Career/Employment

Birth:

3rd May 1969, Taranto, Italy

Education:

1991: Biological Science degree at the University of Padova, Italy. (Grade: 110/110, cum laude)

1995: Ph.D in Evolutionary Biology, University of Padova, Italy.

Positions:

1991-1995: PhD student, Department of Biology, University of Padova, Italy.

March 1995-May 1999: Scientific Member of the Basel Institute for Immunology, Switzerland.

June 1999-Dec 2000: EMBO fellow, EMBL Monterotondo, Italy.

2001- 2017: Group Leader, Venetian Institute of Molecular Medicine, Padua, Italy.

2002 - 2007: Assistant Professor of Pathology, Faculty of Medicine, University of Padua, Italy.

2006 - 2014: Group Leader, Istituto Clinico Humanitas, Rozzano (MI), Italy.

2007 - 2014: Assistant Professor of Pathology, Faculty of Medicine, University of Milan, Italy

2014 - 2015: Associate Professor of Pathology, University of Padua, Italy

2014 – present: Faculty, PhD Program in Biomedical Sciences, University of Padua, Italy

2015 - 09/2017 Deputy Director, Venetian Institute of Molecular Medicine (VIMM), Padua, Italy

2015 - present: Full Professor of Pathology, Univeristy of Padua, Italy

2017 - present: Scientific Director, Pediatric Research Institute (IRP), Padua, Italy

Research interests and career highlights

1. T cell activation

During my years at the Basel Institute of Immunology (Switzerland), I focused my research on the role of T cell coreceptors and costimulatory molecules in TCR signaling and T cell priming. My studies on CD28 allowed defining a clear role for this key T-cell molecule as a TCR signaling amplifier. In addition, the demonstration that the mechanism of signaling amplification is due to CD28-induced reorganization of lipid membrane microdomains at the immunological synapse represents a seminal discovery that opened a new research field in immunology (*Viola and Lanzavecchia, Science 1996; Viola et al., Science 1999*).

In 2002, I established my group in Italy and continued the investigation on the **crosstalk between CD28 and TCR, the actin cytoskeleton and lipid rafts at the immunological synapse**. The most important discovery was the identification of Filamin-A as a new CD28-

binding protein and the demonstration that Filamin-A induces membrane raft clustering at the T cell immunological synapse (*Tavano et al. Nat Cell Biol 2006; Viola and Gupta, Nat Rev Immunol 2007*).

In 2005, the demonstration that **chemokine receptors are recruited into the immunological synapse, where they provide costimulatory signals to T lymphocytes**, identified a novel role of the chemokine system in immunity *(Molon et al., Nat Immunol 2005*). Recently, we have focused on the unknown pathogenesis of the rare human disease WHIM syndrome, which is caused by C-terminal truncating, dominant mutations in the chemokine receptor CXCR4. We found that the WHIM-mutant CXCR4 disrupts the stability of T cell immunological synapse and reduces in vivo T cell activation (*Kallikourdis et al., Blood 2013 and manuscript in preparation*). These data allow us to propose a mechanism for the adaptive response-related symptoms of the WHIM syndrome.

Having a strong interest for cell biology, we have also analyzed the **role of mitochondria and calcium signaling in T cell migration and activation**. We demonstrated a new structural and functional connection between mitochondrial shape and leukocyte migration (*Campello et al., J Exp Med 2006*). We found that during leukocyte migration mitochondria are transported to the uropod along microtubules, in a process requiring G_i protein signaling and mitochondrial fission. Our data suggest that mitochondria redistribution is required to fuel the cell motor of migrating cells. We have also shown that in T cells, chemokine-induced LFA-1 activation results in fast and stable recruitment of mitochondria toward the adhesive contacts, a process required to amplify TCR Ca^{2+} signaling at the upcoming immunological synapse (*Contento et al., EMBO J 2010*). More recently, we have analyzed the role of calcium waves during lymphocyte stimulation and found that ATP released by stimulated T cells is a paracrine signal to alarm the neighboring lymphocytes and reduce their motility (*Wang et al., EMBO J 2014*).

