

Sujet de thèse Equipe FENNEC – ILM :

**« Development of second generation of AGuIX nanoparticles as a theranostic multimodal platform »
« Développement d’une seconde génération de nanoparticules AGuIX à visée multimodale »**

The FENNEC team of Institute of Light and Mater has developed a new type of ultras-small multimodal nanoparticles: AGuIX[®], made of polysiloxane and gadolinium chelates (F. Lux *et al.*, *Angew. Chem. Int. Ed.*, **2011**). These nanoparticles displayed high potential for radiotherapy guided by MRI (F. Lux *et al.*, *Br. J. Radiology*, **2018**) due to high radiosensitizing effect and MRI contrast agent properties (S. Kotb *et al.*, *Theranostics*, **2016**). These nanoparticles are now implicated in two clinical trials:

- (i) Nano-Rad in CHU Grenoble for the treatment of multiple brain metastases by whole brain radiation radiotherapy (NCT02820454). 15 patients have been treated for the moment showing first evidence of efficacy.
- (ii) Nano-Col in Institute Gustave Roussy for the treatment of locally advanced cervical cancer by external radiotherapy and Curie-therapy (NCT03308604). 3 patients treated.

In this context, FENNEC team wants to develop a new generation of targeted ultras-small nanoparticles for diagnostic and therapy. The aim of the PhD will be to develop such kind of nanocompounds and will benefit from the numerous preclinical collaborations of FENNEC team.

All the platforms will be obtained by specific formulation or functionalization of AGuIX NPs. 4 different types of platform will be proposed during the PhD:

- (i) NPs for radiotherapy combined to chemotherapy to propose a therapeutic solution to multidrug resistance. AGuIX NPs will be formulated with Doxorubicin or Paclitaxel two blockbusters of the pharmacopeia. Deliverance of the drug will be tested in different media: water, blood before *in vitro* and *in vivo* tests in collaboration with Dr Claire Rodriguez-Lafrasse (IN2P3, Lyon) for Paclitaxel and with Dr Jean-Luc Perfettini (Institut Gustave Roussy, Villejuif).
- (ii) NPs for labelling of radioactive isotopes. Proofs of concept of the possibility to label the NPs by radioactive isotopes has been shown during the PhD of E. Thomas. New ligands will be functionalized on the NPs for labelling by radioactive isotopes for PET imaging and for brachytherapy. Design of the ligands will be performed in tight collaboration with Pr Franck Denat (ICMUB, Dijon). PET experiments after labelling by ⁸⁹Zr and ⁶⁸Ga will be performed in collaboration with Dr Charles Truillet (Hôpital Joliot, Orsay). Brachytherapy will be performed after labelling by ¹⁷⁷Lu ²¹²Bi and ²²⁵Ac in collaboration with Dr Jean-Pierre Pouget (IRCM, Montpellier).
- (iii) NPs for targeting therapy and immunotherapy. Protocols will be developed to functionalize the nanoparticles with nanobodies specific of Pd-L1 (an immune checkpoint) and neuropilin 1 (receptor overexpressed in neoangiogenesis). This work will be done in collaboration with Dr Ross Berbeco (Harvard Medical School, Boston, USA). This collaboration is supported by UdL in the program “Soutien UCBL aux projets de collaborations internationales”.

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