Name	Position Title	Birth date
Laudanna Carlo, MD, PhD	Full Professor of Pathology	10/12/1962

EDUCATION/TRAINING			
Institution and Location	**Degree**	**Completion Date (month/year)**	**Field of Study**
Classic Lyceum, Scipione Maffei, Verona, Italy	Baccalaureate	1976-1981	Humanistic
University of Verona, Italy	Degree	1982-1988	Medicine and Surgery (MD)
University of Verona, Italy	Master	1989-1992	Molecular Biology
University of Verona, Italy	PhD	1992-1996	Molecular and Cellular Biology and Pathology
Stanford University School of Medicine, Stanford, USA	Postdoc	1993-1997	Molecular Immunology

POSITIONS:

2001-2005: Assistant Professor at the Section of General Pathology, Department of Pathology, University of Verona.

2005-2010: Associate Professor of General Pathology at the Department of Pathology, University of Verona.

2010-today: Full Professor of General Pathology at the Department of Medicine, University of Verona

2001-today: Director of the "Laboratory of Cell Trafficking and Signal Transduction", department of Medicine, University of Verona

2006-2012: Director of the “Center for Biomedical Computing” (CBMC), University of Verona

Main research activity is in the field of signal transduction, immune system regulation, inflammation, cancer, bioinformatics and systems biology. Prof. Laudanna main contributions concern the identification of key signaling mechanisms controlling leukocyte trafficking under physio-pathological condition, as well as leukemia cell development and trafficking to secondary lymphoid organs. As President of the Center for Biomedical Computing (www.cbmc.it), a research center devoted to research in the field of systems biology, and following as CBMC main PI, he coordinated several projects concerning computational analysis of signaling network, with specific focus on phosphoproteomics. He also developed and patented many cell-penetrating peptide tools (CPPs) allowing modulation of many signaling proteins in primary human cells.

Prof. Laudanna is co-founder of the following start-ups:

2010: Co-founder of the university spin-off Veneto Pharma, focused on the development of new small inhibitory drugs of the integrin VLA-4 to be applied to the therapy in autoimmune diseases (SM) and epilepsy.

2014: Co-founder of the US start-up Leuvas, DW, USA, focused on development of treatments for inflammatory and autoimmune diseases, with more specific focus on PTPRG modulating compounds.

Prof. Laudanna is inventor of the following international patents:

(1) Peptide Inhibitors of RHOA Signaling. C. Laudanna, E.C. Butcher. International Patent PCT/US2005/001251 – STAN-346WO - 2004.

(2) V-ATPASE Inhibitors for the treatment of inflammatory and autoimmune diseses. C. Farina, G. Constantin, C. Laudanna, P. Misiano. International Patent Application 2005, 05110149.1.

(3) V-ATPASE Inhibitors for the treatment of septic shock. C. Farina, G. Constantin, C. Laudanna, P. Misiano. International Patent Application 2005, 05110163.2.

(4) Modulators of Protein Tyrosine Phosphate and Uses Thereof. (Leuvas) Application No. 62/109,555, 2015.

Prof. Laudanna was consultant for signal transduction systems of the following biotech:

In 2000 was consulting for "intracellular signal transduction systems" of the Systems Biology company "BioSeek", Burlingame, CA, USA (www.bioseek.com).

From the 2004 was consulting for the chemitechnology company Nikem (Milan) for study of anti-adhesive

drugs in inflammatory diseases (www.nikemresearch.com).
From 2006 was consulting for the biotech KAI, for the development of Trojan nanovectros (CPPs) to modulate the activity PKCs isoforms.

