Personal information

First and last name	Mariagrazia Uguccioni
Gender	Female
Place and date of birth	Pesaro, Italy - September 28, 1961
Nationality	Italian, Swiss
Google scholar	https://scholar.google.ch/citations?user=84f02BYAAAAJ&hl=en
OrcID	0000-0002-9570-7011
Current position	Deputy director, Institute for Research in Biomedicine Head of the "Chemokines in Immunity" laboratory
2009	Elected Member of the Academy of Science, Institute of Bologna, for her studies on the relevance of chemokines in human pathology http://www.accademiascienzebologna.it/en/academy-of-sciences-of-bologna-institute

Education

1990	MD degree - University of Bologna, Italy – State Exam – Bologna, Italy
1994	Specialization in Haematology - University of Bologna, Italy

Employment and teaching history

1990-1993	Research fellow, Immunology and Genetic, University of Bologna, Italy
1992	Visiting scientist, Guy's Hospital, Department of Rheumatology, London, UK
1993-2000	Research scientist, Theodor Kocher Institute, University of Bern, Switzerland
1999-2004	Adjunct Professor, School of Toxicology, Faculty of Pharmacology, University of Bologna, Italy
2006-2011	Adjunct Professor, School of Rheumatology, Faculty of Medicine, University of Bologna, Italy
2000-present	Head of laboratory "Chemokines in Immunity", Biosafety officer, IRB, Bellinzona, Switzerland
2000-2006	Coordinator PhD students journal club
2005-present	Coordinator internal IRB scientific seminars
2010-present	Deputy director, Institute for Research in Biomedicine
2016-2022	Extraordinary Professor, Humanitas University, Rozzano (Milan), Italy
2022-present	Full Professor, Università della Svizzera italiana (Lugano), Switzerland

Memberships in panels, boards, and individual scientific activities

1998-2000	Chair 7th workshop on Human Leukocyte Differentiation Antigens (Cytokine-chemokine receptors)
2000-2004	Chair 8th workshop on Human Leukocyte Differentiation Antigens (Cytokine-chemokine receptors)
2005-2011	EU independent expert, panel evaluation Health-Innovation.
2009-2011	Member of the Commission for selection of candidates for the PhD programme in Molecular Medicine, San Raffaele University, Milan (Italy)
2009-2011	Member of Telethon Switzerland Scientific Committee.
2015-present	Member of the Commission for selection of candidates for the PhD programme in Molecular and Experimental Medicine at Humanitas University, University of Palermo and Italian National Council for Research (Italy).

Ad hoc reviewing for several scientific Journals, among which Science, Nature, Nature Immunology, Nature Communication, Journal of Experimental Medicine.

Reviewer for Swiss and European Funding Agencies, such as SNSF, Welcome Trust UK, MIUR IT, MRC UK, Versus Arthritis UK.

Approved research projects

2004-2016	**SNSF**: i) Impact of multiple chemokine expression in human disease; ii) Impact of multiple chemokine expression in human disease (follow on); iii) Analysis of molecular and cellular mechanisms in immune-mediated tissue damage of the skin: Hidradenitis suppurativa as a model disease (Co-investigator); iv) Impact of synergy-inducing molecules on chemokine activities.
2006-2009	**SNSF/Cloetta MD/PhD programme**- Chemokines in extranodal Lymphomas (Supervisor, to Daniel Venetz).
2012-2014	**SNSF-HIV Cohort Studies** – Migration and differentiation of TH17 cells in HIV infection.
2012-2015	**SNSF-ProDoc** – Cell migration.
2007-2015	**SNF REquip co-applicant**: Confocal microscopy, high-throughput cellular screening, NMR spectrometer.
2000-2004	**EU FP4** – i) DETEC; ii) SIV/HIV vaccines – detecting efficacy and explaining inefficacy
2002-2005	**EU FP5** – MUVADEN, Mucosal vaccines against human and simian immunodeficiency viruses based on dendritic cells
2004-2010	**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)
2009-2017	**EU FP7**: i) IEF– MD-THIV, Migration and Differentiation of Th17 Cells in HIV/SIV Infection (Supervisor to Valentina Cecchinato); ii) TIMER, TargetIng novel MEchanisms of Resolution in inflammation; iii) ADITEC, Advanced Immunization Technologies.

