DEVELOPMENT OF PROTAC TARGETING KINASES FOR THE TREATMENT OF CANCERS

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Cancer is a major public health issue worldwide. In France, it is considered as the leading cause of mortality in men and the second in women.[1,2] This high incidence is primarily attributed to metastases, which account for 90% of cases and which pose significant treatment challenges.[3,4] Recent studies in the literature have demonstrated the involvement of CDK5 in tumors, with functions ranging from metastasis to angiogenesis. The inactivation of this kinase in melanoma cell lines has been shown to reduce cell motility in vitro, as well as the formation of lung and liver metastases in vivo in a human melanoma mouse model. CDK5-mediated cell motility is therefore a key driver of cancer metastasis.[5,6,7] Several orthosteric kinase inhibitors are already used in clinics; however, their selectivity remains relatively low due to their mechanism of action, which relies on ATP-pocket binding. To date, few allosteric inhibitors of protein kinases have been reported in the literature.[8,9] A promising strategy leverages the Ubiquitin-Proteasome System (UPS) for targeted protein degradation, particularly through Proteolysis-Targeting Chimeras (PROTACs), an emerging therapeutic approach. PROTACs are hetero-bifunctional molecules composed of a ligand for the protein of interest (POI) connected via a linker to a ligand for the E3 enzyme of the UPS system (Figure 1).

This project focuses on the design and synthesis of PROTACs capable of targeting both the orthosteric and allosteric pockets of CDK5. Indeed, potential allosteric modulators of CDK5 (unpublished data) have been identified in the laboratory, with compounds acting on cell migration (metastases). The use of the PROTAC system aims to selectively inhibit CDK5 by degradation. Additionally, it will play a key role in elucidating the mechanism of action of allosteric molecules. It is often challenging to link a cellular phenotypic effect to an allosteric mechanism on a given target. PROTAC-induced protein degradation can be monitored at the cellular level and directly correlated with phenotypic effects such as proliferation and migration.

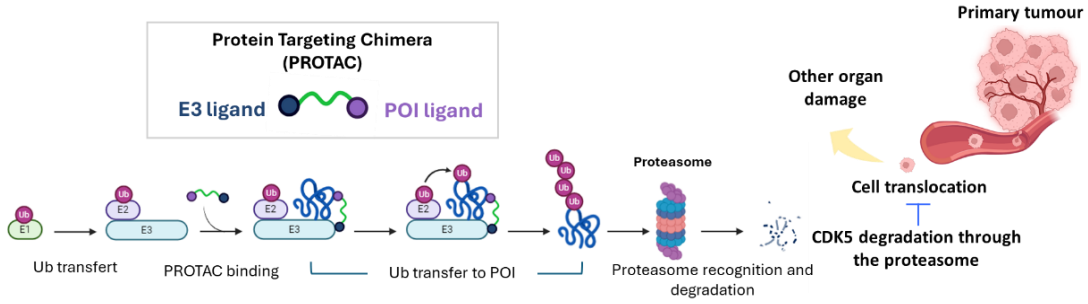

Figure 2:Mechanism of CDK5 degradation by UPS machinery to block cell migration in tumor metastasis

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