Title of the thesis: Synthesis of specific haspin inhibitors for application in cancer therapy

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Summary:
More than five hundred human protein kinases have been identified. These transferases catalyze the transfer of a phosphate group from ATP to the hydroxyl residue of serine/threonine and/or tyrosine of a protein substrate, leading to its activation or inactivation (Fig. 1). Therefore, they regulate many cellular signaling pathways and constitute attractive targets as they are implicated in different diseases. Haspin is an atypical Ser/Thr kinase essential to mitosis, and thus, appears as a potential target against cancer.

Fig. 1: Phosphorylation reaction catalyzed by protein kinases. Usual binding mode between ATP and kinase ATP binding pocket (H-bond in dashed lines)

Most of known protein kinase inhibitors target the kinase ATP-binding pocket and present an heteroaromatic part that could mimic the adenine moiety of ATP. Based on our experience in the design and synthesis of protein kinase inhibitors, using a preclinical drug discovery approach (Fig. 2), the aim of this project is the synthesis of new ATP-competitive specific haspin inhibitors to identify new biological tools to better understand haspin cellular functions and/or treat associated diseases, such as cancer.

Fig. 2: Preclinical drug discovery approach used

In order to achieve these goals, the PhD student will use all necessary methods for the organic synthesis, purification and structural characterization of target molecules. The design and synthesis will be performed at the ICCF (Institute of Chemistry of Clermont-Ferrand). In-depth knowledge in organic chemistry is required to apply. Biological evaluations will be achieved in collaboration with Dr. Sandrine Ruchaud (Biological Station in Roscoff, France).