Mariagrazia Uguccioni, MD

1. Personal information

Date of birth: September 28, 1961
Nationality: Italian, Swiss
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Current position(s)
Deputy Director, IRB
Group Leader, IRB
Full Professor, Università della Svizzera italiana (USI)

2. Education

1994	Specialization in Haematology, University of Bologna, IT
1993-1995	Postdoctoral, Theodor Kocher Institute, University of Bern, CH
1992	Visiting scientist, Guy's Hospital, Rheumatology Department, London, UK
1990	Visiting scientist, Guy's Hospital, Rheumatology Department, London, UK
1990-1993	Postdoctoral, Dept. of Immunology, University of Bologna, IT
1990	MD degree, Faculty of Medicine and Surgery, University of Bologna, IT

3. Employment history

2010-now	Deputy Director, Institute for Research in Biomedicine, CH
2000-now	Group Leader, Institute for Research in Biomedicine, CH
2016-2022	Extraordinary Professor, Humanitas University, Faculty of Biomedical Sciences, Milan, IT
1995-1999	Senior scientist, Theodor Kocher Institute, University of Bern, CH
1993-1995	Postdoctoral fellow, Theodor Kocher Institute, University of Bern, CH
1990-1993	Research fellow, Dept. of Immunology, University of Bologna, IT

4. Institutional responsibilities

2010-now	Deputy Director, Institute for Research in Biomedicine, CH
2000-now	Health Officer, Institute for Research in Biomedicine, CH
2000-now	Biosafety Officer, Institute for Research in Biomedicine, CH
2001-now	Ethical Committee coordinator, Institute for Research in Biomedicine, CH
2005-now	Coordinator internal seminars: IRB Monday discussions, CH
2021-now	Co-Coordinator Monday Noon Discussions Bios+, CH
2018-2023	Data Protection Officer, Institute for Research in Biomedicine, CH
2009-2022	IRB coordinator for the new building construction and purchases, CH
2000-2006	PhD programme coordinator, Institute for Research in Biomedicine, CH
1995-1999	Coordinator microscopy/histology, Theodor Kocher Institute, University of Bern, CH

5. Approved research projects (last 10 years)

2023-2026	Fondazione Ceschina: Unbiased immune profiling of circulating leukocytes in Ankylosing Spondylitis: from new makers discovery to their role in osteoimmunity (PI)
2020-2023	INNOSUISSE: Development of an innovative therapy for ANCA vasculitis (PI)
2021-2023	Fondazione Fidinam – The innate immune response against SARS-CoV-2 (PI)
2019-2023	Fondazione Rocca – The role of MFS in cell migration (PI)
2019-2022	Fondazione Ceschina – The role of chemokines in tuning the inflammatory responses in ankylosing Spondylitis
2018-2020	Foundation for Research on Viral Diseases: The role of chemokines in tuning the inflammatory responses during infection (PI)
2005-2020	San Salvatore Foundation: i) Molecular and biological mechanisms of non-Hodgkin's lymphomas growth at extranodal sites; ii) Molecular and biological mechanisms of non-Hodgkin's lymphomas growth at extranodal sites (follow on);

