

BIOGRAPHICAL SKETCH

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NAME: **CASSATELLA, MARCO A.**

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: **Professor of General Pathology**

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Verona, Italy	MD.	07/83	Medicine and Surgery
University of Verona, Italy	Specialization	12/88	Clinical Biochemistry
The Wistar Institute, Philadelphia, USA	Post-doc	01/87-03/89	Immunology

A. Personal Statement

As an immunologist in training, I have always been involved in studies focused on the regulatory mechanisms involved in controlling effector functions of cells belonging to the innate immune system in the field of inflammation and innate immunity. In such regard, my group was the first to uncover the notion that polymorphonuclear neutrophils are not only targets of cytokines that modulate their effector functions but may also represent important sources of a variety of cytokines themselves. Uncovering this unexpected function of neutrophils has changed the immunologists' view so that neutrophils currently emerge as key components of the effector and regulatory circuits of innate and adaptive immune systems. Moreover, the fact that neutrophils produce cytokines, along with other features, has led to a renewed interest in neutrophil biology, with a growing focus on their previously unappreciated potential role in cancer. I have published over 250 peer-reviewed publications in high-impact journals, including Nature, Immunity, Science Immunology, Journal of Experimental Medicine, Blood, Journal of Clinical Investigation, Nature Communications, PNAS, Journal of Immunology, and *Journal of Leukocyte Biology*.

The proposed research aims to define how the interaction between neutrophils and the oral pathogen *Filifactor alocis* results in profound chromatin reprogramming and impacts the functional neutrophil responses. Periodontitis is a chronic inflammatory disease that affects an individual's overall health. Evidence of periodontitis' association with other systemic diseases such as rheumatoid arthritis, diabetes, cardiovascular disease, and cancer keeps growing. Neutrophil functional responses typically protect the host against oral pathogens. However, periodontal bacteria developed sophisticated strategies to evade neutrophils' microbicidal functions and benefit from the dysregulated inflammation produced at the oral mucosal barrier. A better understanding of how *F. alocis* evades neutrophil killing and the consequences of that interaction to disease progression represents an unexplored and relevant area of investigation. Defining the cellular and molecular events that lead to neutrophil epigenetic marks driven by pathogen interaction is an unexplored area that will move the field forward. Understanding how pathogens can modulate neutrophil functions in the context of periodontitis will aid in developing novel drug targets to correct neutrophil dysfunction in this disease. My team and I have been working with Dr. Uriarte's team for more than a year to generate the preliminary data presented for Aim 1 of this application. I am very delighted to serve as a consultant and advise on any issues related to the proposed study, and I look forward to a productive collaboration.

Ongoing projects:

Identification of novel, very immature, specific progenitors of human neutrophils:

In this context, Cassatella's group has discovered novel CD34⁺ and CD34^{dim/-} neutrophil-committed progenitors (NCPs) which currently represent the earliest neutrophil precursors that, to date, can be identified and sorted by flow.

1. SIGNORETTO I, CALZETTI F, FINOTTI G, LONARDI S, BALANZIN C, BIANCHETTO-AGUILERA F, GASPERINI S, GARDIMAN E, CASTELLUCCI M, RUSSIGNAN A, BONIFACIO M, SICA A, VERMI W, TECCHIO C, SCAPINI P, TAMASSIA N, **CASSATELLA MA**. Uncovering two neutrophil-committed progenitors that immediately precede promyelocytes during human neutropoiesis **Cell Mol Immunol**. 2025 Mar;22(3):316-329. doi: 10.1038/s41423-025-01259-w. Epub 2025 Feb 13.
2. CALZETTI F, FINOTTI G, **CASSATELLA MA**. Current knowledge on the early stages of human neutropoiesis. **Immunol Rev**. 2023 Mar;314(1):111-124. doi: 10.1111/imr.13177. Epub 2022 Dec 9. PMID: 36484356 Review.
3. CALZETTI F, FINOTTI G, TAMASSIA N, BIANCHETTO-AGUILERA F, CASTELLUCCI M, CANÈ S, LONARDI S, CAVALLINI C, MATTE A, GASPERINI S, SIGNORETTO I, BENEDETTI F, BONIFACIO M, VERMI W, UGEL S, BRONTE V, TECCHIO C, SCAPINI P, **CASSATELLA MA**. CD66b⁺CD64^{dim}CD115⁻ cells in the human bone marrow represent neutrophil-committed progenitors. **Nat Immunol**. 2022 May;23(5):679-691. doi: 10.1038/s41590-022-01189-z. Epub 2022 Apr 28. PMID: 35484408

