ICCF - COM - Group "Inhibitors of Enzymes and Receptors"

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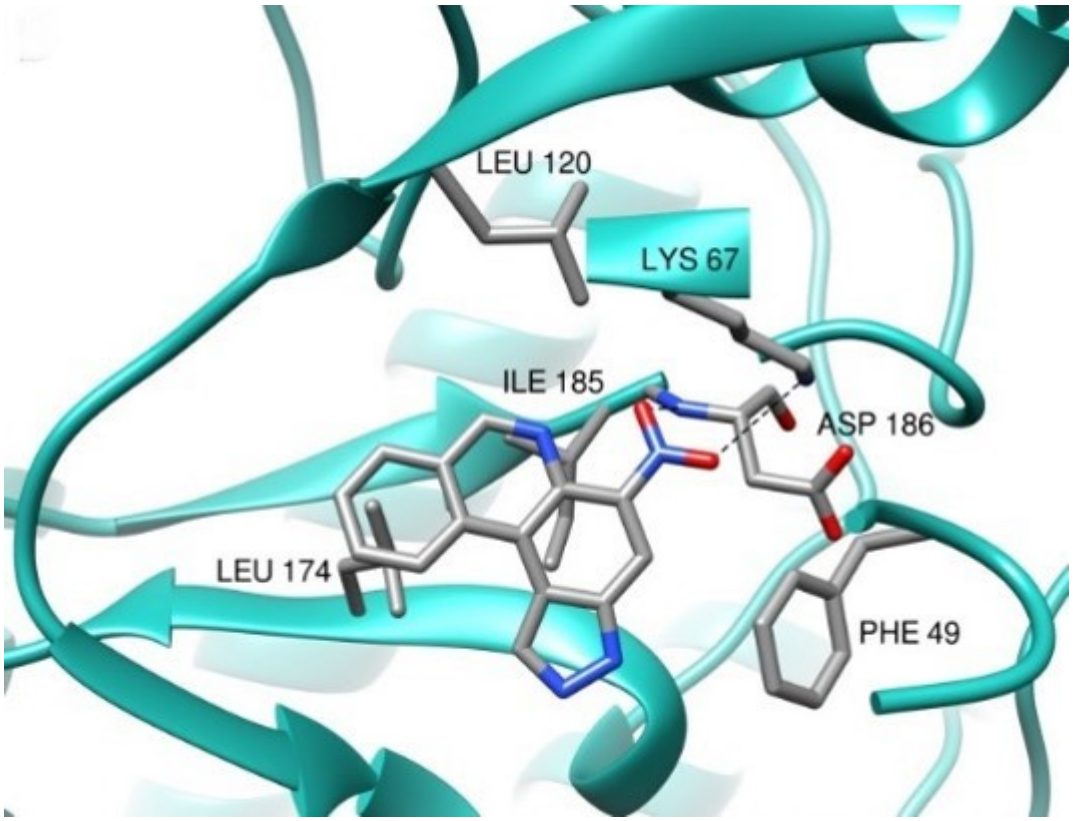

Docking model, generated with AutoDock Vina of the binding mode of the pyrazolophenanthridine VS-II-173 within the ATP-binding pocket of Pim-1 protein kinase.

Design and synthesis of new protein kinases inhibitors.

Since Imatinib (Bcr-Abl inhibitor) was granted marketing approval, which constitutes the proof of concept for the use of protein kinase inhibitors in cancer therapy, many studies aimed to **develop inhibitors of other protein kinases** involved in cancer phenotypes. Considering the existence of a large number of protein kinases in the human kinome (more than 500), sharing ATP as phosphate donor, **one of the major difficulties for the development of inhibitors is selectivity**, since the majority of inhibitors bind to the homologous ATP-binding pocket. Thus, our objectives are the **design and synthesis of new ATP-competitive kinase inhibitors, mainly original heterocycles** aiming at filling the unused chemical space. Currently, our work is targeting :

- **a mitotic kinase, Haspin**. In this context, in collaboration with a group from Roscoff, we identified a chemical family exhibiting nanomolar activity on Haspin with a good selectivity index over kinases having a structural homology with Haspin.

- **the Pim kinase family**. This work carried out in collaboration with a Norwegian group from Bergen enabled the identification and characterization of a myeloid leukemia cell-selective pyrazolophenanthridine derivative. This compound also exhibited potent activities toward cells from patient blasts resistant to conventional treatments or with mutations associated with poor prognosis.

