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| **Title: Adjuvant strategies to immunotherapy in lung cancer: ketone bodies, fatty acids and physical activity against muscle wasting** |
| **thesis program’s description**Immunotherapy (IT) is a promising anti-cancer strategy that stimulates the patient's own immune defenses to target the tumor. IT is notably used in advanced form of lung cancer. It is based on the use of antibodies targeting inhibitors of immune control checkpoints expressed on the surface of cancer cells (PD-L1 Programmed cell Death protein Ligand 1) or their receptors on immune cells (PD-1). Although effective and with few side effects, only a subset of cancers responds to treatment, leaving many patients without clinical benefits. Several factors, including genetics and the environment (diet, exercise), can modulate immune responses to cancer. Recent data suggest the value of ketone bodies as adjuvant therapy for IT, and the ability of polyunsaturated fatty acids (PUFAs) in promoting cancer cell death by inducing lipid peroxidation and ferroptosis. Physical activity could also determine patients' response to treatment by stimulating the immune system, reducing fatigue, treatment toxicity and the risk of recurrence. The proposed PhD program aims to investigate if ketone bodies, PUFAs and physical activity could be used as a multimodal strategy by improving response to immunotherapy (IT)-based cancer treatments to inhibit cancer development and reduce cancer cachexia.Tumorigenesis will be induced in mice by injection of TC1 cells in tail vein. This syngeneic and orthotopic model of lung tumorigenesis will be set up in collaboration with Prof. L Zitvogel's team. Animals will receive IT using anti PD-1 antibodies in combination or not with ketone bodies/PUFAs supplementation and voluntary exercise. Impact on tumor development, cachexia, muscle functionality, and mechanisms triggering ferroptosis will be explored. An *in vitro* part of the thesis will be devoted to characterize mechanisms of ferroptosis, including oxidative damages, cell survival, expression of PD-L1, triggered by main metabolites induced by KD (β-hydroxybutyrate), PUFAs and by exercise (myokines/exerkines) explaining anti-cancer and anti-cachexia effects.  |

Mots clefs : cancer, nutrition, activité physique, muscle, lipides, immunité, modèles animaux, recherche translationnelle.

Compétences : animal experiments, cell culture (not mandatory)

Conditions d’éligibilité : Niveau Master 2 en recherche, moyenne supérieure à 12 et classement dans la 1ere moitié de promotion.

Lieu de travail : Faculté de médecine/pharmacie de Clermont-Ferrand

Structure de rattachement : UMR 1019, Unité de Nutrition Humaine, INRAE-UCA

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