Ongoing Research Support

- 1) Project Number (PD/PI) (Cassatella): IG20339 02/01/2023 - 01/01/2028
Source: AIRC (Italian association for research against cancer)
Title: Dissecting the role of novel neutrophil-progenitors in malignancy pathogenesis and in neutrophil subset generation
Major Goals: The aim of this proposal is to determine the fate of recently discovered CD34⁺neutrophil progenitors
Role: PI
- 2) Project Number (PD/PI) (Cassatella): PRIN 20227YR8AW 30/05/2023 - 29/05/2025
Source: Ministero dell'Istruzione, dell'Università e della Ricerca
Title: Advancing the knowledge of human neutrophils displaying polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC) functions
Major Goals: The aim of this proposal is to determine the molecular features of human mature PMN-MDSCs
Role: PI

Citations:

- 1 SIGNORETTO I, CALZETTI F, FINOTTI G, LONARDI S, BALANZIN C, BIANCHETTO-AGUILERA F, GASPERINI S, GARDIMAN E, CASTELLUCCI M, RUSSIGNAN A, BONIFACIO M, SICA A, VERMI W, TECCHIO C, SCAPINI P, TAMASSIA N, **CASSATELLA MA**. Uncovering two neutrophil-committed progenitors that immediately precede promyelocytes during human neutropoiesis **Cell Mol Immunol**. 2025 Mar;22(3):316-329. doi: 10.1038/s41423-025-01259-w. Epub 2025 Feb 13.
- 2 2PETTINELLA F, MARIOTTI B, LATTANZI C, BRUDEREK K, DONINI M, COSTA S, MARINI O, IANNOTTO G, GASPERINI S, CAVEGGION E, CASTELLUCCI M, CALZETTI F, BIANCHETTO-AGUILERA F, GARDIMAN E, GIANI M, DUSI S, CANTINI M, VASSANELLI A, PAVONE D, MILELLA M, PILOTTO S, BIONDANI P, HÖING B, SCHLEUPNER MC, HUSSAIN T, HADASCHIK B, KASPAR C, VISCO C, TECCHIO C, KOENDERMAN L, BAZZONI F, TAMASSIA N, BRANDAU S, **CASSATELLA* MA**, SCAPINI* P. Surface CD52, CD84, and PTGER2 mark mature PMN-MDSCs

from cancer patients and G-CSF-treated donors. **Cell Rep Med.** 2024 Feb 20;5(2):101380. doi: 10.1016/j.xcrm.2023.101380. Epub 2024 Jan 18. PMID: 38242120 Free PMC article.

- 3 MONTALDO E, LUSITO E, BIANCHESSI V, CARONNI N, SCALA S, BASSO-RICCI L, CANTAFFA C, MASSERDOTTI A, BARILARO M, BARRESI S, GENUA M, VITTORIA FM, BARBIERA G, LAZAREVIC D, MESSINA C, XUE E, MARKTEL S, TRESOLDI C, MILANI R, RONCHI P, GATTILLO S, SANTOLERI L, DI MICCO R, DITADI A, BELFIORI G, ALEOTTI F, NALDINI MM, GENTNER B, GARDIMAN E, TAMASSIA N, **CASSATELLA MA**, HIDALGO A, KWOK I, NG LG, CRIPPA S, FALCONI M, PETTINELLA F, SCAPINI P, NALDINI L, CICERI F, AIUTI A, OSTUNI R. CELLULAR AND TRANSCRIPTIONAL DYNAMICS OF HUMAN NEUTROPHILS AT STEADY STATE AND UPON STRESS. **Nat Immunol.** 2022 Oct;23(10):1470-1483. doi: 10.1038/s41590-022-01311-1. Epub 2022 Sep 22. PMID: 36138183 Free PMC article.
- 4 CALZETTI F, FINOTTI G, TAMASSIA N, BIANCHETTO-AGUILERA F, CASTELLUCCI M, CANÈ S, LONARDI S, CAVALLINI C, MATTE A, GASPERINI S, SIGNORETTO I, BENEDETTI F, BONIFACIO M, VERMI W, UGEL S, BRONTE V, TECCHIO C, SCAPINI P, **CASSATELLA MA**. CD66b⁺CD64^{dim}CD115⁺ cells in the human bone marrow represent neutrophil-committed progenitors. **Nat Immunol.** 2022 May;23(5):679-691. doi: 10.1038/s41590-022-01189-z. Epub 2022 Apr 28. PMID: 35484408

