

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 01 del 21/02/2025 PO 20 Page 4 of 11</p>
---	--	--

PROJECT

Supervisor:

Mona-Rita Yacoub

Title:

"Tracking the eosinophilic trail: molecular and cardiac MRI findings
for early detection of myocardial involvement"

Curriculum:

Clinical and Experimental Medicine

Link to the personal page of the
University or relevant hospital site
website:

<https://www.hsr.it/dottori/mona-rita-yacoub>

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

The diagnosis of hypereosinophilic syndrome (HES) requires hypereosinophilia—eosinophil count $>1,500$ cells/ μL —alongside organ damage from eosinophil-driven inflammation¹. However, identifying reliable biomarkers for disease activity and progression still represent a challenge in clinical practice. Peripheral eosinophil counts are often used as surrogate markers for eosinophilic tissue inflammation, but discrepancies between blood eosinophilia and clinical manifestations are common²⁻⁴, suggesting limitations in their ability to accurately gauge disease activity. Eosinophil activation involves the release of cytotoxic granule proteins such as eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN), through mechanisms like exocytosis, piecemeal degranulation, and cytolytic extracellular trap cell death (ETosis)⁵⁻¹². Galectin-10, a key component of Charcot-Leyden crystals (CLCs), is actively released during eosinophil extracellular trap cell death (EETosis) and serves as a marker of eosinophil activation^{13,14}. Despite the importance of these mediators in eosinophilic inflammation, their potential as biomarkers for HES remains poorly explored.

Cardiac involvement worsens prognosis in HES, with eosinophilic myocarditis and endomyocardial fibrosis being major complications. There is no consensus on optimal tests for early cardiac involvement. Echocardiography often shows normal results in early stages, while cardiac magnetic resonance (CMR) offers greater sensitivity and specificity for detecting ventricular thrombi, myocardial inflammation, and fibrosis, enabling earlier identification of cardiac disease¹⁵. However, no strategy exists to prioritize patients for early CMR evaluation.

This project aims to explore the relationship between eosinophil-derived soluble mediators, clinical disease activity, and cardiac involvement, addressing key gaps in early detection and



risk stratification for HES. The PhD student will play a central role in study design and interpretation of clinical, imaging, and laboratory data. Objectives include: 1) evaluating eosinophilic activation markers at baseline, 6, and 12 months, correlating them with disease activity and response to eosinophil-targeted therapies; 2) identifying biomarkers linked to cardiac involvement; 3) assessing CMR's diagnostic performance for early eosinophilic myocarditis. The PhD student will lead the longitudinal assessment of eosinophil-derived mediators and their correlation with disease activity. Expected outcomes include defining the clinical utility of these mediators as biomarkers of immunopathologic activity in HES. The student will also investigate their association with cardiac involvement and evaluate CMR's role in detecting subclinical eosinophilic myocarditis. Integrating biomarker profiling with advanced imaging may offer a novel strategy for early diagnosis and timely, targeted treatment in high-risk patients.

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

Through this project, the student will acquire advanced skills in eosinophil biology, including cell isolation, flow cytometry, ELISA, and analysis of eosinophil activation markers (ECP, EDN, Galectin-10). The student will gain experience in clinical research focusing on characterization of patients with HES, biobanking. Additionally, the student will gain experience in conducting degranulation and ETosis assays. Training will include data analysis, correlation with cardiac MRI findings, and scientific writing, fostering independence in translational immunology research.

References (max. 15)

1. Shomali W, Gotlib J. World Health Organization and International Consensus Classification of eosinophilic disorders: 2024 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2024 May;99(5):946-68.
2. Miyabe Y, Kobayashi Y, Fukuchi M, Saga A, Moritoki Y, Saga T, Akuthota P, Ueki S. Eosinophil-mediated inflammation in the absence of eosinophilia. *Asia Pac Allergy.* 2021 Jul 13;11(3):e30.
3. Kita H. Eosinophils: multifaceted biological properties and roles in health and disease. *Immunol Rev.* 2011 Jul;242(1):161-77.



4. Khoury P, Akuthota P, Ackerman SJ, Arron JR, Bochner BS, Collins MH, et al. Revisiting the NIH Taskforce on the Research needs of Eosinophil-Associated Diseases (RE-TREAD). *J Leukoc Biol.* 2018 Jul;104(1):69-83.
5. Cengiz C. Serum eosinophilic cationic protein is correlated with food impaction and endoscopic severity in eosinophilic esophagitis. *Turk J Gastroenterol.* 2019 Apr;30(4):345-9.
6. Koh GC, Shek LP, Goh DY, Van Bever H, Koh DS. Eosinophil cationic protein: is it useful in asthma? A systematic review. *Respir Med.* 2007 Apr;101(4):696-705.
7. Rank MA, Ochkur SI, Lewis JC, Teaford HG 3rd, Wesselius LJ, Helmers RA, et al. Nasal and pharyngeal eosinophil peroxidase levels in adults with poorly controlled asthma correlate with sputum eosinophilia. *Allergy.* 2016 Apr;71(4):567-70.
8. Jin J, Guo B, Zhang W, Chen JJ, Deng YQ, Xiang R, et al. Predictive Value of Eosinophil Cationic Protein in Nasal Secretions in Eosinophilic Chronic Rhinosinusitis. *Laryngoscope.* 2023 Dec;133(12):3304-12.
9. Idler BM, Iijima K, Ochkur SI, Jacobsen EA, Rank MA, Kita H, et al. Eosinophil Peroxidase: A Biomarker for Eosinophilic Chronic Rhinosinusitis Agnostic of Polyp Status. *Laryngoscope.* 2024 Jan;134(1):69-78.
10. Metcalfe, D. D. et al. Biomarkers of the involvement of mast cells, basophils and eosinophils in asthma and allergic diseases. *World Allergy Organization Journal* vol. 9 Preprint at <https://doi.org/10.1186/s40413-016-0094-3> (2016).
11. Makiya MA, Khoury P, Kuang FL, Mata AD, Mahmood S, Bowman A, et al. Urine eosinophil-derived neurotoxin: A potential marker of activity in select eosinophilic disorders. *Allergy.* 2023 Jan;78(1):258-69.
12. Tomizawa H, Yamada Y, Arima M, Miyabe Y, Fukuchi M, Hikichi H, et al. Galectin-10 as a Potential Biomarker for Eosinophilic Diseases. *Biomolecules.* 2022 Sep 27;12(10):1385.
13. Melo, Rossana. "Charcot-Leyden Crystal Formation Is Closely Associated with Eosinophil Extracellular Trap Cell Death." *Blood*, American Society of Hematology, 2018.



UniSR

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

Page 7 of 11

14. Takeda M, Ueki S, Yamamoto Y, Nara M, Fukuchi M, Nakayama K, et al. Hypereosinophilic syndrome with abundant Charcot-Leyden crystals in spleen and lymph nodes. *Asia Pac Allergy*. 2020 Jul 8;10(3):e24.
15. Zhong Z, Yang Z, Peng Y, Wang L, Yuan X. Diagnosis and treatment of eosinophilic myocarditis. *J Transl Autoimmun*. 2021 Sep 2;4:100118.