- **PROJECT SUMMARY**

Giant cell arteritis (GCA) is a systemic disease characterized by chronic inflammation of large-sized blood vessels, leading to life-threatening complications, such as aortic aneurysm and irreversible blindness. GCA predominantly affects women, with the highest incidence occurring at the age of 70 years (*Lancet. 2008; 372(9634):234-45*). While glucocorticoids, the primary treatment for GCA, are highly effective at high doses, relapses occur in up to 50% of patients, and this treatment is associated with severe morbidity and mortality (*Curr Rheumatol Rep. 2015;17(6):513*). GCA presents a complex etiology influenced by environmental triggers and genetic factors. In recent years, our understanding of the genetic landscape of GCA has significantly expanded (*Front Immunol. 2019;10:1796*). However, its pathogenesis remains largely unknown. In addition, the great majority of GCA-associated variants identified so far lie within non-coding regions of the genome, posing challenges in assigning them a functional role and uncovering disease-causing genes.

In the last years, epigenetic mechanisms have emerged as pivotal factors in the pathogenesis of complex diseases (*Nat Rev Rheumatol. 2020;16(9):514-524*). Regarding GCA, our group has recently reported profound disturbances in the methylation profile of GCA monocytes (*Ann Rheum Dis. 2022;81(9):1290-300*). Notably, identifying disease-specific epigenetic changes may have a major clinical impact, given the potential reversibility of these aberrant alterations, and, in fact, epigenetic therapies are already being used in cancer treatment (*Nat Rev Cancer. 2019;19(3):151-161*). Recently, two epigenomic approaches, ATAC-seq, enabling the direct detection of open chromatin regions with potential regulatory functions, and ChIP-seq, allowing the mapping of DNA-binding proteins like histone marks and transcription factors, have proven valuable in identifying the epigenetic profiles and regulomes underlying the pathogenesis of immune-mediated diseases (*Nat Commun. 2020;11(1):5843*; *BMC Biol. 2021;19(1):79*; *PLoS Genet. 2022;18(5):e1009973*). Furthermore, integrating genomic data with ATAC-seq and ChIP-seq data has been instrumental in pinpointing genetic variants affecting chromatin accessibility as well as transcription factor binding sites and/or histone marks, thus allowing to assign functional roles to non-coding variants and to identify genes involved in disease pathogenesis (*Nat Genet. 2021;53(7):962-971*; *Nat Genet. 2018;50(8):1140-1150*; *Cell. 2021;184(24):5985-6001.e19*).

Considering all the above, we aim to perform the first study of the epigenomic landscape of GCA in artery tissue, as well as in two cell types central in this vasculitis: monocytes and CD4+ T cells, using ATAC-seq and ChIP-seq. In addition, we will perform an integrated analysis of these data with genomic and transcriptomic data to assign a functional role to non-coding genetic variation associated with GCA and to identify genes contributing to its development. Furthermore, considering the sexual dimorphism characterizing this vasculitis, we will investigate the differential impact of sex on the disease by comparing epigenetic regulatory patterns between female and male GCA patients, thus advancing our understanding of the specific pathological mechanisms driving this sex-biased condition.

Recently, Genetic Risk Scores (GRS) have been developed for several immune-mediated diseases, demonstrating predictive capabilities substantial enough to be potentially useful in the clinic (*Ann Rheum Dis. 2021;80(1):118-127*; *Sci Transl Med. 2020;12(545):eaay1548*). Considering this, a final goal of this project is to develop a GRS including the functional GCA-associated variants identified in our integrated analysis. This will enable us to identify individuals at significantly higher genetic risk for GCA and may be used for informed therapeutic intervention or disease screening.

- **TRAINING PROGRAM**

The project the student would join includes researchers with extended experience in different areas, including immunology, genetics, epigenetics, internal medicine, and bioinformatics. This multidisciplinarity is a perfect context for the training of the PhD student in the different aspects related to the disease under study, from its pathophysiology to the main clinical characteristics, as well as for the acquisition of skills in the most innovative epigenomic techniques and bioinformatic tools.

The PhD student would be involved in the Doctoral Program in Biomedicine of the University of Granada, which has as fundamental objectives to train researchers with the ability to do quality science, to promote quality research in Biomedicine, and to translate knowledge to society. The training plan would include the following activities:

- Training in the cutting-edge epigenomic and transcriptomic methodologies of this project.
- Stays in renowned research centers.
- Participation in lab meetings and seminars of the IPBLN.
- Assistance to specialized courses (bioinformatics, genomics, epigenomics).
- Assistance to national and international congresses to present ongoing research.