DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41st CYCLE
Project proposal for a Sapienza PhD scholarship

Title of the research: Dissecting the role of T lymphocytes and their HLA-B27-mediatedcrosstalk with chondrocytes in autoimmune Spondyloarthritis

Supervisor: Maria Teresa Fiorillo
mariateresa.fiorillo@uniroma1.it

https://corsidilaurea.uniroma1.it/it/users/mariateresafiorillouniroma1it
https://orcid.org/0000-0002-6859-5851

Summary
Ankylosing Spondylitis (AS) is the prototype of Spondyloarthritis (SpA), a cluster of multifactorial autoimmune rheumatic disorders whose pathogenetic molecular mechanisms are far to be fully elucidated. The established 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 antigens to CD8+ T lymphocytes by the HLA-B*27 molecules. A plausible scenario would envisage the intestinal 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 useful to characterize the migration and phenotype of putative pathogenic T lymphocytes and, hopefully, to identify within these cells a core
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 generated in the inflamed tissues. 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 to the disease. Overall, this study could be instrumental 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 advance a more accurate and personalized therapeutic strategy.

Pertinent Publications of the proponent (last 5 years)

1. Paldino G, Tedeschi V, Proganò V, Salvati E, Licursi V, Vertecchi E, Bivolaru AL, Molteni E, Scrivo R, Congia M, Cauli A, Caccavale R, Paroli M, Kunkl M, Tuosto L, Sorrentino R, Fiorillo MT. An immunosenescent CD8+ T cell subset in patients with axial Spondyloarthritis and Psoriatic Arthritis links spontaneous motility to telomere shortening and dysfunction. Accepted for publication in Arthritis Rheum.

2. Amormino C, Russo E, Tedeschi V, Fiorillo MT, Paiardini A, Spallotta F, Rosanò L, Tuosto L, Kunkl M. 2024. Targeting staphylococcal enterotoxin B binding to CD28 as

a new strategy for dampening superantigen-mediated intestinal epithelial barrier dysfunctions. Front Immunol. 15:1365074.

3. Tedeschi V, Paldino G, Alba J, Molteni E, Paladini F, Scrivo R, Congia M, Cauli A, Caccavale R,Paroli M, Di Franco M, Tuosto L, Sorrentino R, D'Abramo M, Fiorillo MT. 2023. ERAP1 and ERAP2 Haplotypes Influence Suboptimal HLA-B*27:05-Restricted Anti-Viral CD8+ T Cell Responses Cross- Reactive to Self-Epitopes. Int J Mol Sci. 24:13335.

4. Kunkl M, Amormino C, Spallotta F, Caristi S, Fiorillo MT, Paiardini A, Kaempfer R, Tuosto L. 2023. Bivalent binding of staphylococcal superantigens to the TCR and CD28 triggers inflammatory signals independently of antigen presenting cells. Front Immunol. 14:1170821.Paroli M, Caccavale R,

5. Fiorillo MT, Spadea L, Gumina S, Candela V, Paroli MP. 2022. The Double Game Played by Th17 Cells in Infection: Host Defense and Immunopathology. Pathogens. 11:1547.

6. Mattorre B, Tedeschi V, Paldino G, Fiorillo MT, Paladini F, Sorrentino R. 2022. The emerging multifunctional roles of ERAP1, ERAP2 and IRAP between antigen processing and reninangiotensin system modulation. Front Immunol. 13:1002375.

7. Amormino C, Tedeschi V, Paldino G, Arcieri S, Fiorillo MT, Paiardini A, Tuosto L, Kunkl M. 2022. SARS-CoV-2 Spike Does Not Possess Intrinsic Superantigen-like Inflammatory Activity. Cells. 11:2526.

8. Tedeschi V, Paldino G, Kunkl M, Paroli M, Sorrentino R, Tuosto L, Fiorillo MT. 2022. CD8+ T Cell Senescence: Lights and Shadows in Viral Infections, Autoimmune Disorders and Cancer. Int J Mol Sci. 23:3374.

9. Kunkl M, Amormino C, Tedeschi V, Fiorillo MT, Tuosto L. 2022. Astrocytes and Inflammatory T Helper Cells: A Dangerous Liaison in Multiple Sclerosis. Front Immunol. 13:824411.

10. Kunkl M, Amormino C, Caristi S, Tedeschi V, Fiorillo MT, Levy R, Popugailo A, Kaempfer R, Tuosto L. 2021. Binding of Staphylococcal Enterotoxin B (SEB) to B7 Receptors Triggers TCR- and CD28-Mediated Inflammatory Signals in the Absence of MHC Class II Molecules. Front Immunol.12:723689.

11. Tedeschi V, Paldino G, Paladini F, Mattorre B, Tuosto L, Sorrentino R, Fiorillo MT. 2020. The Impact of the 'Mis-Peptidome' on HLA Class I-Mediated Diseases: Contribution of ERAP1 and ERAP2 and Effects on the Immune Response. Int J Mol Sci. 21:9608.

12. Paladini F, Fiorillo MT, Tedeschi V, Mattorre B, Sorrentino R. 2020. The multifaceted nature of aminopeptidases ERAP1, ERAP2 and LNPEP: from evolution to disease. Front Immunol. 11:1576.