MAIN CONTRIBUTIONS TO SCIENCE:

1) Signaling mechanisms controlling leukocyte trafficking. Leukocyte trafficking is controlled by complex signaling events triggered by many environmental cues, including integrin ligands (outside-in signaling) and chemotactic factors (inside-out signaling). In this context prof. Laudanna discovered the critical regulatory role of rho small GTP binding proteins and of zeta PKC in the regulation of integrin activation by classical chemoattractants and chemokines. These findings triggered many further studies related to the role of small GTPases in leukocyte trafficking and the application of inhibitory compounds to therapy of autoimmune diseases and cancer. (*Laudanna, C., J.J. Campbell, and E.C. Butcher, Role of Rho in chemoattractant-activated leukocyte adhesion through integrins. **Science**, 1996. 271(5251): p. 981-3. Laudanna, C., J.J. Campbell, and E.C. Butcher, Elevation of intracellular cAMP inhibits RhoA activation and integrin-dependent leukocyte adhesion induced by chemoattractants. **J Biol Chem**, 1997. 272(39): p. 24141-4. Laudanna, C., et al., Evidence of zeta protein kinase C involvement in polymorphonuclear neutrophil integrin-dependent adhesion and chemotaxis. **J Biol Chem**, 1998. 273(46): p. 30306-15. Giagulli, C., et al., RhoA and zeta PKC control distinct modalities of LFA-1 activation by chemokines: critical role of LFA-1 affinity triggering in lymphocyte in vivo homing. **Immunity**, 2004. 20(1): p. 25-35.).* Toffali L, et al. *SOS1, ARHGEF1, and DOCK2 rho-GEFs Mediate JAK-Dependent LFA-1 Activation by Chemokines*. ***J Immunol***. 2017 Jan 15;198(2):708-717. Most recently, the group of prof. Laudanna discovered the critical role of leukocyte-specific isoforms of the giant protein Titin (TTN) in the regulation of T-lymphocyte recruitment and resilience to mechanical stress and deformation occurring in the microcirculation (Toffali L, D'Ulivo B, Giagulli C, Montresor A, Zenaro E, Delledonne M, Rossato M, Iadarola B, Sbarbati A, Bernardi P, Angelini G, Rossi B, Lopez N, Linke WA, Unger A, Di Silvestre D, Benazzi L, De Palma A, Motta S, Constantin G, Mauri P, Laudanna C. *An isoform of the giant protein titin is a master regulator of human T lymphocyte trafficking*. **Cell Rep.** 2023 May 30;42(5):112516.)

2) Role integrin affinity in leukocyte trafficking. Integrins are fundamental regulators of immune cell adhesion, including cell trafficking and immunological synapse generation and function. A long debated question in the field was the differential and prevalent role of integrin conformational changes (affinity) versus clustering (valency) in the overall regulation of cell recruitment. Prof. Laudanna demonstrated in a seminar paper on Immunity that chemokines control both the aspects of integrin activation, differently involved depending on the nature of the adhesive surface. Furthermore, in a second fundamental contribution, prof. Laudanna demonstrated that integrin affinity activation is differently controlled by distinct signaling events controlled by RhoA, Rac1 small GTPases and by PLD1 and PIP5Kgamma. These findings definitively demonstrated the critical role of high affinity state in the immediate arrest under flow of circulating leukocytes. (*Constantin, G., et al., Chemokines trigger immediate beta2 integrin affinity and mobility changes: differential regulation and roles in lymphocyte arrest under flow. **Immunity**, 2000. 13(6): p. 759-69. Giagulli, C., et al., RhoA and zeta PKC control distinct modalities of LFA-1 activation by chemokines: critical role of LFA-1 affinity triggering in lymphocyte in vivo homing. **Immunity**, 2004. 20(1): p. 25-35. Bolomini-Vittori, M., et al., Regulation of conformer-specific activation of the integrin LFA-1 by a chemokine-triggered Rho signaling module. **Nat Immunol**, 2009. 10(2): p. 185-94. Montresor, A., et al., Chemokines and the signaling modules regulating integrin affinity. **Front Immunol,** 2012. 3: p. 127).*