2004-2006	**OncoSwiss** - Primary central nervous system lymphoma: from an improved biology knowledge of its peculiar molecular and biologic feature towards the optimization of treatment.
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.
2012-2013	**Novartis Stiftung für Medizinisch-Biologische Forschung** – Dampening Inflammation in Autoimmunity by Targeting Chemokine synergy-inducing molecules.
2011-2016	**Institute for Arthritis Research** – Chemokines in arthritis.
2013	**Jubilee Foundation Novartis** - Dampening Inflammation by targeting chemokine synergy-inducing molecules (Supervisor to Lorenzo Raeli).
2013-2016	**Gottfried und Julia Bangerter-Rhyner Stiftung -** Dampening Inflammation in Autoimmunity by Targeting Chemokine Synergy-inducing Molecules.
2018-2020	**Foundation for research on viral diseases** – The role of chemokines in tuning the inflammatory responses during Hepatitis C virus infection.
2015-2024	**Fondazione Ceschina:** i) The role of chemokines in tuning the inflammatory responses in Ankylosing Spondylitis; ii) The role of chemokines in tuning the inflammatory responses in Ankylosing Spondylitis.
2019-2022	**Fondazione Rocca** – The role of MSF in cell migration.
2021-2023	**Fondazione Fidinam** – The innate immune response against SARS-CoV-2.
2020-2023	**Innosuisse** - Development of an innovative therapy for ANCA - associated vasculitis (AAV).

Supervision of junior researchers at graduate and postgraduate level

1994-1999: MD students (Dr.Med thesis) enrolled at the University of Bern, Medical School.
2000-present: Master students (Master thesis in Pharmacology, University of Basel; Medical Biology, University of Lausanne; Medicine, University of Pavia; Pharmacology, University of Milan; Biomedical Sciences, USI.
1995- present: PhD students and Post-doc enrolled at the Theodor Kocher Institute, University of Bern and at the Institute for Research in Biomedicine.
2000- present: Visiting scientists from Italy, Germany, Spain, United Kingdom, USA, Canada, Argentina, and Egypt.

Memberships in panels, boards, and individual scientific activities

1998-2000	Chair 7th workshop on Human Leukocyte Differentiation Antigens (Cytokine-chemokine receptors)
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2015- present	Member of the Commission for selection of candidates for the PhD programme in Molecular and Experimental Medicine at Humanitas University, University of Palermo and Italian National Council for Research (Italy).

Ad hoc reviewing for several scientific Journals, among which Science, Nature, Nature Immunology, Journal of Experimental Medicine. Reviewer for Swiss and European Funding Agencies, such as SNSF, Welcome Trust UK, MIUR IT, MRC UK, Versus Arthritis UK.

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.

Organization of international conferences

2010	Cytokines and Chemokines – Post transcriptional regulation – Saint Sorlin d'Arves (FR) – 22-24.03
2014	The chemokine system: molecules, mechanisms and functions – Borgo Santa Giulia (IT) – 25-27.09
2012-2020	European Academy of Dermatology and Venereology "From the Bench to the Clinic" - every year
2017	Ankylosing Spondylitis: tales of molecules and patients – Lugano (CH) – 30.09/01.10
2019	ECMC – European chemokine and cell migration conference – Salamanca (ES) – 26- 29.06
2023	Ankylosing Spondylitis: tales of molecules and patients – Bellinzona (CH) – 22-24.09

Publications – h-index 56 - i10Index: 90

Publications in peer reviewed journals: 88.
Publications in peer reviewed journals on the 7th and 8th workshops on Human Leukocyte Differentiation Antigens: 11.
Book chapters: 8. https://scholar.google.ch/citations?hl=en&user=84f02BYAAAAJ&view_op=list_works&sortby=pubdate

The research activities performed in my group have been always focused on the modulation of cell migration in health and disease in humans. This led us to characterize as first the activity of novel chemokines, the expression of chemokine receptors in leukocyte subpopulations, such as basophils, Th1 and Th2 lymphocytes, and the ***in situ* expression of several chemokines**, in secondary lymphoid organs and in tissues from patients with different pathological conditions. Over the years, we have published several article on this topic. Among those: Journal of Clinical Investigation (DOI: 10.1172/JCI119624), Nature (DOI: 10.1038/34814), Current Biology (DOI: 10.1016/s0960-9822(06)00371-x), Journal of Clinical Investigation (DOI: 10.1172/JCI7830).