2. Tumor immunology

In 2005, we published the discovery of **a novel and dominant mechanism by which human cancers induce immunosuppression *in situ*** (*Bronte et al., J Exp Med 2005*). We analyzed the modulation of T cell responses by the tumor environment using, for the first time in immunology, collagen gel-matrix supported organ cultures of human prostate carcinomas (PCa). Our results showed that in PCa T lymphocytes are in an unresponsive status. By inhibiting the activity of the enzymes arginase (ARG) and nitric oxide synthase (NOS), which are highly expressed in malignant but not in normal prostate, restoration of T cell responsiveness to tumor was achieved. We are continuing this translational project for a

combined therapy based on novel immune modulators targeting the tumor microenvironment. In 2011, we have demonstrated for the first time the **post-translational modification of chemokines in human - as well as mouse model - cancers by reactive nitrogen species (RNS)** (*Molon et al., J Exp Med 2011*). Intratumoral RNS production induces CCL2 chemokine nitration and hinders T cell infiltration, resulting in the trapping of tumor-specific T cells in the stroma that surrounds cancer cells. We have also produced a novel drug that inhibits CCL2 modification, facilitates CTL invasion of the tumor, and improves cancer immunotherapy. Our results unveil an unexpected mechanism of tumor evasion and introduce new avenues for cancer immunotherapy.

3. Mesenchymal stem cells

MSC have been studied across a range of clinical indications and represent a promising therapeutic approach in many diseases in view of their potent immunomodulatory properties. . In order to design better therapeutic protocols and define the clinical endpoints, it is important to identify the specific targets of MSC anti-inflammatory action in vivo. We have previously shown that encapsulated MSC injected subcutaneously are able to control systemic and local inflammation through soluble factors (*Zanotti et al., Leukemia 2013*). We are trying to identify the mechanism of action of MSC in the treatment of inflammatory diseases, focusing on the proteomic analysis of the MSC secretome and on the cross-talk between MSC and endothelial cells.

In addition, we are partners of the EU project **MERLIN** that will look at developing stem cell-based therapies for liver disease (http://fp7merlin.eu).

4. The phagocytic synapse

Infectious diseases remain the second cause of human death worldwide and the first in developing countries. The emergence of antibiotic resistant strains has reinforced the importance of understanding host-pathogen dynamics and of identifying new avenues for therapeutic intervention. On the other hand, chronic inflammation represents one of the major causes of morbidity and mortality in western countries. Indeed, it is involved in the pathogenesis of several human diseases, such as cancer, atherosclerosis, allergy, inflammatory bowel diseases, autoimmune diseases and metabolic syndrome. Macrophages have direct, crucial and complex roles in both infectious and inflammatory diseases but the cellular and molecular mechanisms responsible for tuning macrophage responses are still elusive, and this represents a major obstacle for the development of new treatments.

The ERC AdG project STePS analyses the molecular interactions leading to the orchestration of phagocytic synapses for phagocytosis and activation, two events crucial for immune responses to pathogens as well as for inflammation.

5. Agrin biology (beyond the NMJ)

Agrin is an extracellular matrix (ECM) protein belonging to the heterogeneous family of heparan sulfate proteoglycans (HSPGs). Agrin's best-characterised role is in the development of the neuromuscular junction during embryogenesis where it is expressed by motor neurons and leads to clustering and activation of the RTK MuSK6. However, agrin is expressed in many tissues and its non-neuronal functions are poorly understood.

We identified a novel, non-redundant role for agrin at the bone marrow niche for hematopoietic stem cells (*Mazzon et al., Blood 2011; commentary in the same issue*). Moreover, we demonstrated that agrin is required for survival, differentiation and functions of macrophages (*Mazzon et al., Blood 2012*). Our results indicate that in the haematopoietic compartment agrin signals through the dystroglycan (DG) receptor by activating the Grb2-SOS-Ras signalling pathway.

Our lab is studying the role of agrin in phagocytosis, erythropoiesis, MSC biology and tumor development.

Awards and Academic Memberships

Awards

1997: Roche Prize for Immunology

2005: Cancer Research Institute Investigator Award, USA.

2006: EMBO Young Investigator

2008: Prize “Donne Eccellenti” Marisa Belisario Foundation (Veneto).