	iii) The role of chemokine synergy-inducing molecules in controlling the tumour microenvironment, cell migration and metastasis.
2016-2018	Fondazione Ceschina: The role of chemokines in tuning inflammatory responses (PI)
2009-2017	EU FP7: i) IEF– MD-THIV, Migration and Differentiation of Th17 Cells in HIV/SIV Infection (PI-Supervisor to Valentina Cecchinato); ii) TIMER, TargetIng novel MEchanisms of Resolution in inflammation (PI and Training Officer); iii) ADITEC, Advanced Immunization Technologies (Co-PI).
2013-2016	SNF: Impact of synergy-inducing molecules on chemokine activities (PI)
2013-2016	Gottfried und Julia Bangerter-Rhyner Stiftung: Dampening inflammation in autoimmunity by targeting chemokine synergy-inducing molecules (PI)
2011-2016	Institute for Arthritis Research: Chemokines in arthritis (PI)
2012-2015	San Salvatore Foundation: The role of chemokine synergy-inducing molecules in controlling the tumour microenvironment, cell migration and metastasis (PI)
2012-2015	SNSF-ProDoc: Cell migration (Co-PI)
2007-2015	SNF REquip co-applicant: Confocal microscopy, high-throughput cellular screening, NMR spectrometer.
2000-2014	EU FP4 – i) DETEC; ii) SIV/HIV vaccines – detecting efficacy and explaining inefficacy. EU FP5 – MUVADEN, Mucosal vaccines against human and simian immunodeficiency viruses based on dendritic cells. EU FP6: i) TIP-VAC, Explaining and Improving Efficacy of targeted Immunodeficiency Virus-like Particle Vaccines against AIDS; ii) DEC-VAC, Development of a Dendritic cell-targeted vaccine against AIDS; iii) INNOCHEM, Innovative Chemokine-based Therapeutic Strategies for autoimmunity and Chronic Inflammation (Deputy Coordinator and Scientific Coordinator).
2012-2014	SNF: Analysis of molecular and cellular mechanisms in immune-mediated tissue damage of the skin: Hidradenitis suppurativa as a model disease (Co-PI)
2012-2014	SNSF-HIV Cohort Studies – Migration and differentiation of TH17 cells in HIV infection (PI).

6. Supervision of junior researchers at graduate and postgraduate level

11 Postdocs: Katherina Williman (TKI, Bern), Patricia Ogilvie, Ulf Panzer, Silvia Sebastiani, Tamara Visekruna, Luisa Stefano, Lorenzo Raeli, Michele Proietti, Valentina Cecchinato, Philippe Paparoditis, Veronica Martini

11 PhD students all at IRB: Samantha Paoletti, Vibor Petkovic, Katrin Kuscher, Daniel Venetz, Milena Schiraldi, Denise Bottinelli, Camilla Marini, Gianluca D'Agostino, Yelena Silvestri, Edisa Pirani, Elaheh Ghovehoud

5 Master's students: Michelle Berni (UniBasel), Francesco Mueller (UniLausanne), Mara Ambrosini (UniBasel); Francesco Bagnis (UniPavia, IT), Enrico Fassi (UniMilan, IT), Elija Diefenbacher (USI), Alejandro Rodriguez-Perez (USI)

5 Students for MD thesis: Davide Robbiani (UniBern), Judith Scharer (UniBern), Jan Braunwalder (UniBern), Cornelia Hallenbarter-Betschart (UniBern), Yves Sommer (USI)

7. Teaching activities

2000-now	Mentoring of graduate students (Master's and PhD level) and postdocs, IRB, CH
2021-2023	Teaching at the University of Bern: "Dynamics of cellular contacts: cell adhesion and motility" programme for Master and PhD students
2016-2022	Teaching at Humanitas University, Faculty of Biomedical Sciences, Milan, IT
2014-2021	Teaching at European School of Oncology: "Chemokines in chronic inflammation and lymphomas" for the Certificate of competence in lymphomas
2006-2011	Teaching as Adjunct Professor, Faculty of Medicine and Surgery, School of Rheumatology, University of Bologna, IT
1999-2004	Teaching as Adjunct Professor, Faculty of Pharmacology, School of Toxicology, University of Bologna, IT
1995-1999	Mentoring of graduate students (Master's and PhD level) and postdocs, UniBe, CH

8. Memberships in panels, boards, etc., and individual scientific review activities

Panels and Boards

2015-2022	Member of the Commission for selection of candidates for the PhD programme in Molecular and Experimental Medicine at Humanitas University, Milan, IT

