Cell-penetrating peptides (CPPs) are currently considered as very promising vectors for drug delivery, with several derivatives under clinical test. Notably, a major class of CPPs derives from the sequence of homeoprotein (HP) cell-penetrating domains. These domains are characterized by the presence of a conserved tryptophan (Trp), which is critical for cell entry. HPs are transcription factors that are involved in crucial physiological processes. Interestingly, Engrailed-2 (En2) HP has been found to provide neuroprotection when it is injected in animal models of Parkinson's disease. The aim of the PhD project is to enhance the cellular uptake of En2-HP by redesigning its associated CPP, in order to improve its therapeutic potential. Our strategy is to replace the conserved Trp by non-canonical analogs to modulate physico-chemical parameters (hydrophobicity, electronic density…) that could be important for the CPP and HP interaction with cell membrane and entry inside cells. We have recently obtained interesting results by incorporating commercial Trp analogs in En2-CPP. Based on these results, the PhD student will synthesize new tailor-made analogs. After study of the modified En2-CPP internalisation properties, the most promising analogs will be introduced into En2-HP derivatives. The CPP domain being by itself responsible for the entry of the HP, enhancements observed at the CPP level should also lead to improvements at the HP level. A synthetic strategy will be optimized to obtain the chemically modified HPs, based on the ligation of an expressed fragment with a synthetic modified fragment. The cellular uptake of the modified En2-HP and of the native protein will be compared. This research project, at the interface of chemistry and biology, will give insight into the role of the conserved Trp and should lead to the identification of chemically engineered CPPs and homeoproteins with enhanced cell-penetration properties.