Despite the most recent advances, there is still a lot to do in the development of kinase inhibitors: increase the number of kinases for which inhibitors have been identified (currently ~ 20% of the kinome), identify allosteric inhibitors rather than compounds targeting the ATP binding pocket, and design compounds specifically targeting mutated kinases. Our next goals aim to meet these expectations.

Centre National de la Recherche Scientifique (http://www.cnrs.fr/en)

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(https://iccf.uca.fr/english-version)

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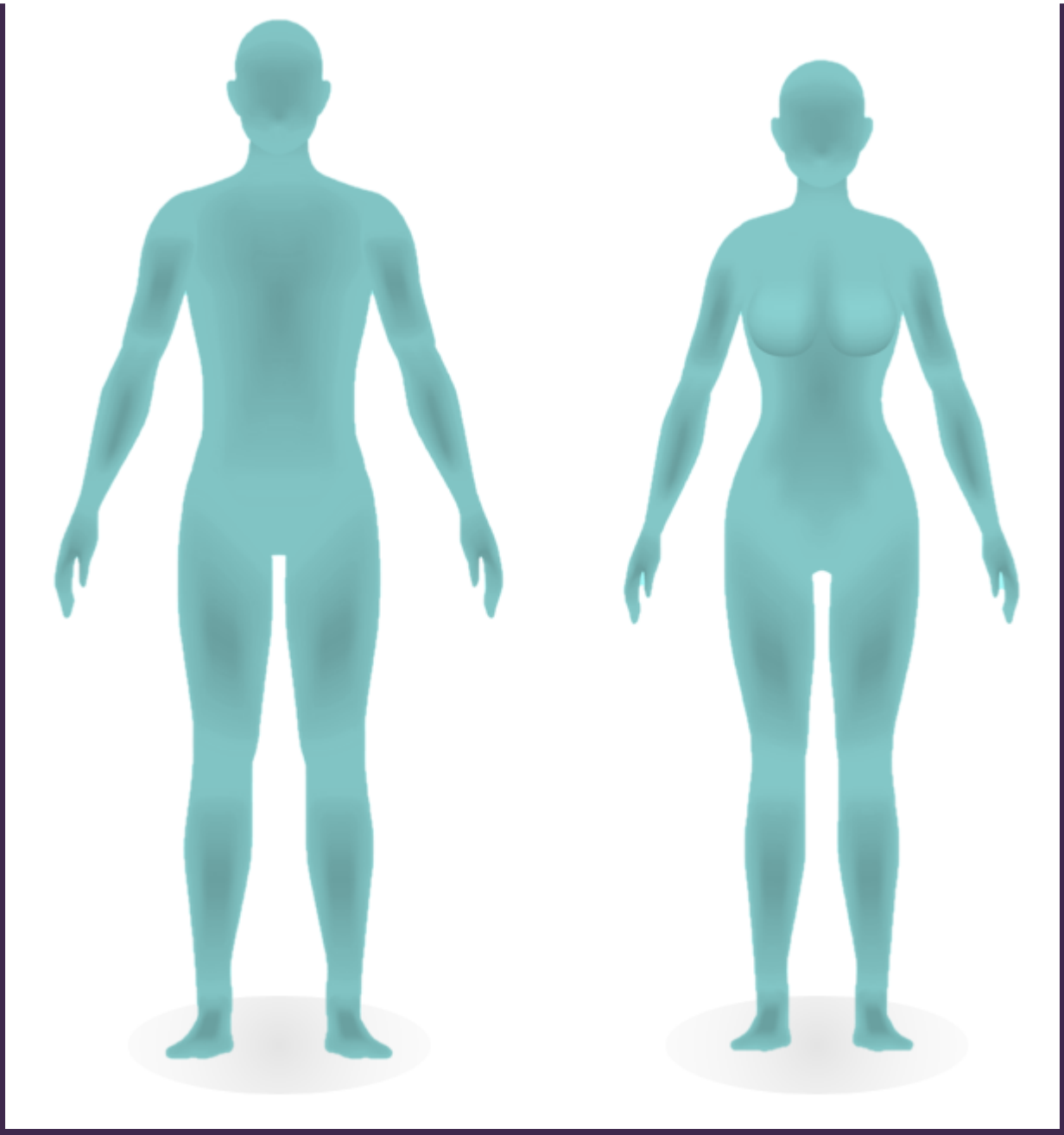
(https://groupe-cancer.uca.fr/en/research/research-activities-by-laboratory-department/iccf-institut-de-chimie-de-clermont-ferrand)

Tumor sites



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