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Università Vita-Salute  
San Raffaele

**APPLICATION TO ACT AS SUPERVISOR AND  
RESEARCH PROJECT PROPOSAL**

**MO 20-5**

ed. 01 del  
21/02/2025

PO 20

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**PROJECT**

**Supervisor:**

EMANUEL DELLA TORRE

Title: Deciphering B and T cell co-stimulation for the targeted treatment of IgG4-Related Disease

Curriculum: MOLECULAR MEDICINE - Clinical and Experimental Medicine

Link to the personal page of the University or relevant hospital site website: <https://www.unisr.it/docenti/d/dellatorre-emanuel>

<https://research.hsr.it/en/divisions/genetics-and-cell-biology/emanuel-della-torre.html>

**Description of the Project (max 3,000 characters including spaces)**

**Background/gap of knowledge.** IgG4-related disease (IgG4RD) is a chronic fibro-inflammatory condition leading to organ damage if left untreated. Most patients respond to glucocorticoids and rituximab but relapse upon treatment discontinuation. Long-term steroid therapy or B-cell depletion are required to prevent disease flare but represent untenable treatment options due to remarkable side effects. Given the increasing recognition of IgG4-RD there is, therefore, urgent need to better understand disease pathogenesis in order to design innovative mechanistic strategies.

Over the last years, we demonstrated that IgG4RD is characterized by oligoclonal expansion of plasmablasts and cytotoxic T lymphocyte. As these cells likely engage in antigen-dependent co-stimulatory signals to sustain chronic inflammation, targeting co-stimulation represents an appealing mechanistic therapeutic strategy.

Our group has previously demonstrated that profound perturbations of the B and T-cell compartment are invariably observed in IgG4-RD and represent potential drivers of this disease. Plasmablasts, T-follicular helper (Tfh) and cytotoxic T cells (CTLs) are oligoclonally expanded in the blood and affected tissues of IgG4RD patients, interact via homotypic interactions, and track with markers of disease activity (Akiyama 2018, Della-Torre 2015,2018,2021, Lanzillotta 2018,2019,2020, Maehara 2018, Mattoo 2014,2016, Perugino 2021).

In addition, we showed that the rapid clinical improvement observed in IgG4-RD patients after B-cell depletion therapy with rituximab is paralleled by a decrease of circulating Tfh cells and CTLs, suggesting a tight dependence of pathogenic T-cell activation from a functional B-cell compartment (Della-Torre 2021, Mattoo 2016).

The possible genetic bases of aberrant B-T cell co-stimulation and the functional outcome of B-cell interaction with putative pathogenic T cells have never been systematically addressed.

**Rationale and hypothesis.** The decrease of circulating pathogenic T-cells after B-cell depletion therapy with rituximab suggests a tight dependence of these cells from a functional B-cell compartment. Hence, the working hypothesis of this study is that persistent aberrant co-stimulation of antigen-specific B and T lymphocytes sustains tissue inflammation in IgG4-RD.



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**Objectives and specific aims.** In the present work we aim:

- to systematically address the relevance of B-T cell interplay in the pathogenesis of IgG4RD.
- to decipher the genetic, immunological, and functional bases of B-T cell co-stimulation in the pathogenesis of IgG4RD

**Expected outcomes.** With this work we expect:

- to reveal a pathological substrate of IgG4-RD related to B-T cell co-stimulation;
- to identify patients who are likely to respond to modulators of co-stimulation;
- to pave the way for a personalized therapeutic approach.

**Skills that the student should acquire** (max. 600 characters including spaces):

- Perform an independent literature review on the issue
- Formulate a research question and a study plan
- Examine and compare the different available research strategies to identify the most appropriate one
- Understand the fundamentals of immunophenotyping and of genetic studies
- Independently perform cell cultures, flow-cytometry, and functional in vitro assays
- Identify a data collection strategy and collect the appropriate data
- Independently analyse, interpret, and draw conclusions from data
- Write a research paper

**References** (max. 15)

Akiyama et al. *Rheumatology*. 2018;57:236-245  
Della-Torre et al. *Rheumatology*. 2021;60:3947-3949  
Della-Torre et al. *ArthritisRheumatol*. 2018;70:1133-1143.  
Della-Torre et al. *AnnRheumDis*. 2015;74:2236-43  
Lanzillotta et al. *BMJ*. 2020;369:m1067  
Lanzillotta et al. *ClinExpRheumatol*. 2019;37:159-166  
Lanzillotta et al. *ArthritisResTher*. 2018;20:222.  
Maehara et al. *LifeSciAlliance*. 2018;1:e201800050  
Mattoo et al. *JAllergyClinImmunol*. 2014;134:679-87  
Mattoo et al. *JAllergyClinImmunol*. 2016;138:825-38  
Perugino et al. *JAllergyClinImmunol*. 2021;147:368-382