Psoriasis is a chronic inflammatory skin disease which may be associated with chronic arthritis manifesting as psoriatic arthritis (PsA). Both are complex diseases with strong heritability and genetic association, notably involving HLA-C\*06:02. Genome-wide association studies (GWAS) have also identified more than 40 additional loci, the majority involving non-coding regulatory variants. Understanding the functional role and impact of these variants in disease aetiology still remains challenging, requiring application of bioinformatics and experimental approaches in a disease setting and cell-specific relevant context to resolve functional causal variants.

We have applied transposase-accessible chromatin (ATAC-seq) profiling to keratinocyte-enriched cell populations obtained from epidermal sheets of uninvolved and lesional psoriatic skin biopsies. ATAC-seq results show nucleosomal periodicity in fragment size distribution and enrichment in overlap with DNase-I hypersensitivity ENCODE data from primary cultured keratinocytes relative to other cell types. However, we find high background limiting further application of this approach in this setting despite optimisation. We are now extending the approach to generate complementary ATAC-seq data for different immune cell types (including CD14+ monocytes, CD4+, CD8+ and CD19+) derived from synovial fluid and/or peripheral blood of psoriasis vulgaris and PsA patients.

We conclude that the low sensitivity of ATAC-seq in skin currently impairs the use of the data for comparison of regulatory landscapes across lesional skin and different immune cell types. Integration of chromatin and transcriptional profiles generated in primary immune cells will be potentially informative in revealing cell and context specific differences in the regulatory landscape and it may help to prioritise GWAS variants associated with disease. Overall, this novel approach could contribute to better understand the mechanisms of action of non-coding variants in a disease and cell specific manner.

Psoriasis is an inflammatory skin disease most commonly manifested as well-demarcated erythematous plaques (psoriasis vulgaris) that in 10 to 30\% of the cases is followed by one or more joint inflammation in the form of psoriatic arthritis (PsA). Both are complex phenotypes resulting from the interaction of environmental factors and genetic associations identified through GWAS studies. The latest technical advances in functional genomics allows to study the epigenetic landscape and gene expression profiles in clinical samples at the bulk and single-cell resolution. This is opening the door to characterise changes in the epigenetic, transcriptomic and proteomic landscape driven by disease state, and to further dissect the context specific functional impact of genetic variability in a tissue and cell type specific manner.

The overall aim of this thesis is to investigate the epigenetic regulatory landscape and transcriptomic profiles in psoriasis and PsA to identify disease, tissue and cell type specific changes to inform the interpretation of genetic associations arising from GWAS.