BIOGRAPHICAL SKETCH

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NAME: Laura Pasqualucci

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POSITION TITLE: Professor of Pathology and Cell Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Perugia Medical School	M.D.	11/1991	Medicine
University of Perugia, Institute of Hematology	Residency	11/1995	Hematology
Institute of Pathology, Universitätsklinikum B. Franklin, Freie Universität Berlin, Germany	Visiting Fellowship	04/1997	Molecular Pathology
Institute for Cancer Genetics, Department of Pathology, Columbia University	Postdoctoral Fellowship	09/2001	Molecular Genetics of Lymphoma

A. Personal Statement

My research interests over the last 20 years have been focusing on the biology of normal and transformed B cells, with emphasis on the identification and functional characterization of genetic lesions that are associated with mature B cell malignancies, including their *in vivo* modeling as a tool to dissect their role in normal B cell physiology and lymphoma development. The ultimate goal of these studies is to identify better biomarkers and effective treatment options for human lymphoid malignancies. I received training in clinical onco-hematology and molecular biology, and acquired specific expertise in the genetics of lymphoma, including a broad range of experimental and bioinformatics approaches. Based on this expertise, I have successfully directed a number of research projects and collaborative efforts that led to the discovery of multiple novel lymphoma-driving genetic lesions and demonstrated their role in the malignant transformation process. More recently, my laboratory has been focusing on elucidating the mechanisms by which inactivating mutations of histone/chromatin modifiers, including the acetyltransferases *CREBBP*/*EP300* and the methyltransferase *KMT2D*, perturb the epigenetic landscape of GC B cells to facilitate their clonal expansion. Our studies established a role for these genes as *bona-fide* tumor suppressors in GC-derived lymphomas, which are disrupted as early events during the history of tumor clonal evolution. Collectively, our work has provided significant contribution to the current knowledge of the pathogenesis of B cell lymphomas, and is currently being exploited for the development of targeted therapeutic approaches in these diseases.

B. Positions and Honors

Positions and Employment

9/2001-1/2009: Assistant Professor of Clinical Pathology, Institute for Cancer Genetics and Department of Pathology, Columbia University, New York, NY
2009-2016 Associate Professor of Pathology & Cell Biology, Institute for Cancer Genetics, Department of Pathology and Cell Biology, Columbia University, New York, NY
2016-present: Professor of Pathology & Cell Biology, Institute for Cancer Genetics, Department of Pathology and Cell Biology, Columbia University, New York, NY

Review panels, Scientific Advisory Boards and Professional Memberships

2009-2014 Blood, Editorial Board
2010-present Member, American Society of Hematology (ASH)
2011-2013 Leukemia Research Foundation: Panel of Scientific Advisors

2011-present	NIH/NCI Peer Review Committees: CAMP Study Section, Developmental Therapeutics Study Section; Special Emphasis Panel Epidemiology of Cancer; Cancer Screening and Biomarker; P01 Study Section
2013-present	Leukemia Research Foundation: Scientific Advisory Board
2014-present	Member, American Association for Cancer Research
2014-present	AACR Millennium Fellowships: Scientific Review Committee,
2014-present	Lymphoma Research Foundation: Grant Oversight Committee
2014-present	Leukemia and Lymphoma Society: Reviewer
2016-present	ASH Committee on Scientific Affairs
2017-present	Journal of Experimental Medicine, Advisory Editorial Board
2018-present	AACR and SU2C, Dream Team Grants: Specific Advisory Committee
2019-present	Blood Cancer Discovery: Scientific Editor

Honors

1996	AIRC (Italian Association for Cancer Research) Annual Fellowship
1998 - 2000	AICF (American Italian Cancer Foundation) Fellowship
2002 - 2005	Leukemia and Lymphoma Society Special Fellowship
2006 - 2007	Julie Gould Scholar

C. Contribution to Science

My work has provided significant contributions to the understanding of the molecular pathogenesis of B cell non-Hodgkin lymphomas –and particularly its most common subtype, DLBCL– through the identification, functional characterization, and in vivo modeling of key genetic lesions that are associated with these cancers.

