Development of PROTACs targeting kinases for the treatment of cancers

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Résumé

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 have demonstrated the involvement of CDK5 in tumours, with functions ranging from metastasis to angiogenesis. CDK5 plays an essential role in cell motility, invasiveness and metastatic spread. 5,6,7

Most protein kinase inhibitors approved by the FDA and used in the clinic target the ATP pocket; however, their selectivity remains relatively low due to their mechanism of action, which relies on ATP-pocket binding. Several strategies have been proposed to target other pockets, essential protein/protein interactions and conformational transitions. A promising strategy which has emerged for therapeutic targeting leverages the Ubiquitin-Proteasome System (UPS) to induce degradation of a protein of interest (POI), thanks to Proteolysis-Targeting Chimeras (PROTACs), hetero-bifunctional molecules composed of a ligand of the protein of interest (POI) connected via a linker to a ligand for the E3 enzyme of the UPS (Figure 1).

This project focuses on the design and synthesis of PROTACs that target the ATP pocket of CDK5. We have synthesized several of the PROTACs derived from a selective CDK5 inhibitor to induce selective degradation of CDK5.8 We have characterized the affinity of our PROTACS to inhibit the catalytic activity of CDK5 in vitro and have investigated their potential to promote degradation of CDK5 in lung cancer cell lines.

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Mots-Clés: PROTAC, metastasis, CDK5, degradation, allosteric modulation, selective inhibition, kinase

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