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 a complex chronic inflammatory disease characterised by skin lesions manifesting in 90% of the cases with plaques in x (psoriasis vulgaris)
* About x% of the psoriasis patients also develop joint affection in the form of PsA which manifest in inflammation of one or many joints
* Both are complex diseases resulting from the interaction of environmental factors and genetic associations identified through GWAS studies, with many commonalities and some phenotype-specific associations.
* Latest technical advances in functional genomic allow to study the epigenetic landscape and gene expression profiles even at the single-cell resolution in clinical samples
* This is opening the door to characterise changes in the functional landscape driven by disease and to further dissecting the context specific functional impact of genetic variability by studying affected tissues and relevant cell types