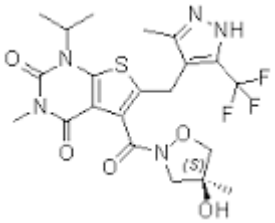
Unité Mixte de Recherche U1240 Imagerie Moléculaire et Stratégies Théranostiques", Inserm, Université d'Auvergne, 58 rue Montalembert, BP 184 – 63005 Clermont-Ferrand cedex
Thesis supervisor: Dr Emmanuel Moreau (emmanuel.moreau@udamail.fr)
Thesis supervisor: Dr Eric Debiton (eric.debiton@udamail.fr)

"Synthesis of iodinated and fluorinated inhibitors of MCT1 / MCT4 receptors"

Most solid tumors produce energy via glycolysis, even under conditions of high oxygen tension (" aerobic glycolysis ", also known as the Warburg effect). The use of this metabolic pathway induces an increased production of lactate, responsible for the extracellular acidification of the tumor microenvironment, favoring tumor invasion and suppressing the anti-cancer immune response. The transport (export or import) of lactate through the plasma membrane is mediated by a family of monocarboxylic acid (MCT) carriers that ensures intracellular pH homeostasis. Four members (MCT1-MCT4) have so far been characterized as lactate and/or carboxylic acid supporters. Overexpression of MCT1 and/or MCT4 has recently been demonstrated in some cancers (neuroblastoma, colon, lung, prostate and breast cancers). In general, CD147 is also co-expressed with MCT1 and MCT4. However, the role of this triad in tumors is far from fully elucidated and their potential as therapeutic targets is only beginning to be explored. A specific inhibitor of MCT1 (AZD 3965) is currently in the Phase I/IIa clinical trial in United Kingdom. Moreover, the pathological involvement of MCT4 was mainly evaluated for colorectal and pulmonary carcinomas and is associated with a poor prognosis in triple-negative mammary carcinomas.

.



AZD3965

The aim of our project is to develop radioiodinated or radiofluorinated molecules having a very good affinity and specificity for MCT1 and/or MCT4. These radiotracers must allow visualization of the expression of MCT1 and/or MCT4 by SPECT or PET imaging in order to allow clinicians to predict the response of possible treatment based on inhibitors of these transporters and to improve the care of the patients concerned .

Références:

Pinheiro C, Reis RM, Ricardo S, Longatto-Filho A, Schmitt F, and Baltazar F. Expression of monocarboxylate transporters 1,2, and 4 in human tumours and their association with CD147 and CD44. 2010. J. Biomed. Biotech. 2010, 169-175.

Polanski R, Hodgkinson CL, Fusi A, Nonaka D, Priest L, Kelly P, Trapani F, Bishop PW, White A, Critchlow SE, Smith PD, Blackhall F, Dive C, and Morrow CJ. Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer. 2013. Clin. Cancer Res. 20, 926-937.

Doyen J, Trastour C, Ettore F, Peyrottes I, Toussant N, Gal J, Ilc K, Roux D, Parks SK, Ferrero JM, and Pouysségur J. 2014. Biochem. Biophys. Res. Com. 451, 54-61.