Title of the thesis: Design of new Ga-complexes for PET imaging of aggrecans

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Scientific background:

Studies undertaken by UMR 1240 IMoST resulted in selecting a bifunctional chelator (BFC) for both selective targeting the articular cartilage and technetium-99m complexation, the most commonly used medical radioisotope for imaging via SPECT (single-photon emission computed tomography). This molecule, named as 99mTc-NTP 15-5, was evaluated in numerous preclinical studies involving different animal models for cartilage imaging1–3. A phase 0-I clinical trial named CARSPECT with first injection to human will start in June 2020 at Clermont-Ferrand. 99mTc-NTP 15-5 Radionuclidic properties and detection techniques determine the advantages of PET (Positron Emission Tomography) over SPECT in term of 100-1000 fold higher sensitivity, higher speed, dynamic image reconstruction and in vivo quantification4. Therefore, in parallel with above studies, we are synthesizing and studding new emitting beta plus complexes. Preliminary studies led to the selection of pharmacomodulated cupric radiocomplexes with a quaternary ammonium function. Some of these copper chelates possess a better biodistribution profile than the 99mTc-NTP 15-5 radiotracer (i.e. less hepatic fixation and increased specificity for cartilage aggrecan). These results were patented in 2015. However, copper-64 has a too low availability (production/high cost) to make it a relevant radiopharmaceutical.

Subject:

The use of gallium-68 radionuclide would avoid the difficulties encountered with copper-64. Its production from a long-life and cost-effective generator make it increasingly available in radiopharmacies. Moreover, its favorable branching ratio (89% beta+) and its short half-life (67.7 min) minimize the radiation dose to patients and personnel. Many ligands functionalized with negatively charged pendant arms at physiological pH such as carboxylates, phosphonates, phosphinates have been developed for gallium-68 complexation6-8. As demonstrated by our previous studies, chelators with negatively charged pendant arms poorly interact with proteoglycans of articular cartilage. Our goal is to select a 68Ga-labeled BFC with the best
preclinical profile for cartilage functional PET imaging in humans. The successful candidate will be able to draw on the expertise of our research unit in this area. This job will give the opportunity to work on new BFCs from their design to their use in medical imaging and will be organized around:

- organic syntheses of new BFCs,
- studies of gallium complexation,
- development of radiolabeling conditions,
- stability and biodistribution studies on small animals (rats, rabbits), in collaboration with biologists of our team,
- PET imaging assessments.

**Keywords:**
organic synthesis, coordination chemistry, chemical analysis, radiochemistry.


