DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

42° CYCLE

Project proposal for a Sapienza PhD scholarship

Main research line

Title of the research: Focus on the role of T cells and HLA-B27-mediated interaction with chondrocytes in autoimmune Spondyloarthritis

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Summary (max 500 words)
Ankylosing spondylitis (AS) is a common inflammatory rheumatic disease belonging to spondyloarthritis (SpA), a group of multifactorial autoimmune diseases affecting 1–2% of the Western population. Despite our growing knowledge, the complete etiology and pathophysiological mechanisms of AS remain unclear. The known contribution of the Human Leukocyte Antigen (HLA-B27) gene beside the genetic association of other genes (ERAP1 and 2, RUNX3; EOMES; ZMIZ1; IL7R and TBX21) identified by genome-wide association studies (GWAS) suggest an altered HLA-B27 pathway for the presentation of microbial/self antigens to CD8+ T lymphocytes. A plausible scenario would see the gut as the primary source of inflammation, likely due to a dysbiosis frequently observed in AS patients, from which pathogenic/cross-reactive and immunosenescent T cells reach other sites such as the axial skeleton and sacroiliac joints, contributing to the spread of inflammation. According to this perspective, it would be useful to characterize the migratory capacity and phenotype of CD8+ T cells and, hopefully, identify a core subset within these cells closely related to specific clinical conditions. In parallel, it would be crucial to investigate the ability of T cells to mount a response against a suboptimal peptidome generated in inflamed tissues. Analysis of the HLA-B27 peptidome of both the AS-associated allele (B*2705) and the non-AS-associated allele (B*2709) and the resulting effects on CD8+ T cells will be extended to chondrocytes expressing B*27 alleles to gain insights into the mechanism of antigen presentation in a disease-relevant tissue context. Overall, these studies could be crucial to clarify the involvement of T cells, particularly CD8+ T cells, in the pathogenesis of AS/SpA and their HLA-B27-mediated crosstalk with cartilage and entheseal chondrocytes. Furthermore, the identification of specific HLA-B27 autoantigens presented by chondrocytes could lead to more accurate and personalized therapeutic strategies.

Pertinent publications of the proponent (last 5 years)

Perelli A, Vichi C, Bevignani G, Scrivo R, Congia M, Cauli A, Caccavale R, Paroli M, Tedeschi V, Paldino G, Kunkl M , Tuosto L, **Fiorillo MT**. Altered peripheral CD4:CD8 T cell ratio in patients with Spondyloarthritis and Rheumatoid Arthritis. *Submitted for publication.*

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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**. (2025)

An immunosenescent CD8+ T cell subset in patients with axial Spondyloarthritis and Psoriatic Arthritis links spontaneous motility to telomere shortening and dysfunction. *Arthritis Rheum*. 77:854-866.

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.

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.

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, **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.

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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.