Design and synthesis of MAPK pathways' modulators with inhibitory and theragnostic properties for the treatment of cancer

Mitogen-Activated Protein Kinase (MAPK) pathways are important cellular pathways that link extracellular signals to cellular function. Abnormalities in MAPK pathways play a prominent role in the development and progression of cancer. Protein kinases (PK) are involved in the cellular cascade of MAPK pathways and thus in cellular function of eukaryotic organisms. Mutated PKs are common oncogenes and are among the most explored targets for cancer therapy. In recent years targeting of oncogenic PKs such as BCR-ABL, EGF, BRAF has led to the development of several agents approved for cancer treatment, such as imatinib, nilotinib, gefitinib, erlotinib, and vemurafenib.

First-generation agents of this kind have shown efficacy in the clinic, but unfortunately in many cases, the response is not long-lasting and resistance can occur as the tumor can switch to alternative signaling to resist therapy and drive growth; to be effective, a therapy must be able to inhibit more than one driver lesion.
There is then an active interest in the field to develop dual-targeting agents to improve treatment outcomes, as combined inhibition should lead to superior anticancer activity through a) total and simultaneous suppression of cooperating oncogenic signals and b) abrogation of bypass signaling that can promote resistance to therapy.

My project aims to develop dual PK inhibitors able to act against other kinases affecting MAPKs pathways. As a starting point, I will focus on developing dual inhibitors of FLT3 and RET; two kinases that are often mutated and concomitantly activated in acute myeloid leukemia (AML). The development of dual inhibitors of RET and FLT3 could meet the medical need of AML patients showing abnormal activities of both these proteins. A specific chemotype identified by the research group has been shown to confer efficacy against specific targets PKs; I will use this chemotype as the starting scaffold for the design of compounds with varying degrees of selectivity for RET over FLT3, hopefully allowing the identification of compounds with promising lead-like properties by the end of my Ph.D. project.