Abnormal functioning of somatic hypermutation (SHM) and role of AID in lymphoma. As a post-doctoral fellow in the laboratory of R. Dalla-Favera at Columbia University, I discovered that the physiologic SHM process, which is normally restricted to the antibody genes in germinal center (GC) B cells, can act outside of these loci and targets the 5' regulatory regions of the GC master regulator BCL6 during the physiologic GC reaction. These results broke a dogma in the B cell immunology field and paved the basis for the subsequent discovery that this same mechanism functions aberrantly in over 50% of DLBCL cases, leading to mutations in multiple proto-oncogenes/tumor suppressor genes, and thus emerging as a powerful oncogenic mechanism in this disease. Documenting the critical role of aberrant SHM in malignant transformation, we showed that AID, the enzyme required for SHM and CSR, is an essential requirement for GC-derived lymphomagenesis in vivo.

1. Pasqualucci L, Migliazza A, Fracchiolla N, William C, Neri A, Baldini L, Chaganti RSK, Klein U, Küppers R, Rajewsky K, Dalla-Favera R. BCL-6 mutations in normal germinal center B cells: evidence of somatic hypermutation acting outside Ig loci. ***Proc Natl Acad Sci USA*** 95 (20): 11816-21, 1998.
2. Pasqualucci L, Neumeister P, Goossens T, Nanjangud G, Chaganti RSK, Küppers R, Dalla-Favera R. Hypermutation of multiple proto-oncogenes in B-Cell Diffuse Large Cell Lymphoma. ***Nature*** 19:341-346, 2001. PMID: 11460166
3. Pasqualucci L*, Kitaura Y,Gu H, Dalla-Favera R. PKA-mediated phosphorylation regulates the function of activation-induced deaminase (AID) in B cells. ***Proc Natl Acad Sci USA*** 103(2):395-400, 2006. PMCID: PMC1326186 (*corresponding author).
4. Pasqualucci L*, Bhagat G, Jankovic M, Compagno M, Smith P, Muramatsu M, Honjo T, Morse HC 3rd, Nussenzweig MC, Dalla-Favera R. AID is required for germinal center-derived lymphomagenesis. ***Nature Genetics*** 40:108-112**,** 2008. PMID 18066064 (*corresponding author).

Genomic and functional characterization of Diffuse Large B cell Lymphoma. Using candidate genomic approaches and, more recently, high throughput next generation sequencing and SNP array analysis, we have defined the genomic landscape of DLBCL and functionally characterized several fundamental pathways that are disrupted by genetic alterations in these tumors.

1. Compagno M, Lim WK, Grunn A, Nandula SV, Bertoni F, Ponzoni M, Scandurra M, Califano A, Bhagat G, Chadburn A, Dalla-Favera R, Pasqualucci L. Mutations in multiple genes cause deregulation of the NF-kB pathway in diffuse large B-cell lymphoma. ***Nature*** 459(7247):717-721, 2009. NIHMSID: NIHMS151757.
2. Pasqualucci L*, Trifonov V, Fabbri G, Ma J, Rossi D, Chiarenza A, Wells VA, Grunn A, Messina M, Elliot O, Chan J, Bhagat G, Chadburn A, Gaidano G, Mullighan CG, Rabadan R, Dalla-Favera R*. Analysis of the coding genome of diffuse large B-cell lymphoma. ***Nature Genetics*** 43:830-837**,** 2011. PMID: 21804550 (*corresponding authors).