B. Positions, Scientific Appointments, and Honors

Positions, Scientific Appointments

2018-present	Member, CTS Member of the Italian Association Against Cancer (AIRC)
2016	Scientific Organizer, 49 th Society of Leukocyte Biology Meeting in Joint with "Neutrophil 2016, Verona, Italy
2013	Steering Committee Member, 15 th International Congress of Immunology, Milano, Italy
2010-present	Editorial Board Member, Cytokine
2010	Scientific Organizer, European Phagocyte Workshops, Bari, Italy
2009	Steering Committee Member, 1 st Joint Meeting of European National Societies of Immunology, 16 th European Congress of Immunology, Berlin, Germany
2008-present	Section Editor, Journal of Leukocyte Biology
2008-2011	Member, Dompe' Advisory Board
2007-2010	Member, Telethon Scientific Committee
2006	Steering Committee Member, 1 st Joint Meeting of European National Societies of Immunology, 16 th European Congress of Immunology, Paris, France
2003	Scientific Organizer, European Phagocyte Workshops, Verona, Italy
2000-present	Reviewer of: Nature, Science, Nature Immunology, Nature Reviews in Immunology, Trends in Immunology, BLOOD, JCI, JEM, Journal of Immunology, European Journal of Immunology, Immunology, Infection and Immunity, Laboratory Investigation, Cancer Research, Arthritis and Rheumatism, British Journal of Pharmacology, Trends in Microbiology
1999	Scientific Organizer, European Phagocyte Workshops, Milano, Italy
2001-present	Professor, University of Verona, Medical School, Institute of General Pathology, Verona, Italy
1992-2001	Associate Professor, University of Verona, Medical School, Institute of General Pathology, Verona, Italy
1988-1992	Research Assistant, University of Verona, Medical School, Institute of General Pathology, Verona, Italy
1988-1992	Verona, Italy

Honors in the last 10 years

2021-2024 SIICA President

2021	Honorary Member of the Society of Leukocyte Biology
2017-2020	President-elect, SIICA
2017-2020	SIICA Honorary Member
2017	Bonazinga Award from the Society of Leukocyte Biology
2005-2008	Councillor, SIICA Board
2002-2003	Councillor, European Society for Clinical Investigation
2000-2004	Councillor, SIICA Board
1988-present	Invited speaker or chairman in numerous national or international congresses including "Gordon Research Conference on Phagocytes", International Congress of Immunology (ICI) and European Congress of Immunology (ECI).

C. Contributions to Science

1. Molecular mechanisms activating CD16/Fc γ RIIIA in human Natural Killer (NK): I have confirmed that NK cell activation by specific ligands occurs through mechanisms distinct from those induced by IL-2 and indicates that extracellular Ca²⁺ represents a stringent requirement for cytokine production induced in NK cells through specific Fc γ R stimulation. I am the first to show that the Ca²⁺ induced upon Fc γ R(CD16) crosslinking, though necessary, is not sufficient per se to induce activation of lymphokine genes, compatible with the hypothesis that Fc γ R(CD16) crosslinking generates additional transducing signals that synergize with IL-2 to maximally activate NK cells.

1.1. **M.A. CASSATELLA**, I.ANEGON, M.C.CUTURI, P.GRISKEY, G.TRINCHIERI, B.PERUSSIA. Fc γ R (CD16) interaction with ligand induces Ca²⁺ mobilization and phosphoinositide turnover in human natural killer cells. Role of Ca²⁺ in Fc γ R (CD16)-induced transcription and expression of lymphokine genes. J. Exp. Med 169:549-566, 1989.

1.2. G.TRINCHIERI, M. KUBIN, G. BELLONE, **M.A.CASSATELLA**. Cytokine cross-talk between phagocytic cells and lymphocytes: relevance for differentiation/activation of phagocytic cells and regulation of adaptive immunity. J. Cell Biochem 53(4):301-308, 1993.

2. Molecular mechanisms regulating the production of reactive oxygen intermediates by myeloid cells. I have dedicated a significant amount of time and resources to unraveling the cellular and molecular mechanisms involved in the expression of NADPH oxidase components in myeloid cells and polymorphonuclear leukocytes.

2.1. **M.A. CASSATELLA**, L.HARTMAN, B.PERUSSIA, G.TRINCHIERI. Tumor necrosis factor and immune interferon synergistically induce cytochrome b heavy chain gene expression and NADPH oxidase in human leukemic myeloid cells. J. Clin Invest. 83:1570-1580, 1989.

2.2. **M.A.CASSATELLA**, F.BAZZONI, R.M.FLYNN, S.DUSI, G.TRINCHIERI, F.ROSSI. Molecular basis of interferon-gamma and lipopolysaccharide enhancement of phagocyte respiratory burst capability. Studies on the gene expression of several NADPH oxidase components. J. Biol Chem. 265(33):20241-20246, 1990.

2.3. **M.A. CASSATELLA**, F.BAZZONI, F.CALZETTI, I.GUASPARRI, F.ROSSI, G.TRINCHIERI. Interferon-gamma transcriptionally modulates the expression of the genes for the high affinity IgG-Fc receptor and the 47-kDa cytosolic component of NADPH oxidase in human polymorphonuclear leukocytes. J. Biol Chem. 266(33):22079-22082, 1991.