2009-2011 Member of Telethon Switzerland Scientific Committee
2009-2011 Member of the Commission for selection of candidates for the PhD programme in Molecular Medicine, San Raffaele University, Milan, IT
2005-2011 EU independent expert, panel evaluation Health-Innovation
2000-2004 Chair 8th workshop on Human Leukocyte Differentiation Antigens (Cytokine-chemokine receptors)
1998-2000 Chair 7th workshop on Human Leukocyte Differentiation Antigens (Cytokine-chemokine receptors)

Editorial activities

Frontiers in Immunology (Cytokines and Soluble Mediators in Immunity), Frontiers in Immunology (Inflammation)

Scientific review activities

Grants: Welcome Trust UK, MIUR IT, MRC UK, Versus Arthritis UK, EU-Health, SNSF

9. Active memberships in scientific societies

British Society for Immunology; Italian Society for Immunology, Clinical Immunology and Allergy; International Society for Vaccines; International Society for Dendritic Cells and Vaccine Science.

10. Organisation of conferences

2010 Cytokines and Chemokines –Post transcriptional regulation– Saint Sorlin d'Arves, FR
2014 The chemokine system: molecules, mechanisms and functions – Borgo S.Giulia, IT
2017-2020 Giornata della Ricerca chair and co-organizer, USI, Lugano (yearly)
2012-2020 European Academy of Dermatology and Venereology "From the Bench to the Clinic", Bellinzona, CH (yearly)
2017 Ankylosing Spondylitis: tales of molecules and patients – Lugano, CH
2019 ECMC – European chemokine and cell migration conference – Salamanca, ES
2023 Ankylosing Spondylitis: tales of molecules and patients – Bellinzona, CH

11. Prizes, awards, fellowships

Prizes and awards

2009 Elected Member of the Academy of Science, Institute of Bologna, for the studies on the relevance of chemokines in human pathology

Fellowships

1993-1994 Italian NIH

12. Career breaks

None

Major scientific achievements

The research performed by my group is the analysis of the activity of chemokines and chemokine receptors, which modulate cell migration, in health and disease in humans. Our long-standing interest are the mechanisms that fine tune modulate chemokine activities and chemokine receptor responses in chronic inflammatory conditions, infections and tumours.

Characterization of chemokines and chemokine receptor expression on leukocytes

From 1993, when I joined the Theodor Kocher Institute at the University of Bern, I have characterized novel chemokines (J.Exp.Med. 1996), discovered the expression of chemokine receptors in leukocyte subpopulations, such as basophils (J.Clin. Invest. 1997) Th1 and Th2 lymphocytes (Current Biol. 1997, Nature 1998), and analysed *in situ* expression of several chemokines, in secondary lymphoid organs and in tissues from patients with different pathological conditions.
My first achievement as PI was the first description of chemokine mRNA in human tissues with the discovery of BCA-1 expression in *Helicobacter pylori (Hp)*–induced mucosa-associated lymphoid tissue and gastric lymphoma (J. Clin. Invest. 1999). The demonstration that BCA-1 is highly expressed in the context of the infection-dependent formation of gastric MALT and MALT lymphomas brought up a new aspect of chemokine biology. A chemokine with a dual function: constitutively expressed in lymphoid tissues where it regulates the homing of B lymphocytes, but also induced, as inflammatory chemokines, in the *Hp*-infected mucosa and involved in the pathology of chronic *Hp*-infection.

a. Uguccioni M., Loetscher P., Forssmann U., Dewald B., Li H., Lima S. H., Li Y., Kreider B., Garotta G., Thelen M., Baggiolini M. Monocyte chemotactic protein 4 (MCP-4), a novel structural and functional analogue of MCP-3 and eotaxin. J Exp Med. 1996, 183:2379-2384.
b. Uguccioni M., Mackay C. R., Ochensberger B., Loetscher P., Rhis S., LaRosa G. J., Rao P., Ponath P. D., Baggiolini M., Dahinden C. A. High expression of the chemokine receptor CCR3 in human blood basophils. Role in activation by eotaxin, MCP-4, and other chemokines. J Clin Invest. 1997, 100:1137-1143.
c. Mazzucchelli L., Blaser A., Kappeler A., Scharli P., Laissue J. A., Baggiolini M., Uguccioni M. BCA-1 is highly expressed in Helicobacter pylori-induced mucosa-associated lymphoid tissue and gastric lymphoma. J Clin Invest. 1999, 104:R49-54.

