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AVIS DE SOUTENANCE DE THÈSE

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Monsieur Milad BAROUD

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UFR Santé
Département Pharmacie
AMPHI GERMAIN
16, boulevard Daviers
49045 ANGERS Cedex

sur le sujet suivant :

Auto-assemblages de prodrogues de l'azacitidine : une stratégie d'intérêt pour le traitement des syndromes myélodysplasiques

Directeur de thèse : **Monsieur Olivier DUVAL**

Composition du jury :
Monsieur Yohann CORVIS, Associate professor Université de Paris Descartes, Rapporteur
Monsieur Patrick DALLEMAGNE, Professeur des Universités Université de Caen Normandie, Examinateur
Monsieur Olivier DUVAL, PU-PH Université d'Angers, Directeur de thèse
Madame Yolla EL-MAKHOUR, Professeur Université Libanaise, Liban, Co-encadrant
Madame Elise LEPELTIER, Maître de Conférences HDR Université d'Angers, Co-directeur de thèse
Madame Lucie SANCEY, Director of Research Université de Grenoble Alpes, Rapporteur
Monsieur Sylvain THEPOT, Praticien hospitalier CHU d'Angers, Examinateur

Résumé de la thèse

Azacitidine, a nucleosidic analogue of cytidine, has played a crucial role in the treatment of MDS and AML. Indeed, advanced cases of MDS, categorized as higher-risk MDS, rely on azacitidine as one of the few options available in their arsenal against this blood disorder. Additionally, it has shown great merit in the cases of delays for hematopoietic stem cell transplantation eligible patients, as well as in post-procedure relapse prevention. Though not commonly used for lower-risk MDS patients, azacitidine is still a treatment option after the failure of regular approaches for this group. Owing to its DNA hypomethylating activity, this molecule is capable of reactivating the tumor suppressor genes. The lack of substitutes further stresses its importance. However, azacitidine suffers from low serum drug levels and high toxicity levels, leaving the patients facing a poor prognosis. It is explained by its hydrophilic nature, leading to poor cell internalization, coupled its degradation by nucleoside deaminases, resulting to a short half-life.This project aimed to counter these limitations on two levels. The first was to protect the labile amine group of azacitidine via its conjugation to a polyunsaturated fatty acid, thus increasing the drugs half-life. The second level was to use the amphiphilic nature of the obtained prodrug and to formulate self-assemblies. This approach additionally lends other advantages, as the newly obtained amphiphilic prodrug should enhance the entry into the cells, not to mention an increased specificity stemming from the unique cleavability of the formed amide bond by cathepsin B enzyme, overexpressed in MDS and cancer cells.Chapter 1 presents a state of the art on myelodysplastic syndromes and acute myeloid leukemia causes, the pre-existing treatments, therapeutic limitations of the azacitidine drug, and related breakthroughs. It finally proposes the novelty of this project and the methodology in which an enhanced treatment is approached.Chapter 2 sheds a light on the approach of conjugating a nucleoside to a polyunsaturated fatty acid (PUFAylation), a generalized approach of the well-known "Squalenoylation" concept developed by Prof. Couvreur and his team[261]. Two omega-3 fatty acids were chosen for the conjugation: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Two PUFAylated prodrugs were successfully obtained via direct conjugation in the presence of ethyl chloroformate: an azacitidine-docosahexaenoic acid conjugate (N^4-azacitidine DHA, called AzaDHA) and an azacitidine-eicosapentaenoic acid conjugate (N^4-azacitidine EPA, called AzaEPA). This chapter then covers the nanoprecipitation of these prodrugs was performed and self-assemblies were successfully achieved. The critical aggregation concentration obtained by the pyrene method confirmed the formation of self-assemblies.Chapter 3 deals with *in vitro* evaluations of each prodrug, on HL-60 promyelocytic cell line. The half maximal inhibitory concentrations were determined via MTT test and present higher half maximal inhibitory concentrations comparable to that of azacitidine. Yet, in the nanoparticle internalization studies, it was observed that the nanoparticles prepared from the prodrug AzaEPA are readily internalized into the cells compared to the AzaDHA ones. The final part of this manuscript offers a discussion on the results obtained in each chapter. Culminating in the conflicting results between the MTT tests and the internalization studies. Following, perspectives including additional experiments are emphasized.

À AFFICHER DANS L'UFR 15 JOURS AVANT LA SOUTENANCE