2008: Prize “Chiara D’Onofrio”

2013: ERC Advanced Investigator Grant

2016: EMBO member

Academic Memberships

2009 - 2011: AIRC Scientific Committee

2006 - 2015: FP7 Expert Evaluator

2014 - 2019: ERC Grants Evaluator

2016 - present: Scientific Council of the Department of Biomedical Sciences, CNR Italy.

2017 - present: CORIS Technical Committee

2019: Croatian Agency for Science and Higher Education

2019 - present: Member of Comitato Scientifico di Osservatorio Terapie Avanzate
2019 - present: Academy of Finland

5 Selected Publications

V. Bronte, T. Kasic, G. Gri, K. Gallana, G. Borsellino, I. Marigo, L. Battistini, M. Iafrate, T. Prayer-Galetti, F. Pagano and **A. Viola**. 2005. Boosting anti-tumor responses of T lymphocytes infiltrating human prostate cancers. The Journal of Experimental Medicine, 201:1257-68.
B. Molon, G. Gri, M. Bettella, C. Goumez-Mouton, A. Lanzavechia, C. Martinez-A, S. Manes and **A. Viola**. 2005. T cell costimulation by chemokine receptors. Nature Immunology, 6:465-71.
R. Tavano, R.L. Contento, S.J. Baranda, M. Soligo, L. Tuosto, S. Manes and **A. Viola**. 2006. CD28 interaction with filamin-A controls lipid raft accumulation at the T cell immunological synapse. Nature Cell Biology, 8:1270-1276.
S. Campello, R.A. Lacalle, M. Bettella, S. Manes, L. Scorrano and **A. Viola**. 2006. Orchestration of leukocyte chemotaxis by mitochondrial dynamycs. The Journal of Experimental Medicine, 203: 2879-2886.
Wang CM, Ploia C, Anselmi F, Sarukhan A, **Viola A**. ATP acts as a paracrine signaling molecule to reduce the motility of T cells. EMBO J 2014, 33(12):1354-64.
View complete list of Publications

Funding ID

- US Army Medical Research and Material Command, USA 2003: Human Prostate Cacner Infiltrating Lymphocytes (PI);
- Associazione Italiana Ricerca sul Cancro (AIRC), Italy 2003, 2004, 2005, 2008 - New strategies in cancer immunotherapy (PI);
- Cancer Research Institute of New York, USA 2005: Boosting anti-tumor responses of T lymphocytes infiltrating human prostate cancer (PI);
- US Army Medical Research and Material Command, USA 2006: Defining novel molecules to rescue immunity against prostate cancer (PI);
- Ministry of Education (PRIN), Italy 2007, 2009 – Immune system against cancer (PI);
- Ministry of Health, Italy 2007, 2008, 2009: Tumor microenvironment (PI);

- Telethon, Italy 2007 - Understanding the WHIM Syndrome (PI);
- E-Rare Programme, EC 2008: Understanding the WHIM syndrome (Coordinator);
- FP7-Health, EC 2008: Systems Biology of T-cell activation in health and disease (Partner);
- Association for International Cancer Research (AICR), UK 2009: Chemokine nitration in the prostate cancer microenvironment (PI);
- Telethon, Italy 2010 - The WHIM syndrome (Coordinator);
- Ministry of Health « Giovani Ricercatori » Italy, 2011 : Mesenchymal Stem Cells (Coordinator);
- ERC Advanded Investigator Grant, EC 2013: Signaling compartmentalization and vesicle trafficking at the phagocytic synapses (PI);
- FP7-Health, EC 2013: Mesenchymal Stem Cells to Reduce Liver Inflammation (Work Package Leader)
- CARIPARO Foundation, Italy 2015: Novel strategies to counteract obesity: immune signaling and mitochondria schape (PI);
- ERC Proof-of-Concept, EC 2019: Monoamine oxidase B inhibitors as novel drugs targeting NLRP3 inflammasome (PI);
- Città della Speranza & Human Technopole Foundations, Italy 2020: COVIDIamo: tracing the dynamics of COVID19 at single-cell multi-omic resolution for drug repurposing and biomarker identification (PI);
- CARIPARO Foundation, Italy 2020: I recettori di SARS-CoV2: modulazione della loro espressione attraverso ormoni e infiammazione (PI).

Fonte: http://www.biomed.unipd.it/people/viola-antonella/