Natural Chemokine Antagonists and Repulsive Chemokines

From the discovery that several chemokines are concomitantly expressed in inflammatory conditions and tumours, my group has started exploring the possibility that the microenvironment milieu could regulate the activity of chemokines and chemokine receptors.
These studies allowed us to discover the first natural chemokine antagonist (Blood 2001) followed by additional discoveries in the following years (Blood 2003, J.Biol.Chem. 2004, J.Leuk.Biol. 2004, Eur.J.Immunol. 2004).

a. Ogilvie P., Bardi G., Clark-Lewis I., Baggiolini M., Uguccioni M. Eotaxin is a natural antagonist for CCR2 and an agonist for CCR5. Blood.2001, 97:1920-1924.
b. Ogilvie P., Paoletti S., Clark-Lewis I., Uguccioni M. Eotaxin-3 is a natural antagonist for CCR2 and exerts a repulsive effect on human monocytes. Blood. 2003, 102:789-794.
c. Panzer U., Uguccioni M. Prostaglandin E2 modulates the functional responsiveness of human monocytes to chemokines. Eur J Immunol. 2004, 34:3682-3689.

The synergism among chemokines and with inflammatory molecules

The discovery of natural chemokine antagonists encouraged us to investigate further the effects of the microenvironment on chemokine activities. We showed in several studies, that chemokines can also form heterocomplexes with other members of the same family rendering the agonist more potent in triggering the selective receptor. The first study on this topic was published in Blood in 2004, and we subsequently identified the structural requirements important for binding without triggering the chemokine receptor (Eur.J.Immunol. 2004).We have named this effect “Synergism between chemokines”. The chemokine community was not truly prepared to accept this additional feature of chemokines, and it took us time, additional evidences (Eur.J.Immunol.2009, Int.J.Cancer 2010), and the concomitant discoveries from the group of Christian Weber in Germany, to convince that this activity is indeed relevant for modulating cell migration. Nowadays, there are no more doubts on the relevance of chemokine heterocomplexes *in vivo*.

The analysis of the microenvironment in human inflammatory conditions led us to evaluate also other molecules, such as the alarmin HMGB1, in modulating cell migration. HMGB1 was reported to be a chemoattractant, but the receptor responsible for this activity was unknown. In 2012, we have been able

to show in two different papers published in Journal of Experimental Medicine, that chemokines, in particular, CXCL12, can form a heterocomplex with HMGB1, and that the effect on cell migration reported for HMGB1 is indeed due to the triggering of the CXCL12 receptor (CXCR4).

a. Paoletti S., Petkovic V., Sebastiani S., Danelon M. G., Uguccioni M.*, Gerber B. O. A rich chemokine environment strongly enhances leukocyte migration and activities. Blood. 2004, 105:3405-3412. *corresponding author.
b. Sebastiani S., Danelon G., Gerber B., Uguccioni M. CCL22-induced responses are powerfully enhanced by synergy inducing chemokines via CCR4: evidence for the involvement of first β-strand of chemokine. Eur J Immunol. 2005, 35:746-756
c. Venetz D., Ponzoni M., Schiraldi M., Ferreri A.J.M., Bertoni F., Doglioni C. and Uguccioni M. Perivascular Expression of CXCL9 and CXCL12 in Primary Central Nervous System Lymphoma: T Cell Infiltration and Positioning of Malignant B Cells. Int J Cancer 2010, 127:2300-2312.
d. Schiraldi M., Raucci A., Livoti E., Apuzzo T., De Marchis F., Celona B., Pedotti M., Thelen M., Varani L., Proudfoot A., Bianchi M.E. and Uguccioni M. The alarmin HMGB1 promotes recruitment of inflammatory cells to damaged tissues by binding CXCL12 and signaling via CXCR4. J Exp Med 2012; 209:551-563.

