***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

***39 CYCLE***

**Project proposal for a Sapienza PhD scholarship**

**Main research line**

**Title of the research: Investigating the role of T lymphocytes and their HLA-B27-mediated crosstalk with chondrocytes in autoimmune Spondyloarthritis**

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**Summary**

Ankylosing Spondylitis (AS) is the prototype of Spondyloarthritis (SpA), a cluster of autoimmune rheumatic multifactorial disorders whose pathogenetic molecular mechanisms are far to be fully elucidated. The ascertained contribution of Human Leucocyte Antigen (HLA)-B\*27 together with the association of several genes identified by Genome Wide Association Studies (GWAS) suggest an altered presentation pathway of peptides to CD8+ T lymphocytes by the HLA-B\*27 molecules. A plausible scenario would envisage the gut site as the first source of inflammation, probably due to a dysbiosis frequently found in AS patients, from which pathogenic/cross-reactive T lymphocytes reach other sites such as axial skeleton and sacroiliac joints contributing to the spread of inflammation. According to this concept, it would be crucial to characterize the migration and phenotype of putative pathogenic T lymphocytes and, hopefully, to identify within these cells a main subset strictly correlated to a specific clinical picture. In parallel, it would be pivotal to investigate the capability of T cells to mount a response towards a suboptimal peptidome presented by HLA-B\*27 alleles that could include atypical peptides, dual non-contiguous peptides or truncated version of classical peptides potentially generated in the inflamed context. The HLA-B\*27 peptidome analysis of both the AS-associated allele (B\*2705) and the non-AS-associated allele (B\*2709) and the consequent effects on CD8+ T cells will be extended to chondrocytes stably expressing B\*27 alleles, to deepen the antigen presentation mechanism in a tissue context relevant for the disease. Overall, this study could be seminal to clarify the T cell involvement, especially CD8+ T lymphocytes in the pathogenesis of AS/SpA and their HLA-B\*27-mediated crosstalk with cartilage chondrocytes. In addition, the identification of specific HLA-B27-restricted autoantigens presented by chondrocytes could be seminal for a personalized and more accurate therapeutic strategy.

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