***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**

**Supervisor: Maria Teresa Fiorillo (**[**mariateresa.fiorillo@uniroma1.it**](mailto:mariateresa.fiorillo@uniroma1.it)**)**

[**https://corsidilaurea.uniroma1.it/it/users**](https://corsidilaurea.uniroma1.it/it/users)

**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.

**References**

1. Tedeschi V, et al. (2022) Int J Mol Sci 23:3374

2. Fiorillo MT, et al. (2000) J Clin Invest 106:47-53

3. Fiorillo MT et al. (2005) J Biol Chem 280:2962-2971

4. Sorrentino R, et al. (2014) Mol Immunol 57:22-7

5. Tedeschi V et al. (2016) Mol Med. 22:215-223

6. Tedeschi V et al. (2019) Cells. 8:E572

7. Yair-Sabag et al. (2018) Proteomics. 18:e1700249

8. Tedeschi V, et al. (2020) Int J Mol Sci 21:9608

9. Xiao Z, et al. (2017) Sci Rep 7:5072

10. Dougados M, Baeten D. (2011) Lancet 377:2127-37

11. Mauro D, et al. (2021) Nat Rev Rheumatol 17:387-404

12. Terenzi R, et al. (2018) Clin Exp Rheumatol 36: 1-14.

13. Sieper J, Poddubnyy D. (2017) Lancet 390:73-84

14. Kuhne M, et al. (2009) Arthritis Rheum. 60:1635-46

15. Ranganathan V, et al. (2017) Nat Rev Rheumatol 13:359-67

16. Simone D, et al. (2021) Front Genet 12:703242

17. Xiong Y, et al. (2022) Front Immunol 13:996103

18. Evans DM, et al. (2011) Nature genetics 43:761-67

19. Cortes A, et al. (2013) Nat Genet 45:730-8

20. Vitulano C, et al. (2017) Clin Exp Immunol 190:281-290

21. Vecellio M, et al. (2019) Front Immunol 9:3132

22. Yang X, et al. (2022) Nature 612:771-777.

23. Fiorillo MT, Sorrentino R. (2009) Adv Exp Med Biol 649:255-262

24. Mauro D, et al. (2021) Semin Immunol 15:101607

25. Fessler J, et al. (2016) Ann Rheum Dis 75:748-754

26. Tamayo M, et al. (2010) Mutat Res 683:68-73

27. Tamayo M, et al. (2014) Mutat Res 765:1-5

28. Li Y, et al. (2016) Immunity 45:903-916

29. Heba AC, et al. (2021) J Autoimmun 123:102699

**Pertinent Publications of the proponent (last 5 years)**

Paroli M, Caccavale R, 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.

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.

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.

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.

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.

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.

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.

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.

Tedeschi V, Alba J, Paladini F, Paroli M, Cauli A, Mathieu A, Sorrentino R, D'Abramo M, Fiorillo MT. 2019. Unusual Placement of an EBV Epitope into the Groove of the Ankylosing Spondylitis-Associated HLA-B27 Allele Allows CD8+ T Cell Activation. Cells. 8:E572.

Fiorillo MT, Haroon N, Ciccia F, Breban M. 2019. Editorial: Ankylosing Spondylitis and Related Immune-Mediated Disorders. Front Immunol. 10:1232.

Paladini F, Fiorillo MT, Tedeschi V, D'Otolo V, Piga M, Cauli A, Mathieu A, Sorrentino R. 2019. The rs75862629 minor allele in the endoplasmic reticulum aminopeptidases intergenic region affects human leucocyte antigen B27 expression and protects from ankylosing spondylitis in Sardinia. Rheumatology. 58:2315-2324.

Paladini F, Fiorillo MT, Tedeschi V, Cauli A, Mathieu A, Sorrentino R. 2019. Ankylosing Spondylitis: A Trade Off of HLA-B27, ERAP, and Pathogen Interconnections? Focus on Sardinia. Front Immunol.

10:35.

Angioni MM, Piga M, Paladini F, Lai S, Erre GL, Floris A, Cauli A, Fiorillo MT, Passiu G, Carcassi C, Sorrentino R, Mathieu A. 2018. AIF-1 gene does not confer susceptibility to Behçet's disease: Analysis of extended haplotypes in Sardinian population. PLoS One. 13:e0204250.

Cauli A, Dessole G, Piga M, Angioni MM, Pinna S, Floris A, Congia M, Mascia E, Paladini F, Tedeschi V, Sorrentino R, Fiorillo MT, Mathieu A. 2018. Expression analysis of HLA-E and NKG2A and NKG2C receptors points at a role for Natural Killer function in Ankylosing Spondylitis. RMD Open. 4:e000597.

Paladini F, Fiorillo MT, Vitulano C, Tedeschi V, Piga M, Cauli A, Mathieu A, Sorrentino R. 2018. An allelic variant in the intergenic region between ERAP1 and ERAP2 correlates with an inverse expression of the two genes. Sci Rep. 8:10398.

Yair-Sabag S, Tedeschi V, Vitulano C, Barnea E, Glaser F, Melamed Kadosh D, Taurog JD, Fiorillo MT, Sorrentino R, Admon A. 2018. The Peptide Repertoire of HLA-B27 may include Ligands with Lysine at P2 Anchor Position. Proteomics. 18:e1700249.