3) Regulation of dissemination of neoplastic CLL B-lymphocytes. B-cell chronic lymphocytic leukemia (B-CLL) is a common, rather heterogeneous, leukemia, characterized by progressive accumulation of functionally incompetent B-lymphocytes in the bone marrow, blood and lymphoid organs. B-CLL cells are primarily characterized by loss of appropriate apoptosis, although this characteristic is lost when B-CLL cells are removed from the host, clearly suggesting a critical role for micro environmental factors and/or adhesive stromal interactions. B-CLL cells also display altered mechanisms of integrin activation and lymphoid tissue dissemination in response to homeostatic chemokines. In this context, prof. Laudanna demonstrated the patient-specific role of a signaling module based on the function of rho small-GTPases in the regulation of integrin activation by CXCL12 in human isolated B-CLL cells. Moreover, the role of the PTK JAK2 was very recently described, thus highlighting the possibility of novel therapies based on JAK inhibitors in the treatment of B-CLL. (*Montresor, A., et al., Comparative analysis of normal versus CLL B-lymphocytes reveals patient-*

specific variability in signaling mechanisms controlling LFA-1 activation by chemokines. ***Cancer Res,*** *2009. 69(24): p. 9281-90. Montresor A, Toffali L, Mirenda M, Rigo A, Vinante F, Laudanna C. JAK2 tyrosine kinase mediates integrin activation induced by CXCL12 in B-cell chronic lymphocytic leukemia.* ***Oncotarget****. 2015*; 6(33):34245-57).

4) Kinome and phosphatome in the regulation of leukocyte trafficking. The very upstream regulators of chemokine-triggered signaling networks leading to integrin affinity triggering have been unknown for many years. Very recently, prof. Laudanna discovered the critical role of the JAK2 and JAK3 PTKs in the overall regulation of the rho-module of integrin affinity modulation. Moreover, in the same study, prof. Laudanna provided the first formal demonstration that rho and rap-small GTPases belong to a hierarchic cascade of signaling events, concurrently regulating leukocyte trafficking. More recently, prof. Laudanna provided the first demonstration of the negative regulatory role of the protein tyrosine phosphatase PTPRG in integrin activation by chemoattractants in human primary monocytes (*Montresor A, Bolomini-Vittori M, Toffali L, Rossi B, Constantin G, Laudanna C. JAK tyrosine kinases promote hierarchical activation of Rho and Rap modules of integrin activation.* ***J Cell Biol****. 2013 Dec 23;203(6):1003-19. Mirenda M, Toffali L, Montresor A, Scardoni G, Sorio C, Laudanna C. Protein Tyrosine Phosphatase Receptor Type γ Is a JAK Phosphatase and Negatively Regulates Leukocyte Integrin Activation.* ***J Immunol.*** *2015 Mar 1;194(5):2168-79.*

5) Network science. The growing complexity of biological networks, as emerging form the application of medium-high throughput 'omics and imaging technologies, urges the development and application of novel, more efficient, computational methods in order to extract all the information stored in the complexity of biological network structure. Prof. Laudanna coordinated several projects leading to development of computational tools allowing automated topological network inference and analysis of a variety of biological networks in physio-pathological contexts, with a specific focus on centrality index computation and multidimensional network analysis of proteomics data sets. (*Scardoni G, et al. Node Interference and Robustness: Performing Virtual Knock-Out Experiments on Biological Networks: The Case of Leukocyte Integrin Activation Network. (2014)* ***PLoS ONE 9(2)****; Scardoni, G, et al. Analyzing biological network parameters with CentiScaPe. (2009)* ***Bioinformatics, 25 (21), 2857-2859****; Karnovsky A, et al., Metscape 2 bioinformatics tool for the analysis and visualization of metabolomics and gene expression data. (2012)* ***Bioinformatics 28(3):373-380****; De Franceschi L, et al. Computational identification of phospho-tyrosine sub-networks related to acanthocytes generation in neuroacanthocytosis.* ***(2015)*** ***PLoS ONE 7(2)****; Scardoni G and Laudanna C. Identifying critical road network areas with node centralities interference and robustness. (2013)* ***Springer Berlin Heidelberg, Studies in Computational Intelligence, 424, 245-255****; Scardoni G and Laudanna C. Network centralities Interference and Robustness. (2011)* ***Int.J.Comp.Syst.Sci****.1(2), pp.164-168;* Scardoni G and Laudanna C. "Graph Theory", book chapter: *Centralities based analysis of networks.* InTech, open access publisher.

- h index = 38
- 9634 citations
- Total IF = 1007,774,
- Average IF = 11,58