

Ecole Doctorale des Sciences Fondamentales

Title of the thesis: Development of new radiotracers for PET imaging of mutated isocitrate dehydrogenases enzymes (mIDH) in solid tumors.

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Summary :

Isocitrate dehydrogenases (IDH) are enzymes that catalyse oxidative decarboxylation of isocitrate to α -ketoglutarate (also known as 2-oxoglutarate) with subsequent reduction of NADP co-factor to NADPH and formation of carbon dioxide. The three IDH isoforms (IDH1, IDH2 and IDH3) are involved in several biological processes such as cellular metabolism, cellular defense against oxidative stress, oxidative respiration, and oxygen-sensing signal transduction. However, mutated IDH enzymes (mIDH) have been observed in several cancers including glioma, acute myeloid leukemia (AML), intrahepatic cholangiocarcinoma, and chondrosarcoma [1]. For mIDH, the normal enzymatic activity described above is then converted into a neomorphic activity producing the 2-hydroxyglutarate (2-HG), known as a potential oncometabolite. High cellular levels of 2-HG can inhibit, for example, enzymes implicated in DNA-demethylation, histone-demethylation, and subsequently impair normal cellular differentiation and promote tumor development.

Thus mIDH became, in the last years, important potential therapeutic targets for pharmaceutical companies [2]. To date, several mIDH inhibitors have been investigated and very encouraging results were obtained with some of them during preclinical and clinical trials (AG-221, enasidenib for example) [3]. In this context, the aim of this PhD thesis will be the development of an innovative radiotracer targeting mIDH, for PET (positron emission tomography) imaging of these mutated enzymes in solid tumors as chondrosarcoma or glioma. Such radiotracer could be of important value to determine mIDH expression levels in tumors, to select admissible patients for anti-mIDH therapies, and to perform treatment follow-up for the evaluation of the therapeutic response rates. This project will be performed in close collaboration with the neuroradiopharmacy laboratory of Prof. P. Brust (HZDR, research site Leipzig, Germany) and the ROTOP Pharmaka GmbH company (Rossendorf, Germany).

Knowledge and skills required: a solid background of organic chemistry and analytical chemistry is required (purification and characterisation organic compounds: NMR, MS, HPLC).

Scientific domains: Organic and medicinal chemistry, radiochemistry.

References:

- [1] B. Mery, S. Espenel, J.-B. Guy, C. Rancoule, A. Vallard, M.-T. Aloy, C. Rodriguez-Lafrasse, N. Magné, *Crit. Rev. Oncol./Hematol.* 126 (2018) 32–36.
- [2] J. Mondesir, C. Willekens, M. Touat, S. de Botton, *J Blood Med.* 7 (2016) 171–180.
- [3] T. Ma, F. Zou, S. Pusch, Y. Xu, A. von Deimling, X. Zha, *J. Med. Chem.* 61 (20) (2018), 8981-9003.