The Synergism and Chemokine receptor activities in chronic inflammation

HMGB1 works as an enhancer of CXCL12, as other synergy-inducing chemokines we have described over the years. The presence of the heterocomplex contributes fuelling the inflammatory response in Rheumatoid Arthritis (Front. Immunol. 2018) due to a differential triggering of the chemokine receptor (Front. Immunol. 2020). With the help of the group of Andrea Cavalli at the IRB, we expanded our research to disclose the structure of the heterocomplex (Comp. Struct. Biotech. J. 2019), and design potent peptides able to disrupt it (J.Med.Chem. 2021 and *in press*), in view of develop innovative pharmacological tools for the treatment of severe chronic inflammatory conditions characterized by an uncontrolled immune response (patent # PCT/EP2019/057125).

Not only the presence of molecules able to complex with chemokines can alter their activities, but also a persistent immune activation, as occurring in individuals living with HIV-1, can alter leukocyte responses to chemokines, even if chemokine receptor expression on the cell surface is not altered (J.Immunol. 2017). The use of a compound able to promote, both *in vitro* and *in vivo*, the remodelling of the cytoskeleton indicates that there is room for further pharmacological approaches, to overcome the failure in repopulating the gut immune system experienced by individuals living with HIV-1.

a. Valentina Cecchinato, Gianluca D'Agostino, Lorenzo Raeli, Alessandra Nerviani, Milena Schiraldi, Gabriela Danelon, Antonio Manzo, Marcus Thelen, Adrian Ciurea, Marco E. Bianchi, Anna Rubartelli, Costantino Pitzalis, and Mariagrazia Uguccioni. Redox-mediated mechanisms fuel monocyte responses to CXCL12/HMGB1 in active Rheumatoid Arthritis. Frontiers in Immunology 2018, Volume 9, Article 2118.
b. Gianluca D'Agostino, Marc Artinger, Massimo Locati, Laurent Perez, Daniel F Legler, Marco E Bianchi, Curzio Rüegg, Marcus Thelen, Adriano Marchese, Marco B L Rocchi, Valentina Cecchinato, Mariagrazia Uguccioni. β-Arrestin1 and β-Arrestin2 Are Required to Support the Activity of the CXCL12/HMGB1 Heterocomplex on CXCR4, Frontiers in Immunology 2020, Volume 11, Article 550824.
c. Cecchinato V., Bernasconi E., Speck R.F., Proietti M., Sauermann U., D'Agostino G., Danelon G., Rezzonico Jost T., Grassi F., Raeli L., Schöni-Affolter F., Stahl-Hennig C., Uguccioni M., and the Swiss HIV Cohort Study. Impairment of CCR6+ and CXCR3+ T-helper cell migration in HIV-1 infection is rescued by modulating actin polymerization. J. Immunol. 2017, 198:184-195.

Auto-antibody against chemokines in human pathology

Thanks to a close collaboration with the group of Davide Robbiani, we have recently disclosed a further mechanism governing chemokine activities. Naturally occurring anti-chemokine antibodies arise after SARS-CoV-2 infection and, monoclonal antibodies derived from convalescent individuals bind to the chemokine N-loop impairing cell migration. Given the role of chemokines in orchestrating immune cell trafficking, and the fact that these antibodies associate with favourable COVID-19, they may be beneficial by modulating the inflammatory response and bear therapeutic potential (Nat.Immunol. 2023, 24:604-611).

a. Muri, J.* Cecchinato, V*. Cavalli, …. Uguccioni, M.* Robbiani, D. F.* ***equal contribution** Anti-chemokine antibodies after SARS-CoV-2 infection correlate with favorable disease course. Nature Immunology 2023, 24:604-611