Investigating the individual contribution of inflammatory chemokine receptors (iCCRs) to cardiovascular disease

Leukocyte migration to the vessel wall and the heart plays a critical role in cardiovascular immune response and is a carefully orchestrated process regulated by chemokines. Inflammatory chemokines are generated by any cell type in the diseased vessel wall and the heart and can interact with multiple inflammatory chemokine receptors. However, redundancy, ligand sharing and overlapping expression patterns typify the inflammatory chemokine/receptor system. Accordingly, we have an insufficient understanding of the complex roles played by individual, and combination of, chemokine receptors in regulating cardiovascular inflammation, which has precluded the development of targeted therapies. To overcome this problem, we have now generated mice with silenced classic inflammatory CC-chemokine receptors, CCRs1,2,3 and 5 (‘iCCRs’) to assess the integrated contribution of iCCRs to cardiovascular disease (CVD). Importantly, the silencing is reversible to allow us to selectively switch on each receptor in turn, as well as in select combinations. In summary, we are now able to gain novel insights into iCCR individual and integrated contribution to CVD and we will clarify if targeting individual or a combination of receptors might be a viable approach to limit cardiovascular inflammation. We will also employ integrated methods of biomolecular NMR experiments in solution and in the solid-state and multiscale molecular simulations to better define the interaction of iCCRs with their ligands and generate knowledge for novel drug design. Finally, we will assess the role of iCCRs as markers of severity in human CVD datasets.

The student will be trained in mouse models of CVD, single-cell RNA sequencing, analysis of clinical datasets and NMR. The tutor/cotutor groups are funded by Federico II, ERC, BHF and the European Commission. Both supervisors are strong publishers with track records of dissemination in the highest quality journals. In summary, the group provides the environment, resources and support that will ensure success of the student's research, together with a significant range of training opportunities.