3. Identification, characterization and function of slanDCs in tumors: Studies from my group characterized a novel human myeloid cell population known as "slanDC" (actually corresponding to the majority of CD16⁺⁺/CD14⁻-monocytes) in human tumors. We reported its specific and selective involvement in the nodal immune responses towards carcinoma cells. Recent studies from my lab demonstrated an efficient CD16-mediated ADCC and antibody-dependent phagocytosis (ADP) by slan⁺-monocytes/slanDCs, which takes place in patients with tumors.

3.1. W.Vermi, A.Micheletti, S.Lonardi, C.Costantini, F.Calzetti, R.Nascimbeni, M.Bugatti, M.Codazzi, P.C.Pinter,

K.Schäkel, N.Tamassia, **M.A.Cassatella**. slanDCs selectively accumulate in carcinoma-draining lymph nodes and marginate metastatic cells. *Nat Commun.* 8;5:3029, 2014.

3.2. W.Vermi, A.Micheletti, G.Finotti, C.Tecchio, F.Calzetti, S.Costa, M.Bugatti, S.Calza, C.Agostinelli, S.Pileri, P.Balzarini, A.Tucci, G.Rossi, L.Furlani, G.Todeschini, A.Zamò, F.Facchetti, L.Lorenzi, S.Lonardi, **M.A.Cassatella**. slan+ monocytes and macrophages mediate CD20-dependent B cell lymphoma elimination via ADCC and ADCP. *Cancer Res.* 1:78 (13):3544-355, 2018.

3.3 A.Micheletti, G.Finotti, F.Calzetti, S.Lonardi, E.ZORATTI, M.Bugatti, W.Vermi, **M.A. Cassatella**. slanDCs/M-DC8+ cells constitute a distinct subset of dendritic cells in human tonsils. *Oncotarget* 7(1):161-175, 2016.

3.4 Finotti G, Pietronigro E, Balanzin C, Lonardi S, Constantin G, Chao MP, Tecchio C, Vermi W, **Cassatella MA**. slan+ Monocytes Kill Cancer Cells Coated in Therapeutic Antibody by Trogoptosis. *Cancer Immunol Res.* 2023 Nov 1;11(11):1538-1552. doi: 10.1158/2326-6066.CIR-23-0239. PMID: 37695535

4. Defining the biology of neutrophils in inflammation and cancer:

In the past decades, studies from my group have established that polymorphonuclear neutrophils are remarkably versatile cells whose functions go far beyond phagocytosis and killing. In fact, besides being involved in primary defense against infections-mainly through phagocytosis, generation of toxic molecules, release of toxic enzymes, and formation of extracellular traps, neutrophils regulate the development and the evolution of inflammatory and immune responses. My lab has shown that these latter neutrophil-mediated functions occur by various mechanisms, including the production of newly manufactured cytokines. Indeed, neutrophils are not only targets of cytokines that modulate their effector functions but may also represent important sources of a number of cytokines themselves, which has implications for antimicrobial immunity, autoimmunity, and anticancer immunity.

4.1. **M.A. CASSATELLA**, L.MEDA, S.BONORA, M.CESKA, G.CONSTANTIN. Interleukin 10 inhibits the release of proinflammatory cytokines from human polymorphonuclear leukocytes. Evidence for an autocrine role of TNF α and IL-1 α in mediating the production of IL-8 triggered by LPS. *J. Exp Med.*, 178:2207-2211, 1993.

4.2. **M.A.CASSATELLA**, L.MEDA, S.GASPERINI, F.CALZETTI, S.BONORA. Interleukin-10 up-regulates IL-1 receptor antagonist gene expression and production from lipopolysaccharide-stimulated human polymorphonuclear leukocytes. *J. Exp. Med.*, 179, 1695-1699, 1994.

4.3. P.Scapini, B.Nardelli, G.Nadali, F.Calzetti, G.Pizzolo, C.Montecucco, **M.A. Cassatella**. G-CSF-stimulated neutrophils are a prominent source of functional B γ LyS. *J. Exp Med.* 197(3):297-302, 2003

4.4. M.S.Davey, N.Tamassia, M.Rossato, F.Bazzoni, F.Calzetti, K.Bruderek, M.Sironi, L.Zimmer, B.Bottazzi, A.Mantovani, S.Brandau, B.Moser, M.Eberl, **M.A.Cassatella**. Failure to detect neutrophil-derived IL-10. *Nat Immunol* 12(11):1017-1028, 2011.

Complete List of Published Work:

<https://pubmed.ncbi.nlm.nih.gov/?term=cassatella+m&sort=date&size=50>