The discovery that several chemokines are concomitantly expressed in inflammatory conditions and tumours, led as to start exploring if the microenvironment milieu could regulate the activity of chemokine receptors. These studies allowed us to discover the first **natural chemokine antagonists** in 2001 (DOI: 10.1182/blood.v97.7.1920) and subsequently in 2003 and 2004. An example of these studies is the characterization of two chemokines, CCL11 and CCL6, as antagonists for CCR1, CCR2, and CCR5. These natural antagonists would counteract the effect of all "classical", inflammatory CC chemokines on any cell type expressing CCR1, CCR2 or CCR5, but lacking CCR3, skewing the balance between a Th1 or Th2 type response towards the Th2 branch.

The discovery of natural chemokine antagonists encouraged us to investigate further the effects of the microenvironment on chemokine activities. In recent years, we showed in several studies, that chemokines could 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 (DOI: 10.1182/blood-2004-04-1648). 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, several papers, and the concomitant discover performed by the group of Christian Weber in Germany, to convince that this activity is indeed relevant for modulating cell migration. The concomitant modulation of chemokine activities due to the presence of glycosaminoglycans (GAGs) expressed on the cell surface, made the analysis of these studies even more complex.

The controversy on the relevance of GAGs and chemokine heterocomplexes acting for enhancing chemokine responses, was discussed in a reconciliatory review that Amanda Proudfoot and I decided to write together in 2016, and that have been published in Frontiers in Immunology (DOI: 10.3389/fimmu.2016.00183 **)**. Nowadays, the entire community has no more doubt on the relevance of chemokine heterocomplexes, and their relevance *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). Thus, HMGB1 works as an enhancer of CXCL12, as the other synergy-inducing chemokines (DOI: 10.1084/jem.20111739)(DOI: 10.1084/jem.20120189) (DOI:

10.1016/j.molimm.2012.10.037), and its presence contributes to fueling the inflammatory response in Rheumatoid Arthritis (DOI: 10.3389/fimmu.2018.02118).

The structural features of the complex CXCL12/HMGB1 and its activity in cancer is a theme of our current research. We have characterized the signalling events that such a complex generates in CXCR4 (DOI: 10.3389/fimmu.2020.550824). We have a better understanding of the heterocomplex structure (DOI: 10.1016/j.csbj.2019.06.020), and discovered potent peptides able to disrupt it, which can be developed as innovative pharmacological tools for the treatment of severe **chronic inflammatory conditions characterized by an uncontrolled immune response fuelled by the heterocomplex** (DOI: 10.1021/acs.jmedchem.1c00852).

The characterization of the surface expression of the different chemokine receptors on T cells have guided the discovery of different T helper cell subsets, and is still a precious tool for the characterization of novel functional subsets. We have studied if pathological conditions can influence the activity of chemokine receptors, even if their expression on the T cell surface remains unaltered compared to healthy individuals. We have shown that, in HIV-1-infected individuals who are receiving clinically effective anti-retroviral therapy (ART), **persistent immune activation causes impairment of lymphocytes to respond to chemotactic stimuli**, thus preventing their trafficking from the blood stream to peripheral organs, such as the gut. These cells have a defect in the rearrangement of the cytoskeleton upon chemokine stimulation. The use of a compound able to promote, both *in vivo* and *in vitro,* the remodelling of the cytoskeleton indicates that there is room for further pharmacological approaches in these patients, to overcome the failure in repopulating the gut immune system (DOI: 10.4049/jimmunol.1600568)(DOI: 10.3389/fimmu.2017.01563)(DOI: 10.3389/fimmu.2017.01563).

Very recently, thanks to a close collaboration with the group of Davide Robbiani, we have disclosed a further mechanism governing chemokine activities. **Naturally 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 favorable COVID-19, they may be beneficial by modulating the inflammatory response and bear therapeutic potential (DOI: 10.1101/2022.05.23.493121 Nature Immunology *in press*).

My group is continuing to study of the modulation of chemokine activity performed by molecules that are present in the inflammatory and tumour microenvironment. Our studies call for additional investigation of the responses to chemokines in patients with pathological conditions characterized by persistent immune activation, in view of identify novel biomarkers and ameliorate current therapies.