Ph.D. Position in BIOLOGY/CHEMISTRY

Research Center for Respiratory Diseases, University of TOURS

Pharmacological targeting of neutrophil cathepsin S with novel chemical inhibitors

Location: University of Tours, Research Center for Respiratory Diseases (CEPR U1100 INSERM)
Supervisors: Dr. Brice Korkmaz, Dr. Cécile Croix
Funding acquired: 3-year Establishment Doctoral Contract from October 2024

Context and description of the research project: An uncontrolled activity of neutrophil serine proteases contributes to neutrophil-mediated inflammatory diseases. Cathepsin C executes the maturation of immune-cell associated serine proteases, including neutrophil serine proteases. Therefore, cathepsin C represents a promising pharmacological target in neutrophil serine protease-mediated diseases. In humans, mutations in the *CTSC* gene are associated with Papillon-Lefèvre syndrome (PLS). In blood neutrophils from patients, only low amounts of active neutrophil serine proteases are detected (<10% vs healthy individuals). Thus, inhibiting cathepsin C would counteract more comprehensively NSP-dependent tissue damage in inflammatory diseases. Recently, we investigated this hypothesis and specifically showed that when human $CD34^+$ progenitor cells were treated with a cathepsin S inhibitor $IcatS_{\#54}$ during their neutrophil differentiation *in vitro*, cathepsin C activity was nearly abrogated, whereas approximately 30% neutrophil serine protease activity remained.

Objectives: The two main aims of this PhD thesis are: i) to develop new cathepsin S inhibitors and ii) to perform pharmacokinetic/pharmacodynamic analysis *in vitro* in cell models and *in vivo* in a mouse model. We plan to block the proteolytic cascade involved in the activation of neutrophil serine proteases by targeting cathepsin S. This strategy would make it possible to inactivate four potent elastinolytic enzymes in inflammatory diseases using a single chemical inhibitor.

Key words: neutrophil, protease, cathepsin S, serine proteases, inhibitor, therapeutic approach, medicinal chemistry

Candidate's profile: The candidate must hold a Master 2 in life science or equivalent, with a strong dominance in biology/chemistry. He/she must have experimental skills and an attraction for setting up and monitoring scientific experiments. Skills in basic techniques of biochemistry, cell biology and organic synthesis are also required. Knowledge on proteolytic enzymes would be a plus. On a personal level, the candidate must show scientific autonomy, thoroughness and initiative, and have good communication skills.

Application: Send a file including detailed CV, cover letter, M1 and M2 or engineer level transcripts to brice.korkmaz@inserm.fr and cecile.croix@univ-tours.fr. Deadline: June 7, 2024.