally purchasing the DOTAGA used for making PSMA I&T from a licensee (i.e., CheMatech) and thus, their product may nonetheless be purchased and used without infringing any law (10).

Whether or not this is true shall not be commented here, since this legal skirmish is just about to become history anyway. It remains to be asked to which extent the imminent expiry of the DOTAGA patent (by May 11th, 2021) bears the potential to change the 'Game of Thrones' that is being played in the field of PSMA theranostics. The fact that a powerful therapeutic PSMA radioligand, ^{177}Lu-PSMA I&T, may be manufactured and used without any patent restrictions from May 11th onwards, will probably have an impact on future development, availability, and pricing of similar agents. To all researchers in the field, this tale might be a lesson—and a warning, to secure their intellectual property in time, in order to save oneself from late regrets.

Disclaimer

I hereby declare that there is no conflict of interest, in particular, that I have no connection to any of the companies, patents, or agents mentioned; neither do I hold any property rights or receive any funding, royalties etc. related to PSMA targeted agents.

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