Gallium-68, Lutetium-177 gain in the pharmaceutical world

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The development of radiopharmaceuticals began in the U.S. during the 1940s, followed by a trial-and-error process which resulted, over the years, in a kind of natural selection for radionuclides. From the original radionuclides and the "exotic" ones that were proposed by researchers and physicians, only Technetium-99m (gamma emitter for SPECT applications — Single Photon Emission Computed Tomography) and Iodine-131 (beta emitter for therapeutic applications) remain the most commonly used. PET technology (Positron Emission Tomography) based on 18F-FDG (fludeoxyglucose), discovered in the '70s, was really developed in the '90s, mainly due to the implementation of dedicated production sites (cyclotrons) and the development of efficient imaging technologies. The recent development in Gallium-68 technology makes 2015 a milestone for the development of radiodiagnostics, which will probably lead in the next five years to a complete new PET environment. It seems that the future of radiodiagnostics will almost entirely be based on Technetium-99m for SPECT and on Fluorine-18 and Gallium-68 for PET.

Gallium-68 gained momentum in the past 18 months with several major technology leaps and new tracer development. ^{68}Ga-PSMA-11, developed by the University of Heidelberg, encountered huge interest among oncologists in the diagnosis and evaluation of disease extension in prostate cancer at the same time the first ^{68}Ge/^{68}Ga generator obtained its marketing authorization (Eckert & Ziegler, Germany). Limited capacity and access to these generators seem to be the bottlenecks for extensive use of ^{68}Ga, but several other companies are close to bringing new approved generators on the market, while some new approaches developed by target engineers (NCM, USA and IBA, Belgium) demonstrated the ability of small cyclotrons to produce curie levels of pure ^{68}Ga. On top of this, cold kits for the ^{68}Ga-labeling of tracers have been made available (ANMI, Belgium) and open a highway for the use of ^{68}Ga in PET similar to ^{99m}Tc in SPECT imaging.

Despite its shorter half-life (68 min.) compared to ^{18}F (half-life 108 min.), ^{68}Ga has a nice and almost ideal profile as a PET imaging agent. However, ^{68}Ga will not jeopardize the market of ^{18}F because of its different chemistry and means of introduction in a molecule. ^{68}Ga and ^{18}F will continue developing in parallel, both filling indications adapted to their physico-chemical properties.

Although nuclear medicine mainly refers to diagnosis, radionuclides used for therapeutic purposes (radiotherapeutics) are gaining in importance, and represented about 10 percent of the total nuclear medicine market in 2015, driven by the success of Bayer with Xofigo (radium-223 dichloride), a radiotherapeutic used in the treatment of prostate and bone cancers. It is expected that radiotherapeutics will represent about 50 percent of the nuclear medicine market in 2030.

Hence, ^{68}Ga is also linked to the therapeutic beta emitter Lutetium-177 radionuclide, as this pair can form a kind of ideal partnership in the development of theranostics. All newly developed ^{177}Lu-labeled radiotherapeutics are associated with the ^{68}Ga-labeled analogue that will help not only to diagnose the patient, but to select the sub-population that should be positive responders to this ^{177}Lu-treatment.

By the end of the year it is expected that the company Advanced Accelerator Applications in France will be able to launch the first ^{177}Lu-labeled molecule, Lutathera, a drug for the treatment of neuroendocrine tumors, also known as ^{177}Lu-DOTATATE. In the next few years, two other molecules, DOTATOC and JR-11, respectively developed by ITG (Germany) and Ipsen (France) may also reach the market as drugs labeled with ^{177}Lu for similar indications. All these molecules will be associated with the ^{68}Ga-labeled analogue. Within the next five years it is expected that very promising prostate cancer therapies based on antibodies (ATL-101 from ATLAB Pharma, France) or on the PSMA analogues may also reach the market, also labeled with ^{177}Lu.

Nuclear medicine remains a niche market representing less than 1 percent of the global pharmaceutical industry. But in recent years the conventional pharmaceutical industry became gradually interested in nuclear medicine with some recent M&A activities: Bayer acquired Algeta; Sun Pharmaceutical took over Pharmalucence; Otsuka Pharmaceuticals entered into a global licensing and collaboration agreement with NuView Life Sciences; Norgine entered into a partnership with Navidea; and most recently, the pharmaceutical group Ipsen acquired OctreoPharm Sciences and then partnered with 3B Pharmaceuticals to develop novel radiotherapeutics.

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