Internship project Master 2 Recherche, 3rd year of Engineering school Year 2018 / 2019

Laboratory: UGA-IAB Inserm 1209, CNRS 5309 / MassOmics **Director:** Pierre Hainaut
Team: Equipe 8 **Head of team:** Patrice MARCHE

Name and status of scientist in charge of the project:
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Title: MALDI Mass Spectrometry Imaging to investigate the efficacy of a novel AKT inhibitor ARQ 751 and a new quinoline derivative, GNS561 as single agent or in combination with sorafenib on hepatocellular carcinoma in a cirrhotic rat model

Objectives: To assess the efficacy of allosteric inhibitor of AKT, ARQ 751 and a new quinoline derivative, GNS561 as single treatment or in combination with sorafenib through MALDI Mass Spectrometry Imaging using a DEN-induced cirrhotic rat model.

Abstract: HepatoCellular Carcinoma (HCC) is a leading reason of death among cirrhotic patients. Worldwide, liver cancer is reported to be the fifth most common cancer, and its mortality is the second highest among all cancers. The viral hepatitis and alcoholic or non-alcoholic steatohepatitis are the major cause of chronic liver inflammation which leads to fibrosis, cirrhosis and finally HCC development. Even though sorafenib was the first drug significantly increasing clinical outcome of advanced HCC, its efficacy is modest with a median overall survival of 10.7 months versus 7.9 months with placebo in the pivotal phase III trial. Moreover, this treatment often causes severe side effects and a long-term treatment often results in reduced sensitivity of the tumor cells causing drug resistance. Therefore, new therapeutic treatments of HCC with better efficacy are urgently needed and should be pre-clinically tested in an appropriate animal model. Amongst the new potential therapeutics, the AKT inhibitor ARQ 751 has proven to significantly suppress tumor progression and improve liver fibrosis and GNS561 was shown to decrease tumor vascularization and to control cell proliferation in the diethylnitrosamine (DEN)-injured rats model which faithfully reproduces human HCC physiopathology. These results were observed using these drugs alone or in combination with sorafenib. We are therefore proposing here to investigate the local proteome changes from liver collected on treated *versus* untreated rat by MALDI MSI and computational imaging to bring out molecular explanations regarding the anti-tumoral effects of ARQ 751 and GNS561.

Methods: MALDI Mass Spectrometry Imaging. Briefly, the fresh-frozen rat livers will be cryosliced, stained for fibrosis analysis and imaged by MALDI MS following dedicated protocols. Molecular reconstructions and subsequent statistical processing will be performed through computational softwares.

Relevant publications of the team:

Jilkova ZM, Kuyucu AZ, Kurma K, Ahmad Pour ST, Roth GS, Abbadessa G, Yu Y, Schwartz B, Sturm N, Marche PN, Hainaut P, Decaens T (2018). Combination of AKT inhibitor ARQ 092 and sorafenib potentiates inhibition of tumor progression in cirrhotic rat model of hepatocellular carcinoma. Oncotarget. 2018 Jan 23;9(13):11145-11158

Masson V, **Arafah K**, Voisin S, **Bulet P**. Comparative Proteomics Studies of Insect Cuticle by Tandem Mass Spectrometry: Application of a Novel Proteomics Approach to the Pea Aphid Cuticular Proteins. Proteomics. 2018 Feb;18(3-4)

Pisani C, Voisin S, **Arafah K**, Durand P, Perrard MH, Guichaoua MR, **Bulet P**, Prat O. (2016) *Ex vivo* assessment of testicular toxicity induced by carbendazim and iprodione, alone or in a mixture. ALTEX. 2016;33(4):393-413

Herren JK, Paredes JC, Schüpfer F, **Arafah K, Bulet P**, Lemaitre B. (2014) Insect endosymbiont proliferation is limited by lipid availability. Elife. 2014 Jul 15;3:e02964

Requested domains of expertise (few keywords): Biochemistry, mass spectrometry, MALDI MS, histology