3. Challa-Malladi M, Lieu YK, Califano O, Holmes A, Bhagat G, Murty VV, Dominguez-Sola D, Pasqualucci L*, Dalla-Favera R*. Combined genetic inactivation of beta2-microglobulin and CD58 reveals frequent escape from immune recognition in diffuse large B cell lymphoma. ***Cancer Cell*** 20(6):728-40, 2011. PMCID: PMC3660995 (*equal contribution).
4. Pasqualucci L*, Khiabanian H, Fangazio M., et al. Genetics of follicular lymphoma transformation. ***Cell Rep*** 6(1):130-140, 2014. PMID: 24388756 (*corresponding author).

Genetic-driven epigenetic dysregulation in FL and DLBCL. Following on the discovery that genes encoding epigenetic modifiers (acetyltransferases and methyltransferases) are among the most common targets of genetic alterations in DLBCL and FL, my research interests have recently focused on the role of these enzymes in normal and transformed GC B cells. We characterized the functional consequences of mutations in the CREBBP acetyltransferase and the KMT2D mehtyltransferase, demonstrated that KMT2D is a bona fide tumor suppressor gene *in vivo*, and provided evidence that these lesions are acquired early during the clonal evolution and histologic transformation of FL. These findings have relevant clinical implications.

1. Pasqualucci L*, Dominguez-Sola D, Chiarenza A, Fabbri A, Grunn A, Trifonov V, Kasper LH, Lerach S, Tang H, Ma J, Rossi D, Chadburn A, Murty VV, Mullighan CG, Gaidano G, Rabadan R, Brindle PK and Dalla-Favera R*. Inactivating mutations of acetyltransferase genes in B-cell lymphoma. ***Nature***, 471:189-95, 2011. PMID:21390126. (*corresponding authors)
2. Zhang J, Dominguez-Sola D, Hussein S, Lee JE, Holmes AB, Bansal M, Vlasevska S, Mo T, Tang H, Basso K, Ge K, Dalla-Favera R, Pasqualucci L. Disruption of KMT2D perturbs germinal center B cell development and promotes lymphomagenesis. ***Nature Medicine*** 21: 1190-98, 2015. PMID: 26366712.
3. Zhang J, Vlasevska S, Wells VA, Nataraj S, Holmes AB, Duval R, Meyer SN, Mo T, Basso K, Brindle PK, Hussein S, Dalla-Favera R, Pasqualucci L. The Crebbp acetyltransferase is a haploinsufficient tumor suppressor in B cell lymphoma. ***Cancer Discovery*** 7: 3220337, 2017. PMID: 28069569.
4. Meyer SN, Scuoppo C, Vlasevska S, Bal E, Holmes AB, Holloman M, Garcia-Ibanez L, Nataraj S, Duval R, Vantrimpont T, Basso K, Brooks N, Dalla-Favera R and Pasqualucci L. Unique and shared epigenetic programs of the *CREBBP* and *EP300* acetyltransferases in germinal center B cells reveal targetable dependencies in lymphoma. ***Immunity*** 2019, 51: 535-547. PMID: 31519498.

In vivo modeling of DLBCL-associated genetic lesions. We have generated several mouse models mimicking the genetic alterations found in human tumors, and documented the direct role of these lesions in the development of neoplasms that faithfully recapitulate the biology of the disease, establishing the oncogenic/tumor suppressor role of the involved genes in lymphomagenesis –e.g. BCL6, BLIMP1, NF-κB, KMT2D and CREBBP (see above). Such models allowed us to elucidate the mechanisms underlying lymphoma initiation and maintenance, and provide relevant tools for the preclinical testing of drugs targeting the disrupted signaling pathway. The manipulation of common mutation target genes *in vivo* also facilitated the characterization of their normal function in the GC.

1. Cattoretti G*, Pasqualucci L*, Ballon G, Tam W, Nandula N, Shen Q, Mo T, Murty VV, Dalla-Favera R. Deregulated BCL6 expression recapitulates the pathogenesis of human diffuse large B-cell lymphomas in mice. ***Cancer Cell*** 7(5): 445-55, 2005 (*equal contribution).
2. Mandelbaum J, Bhagat G, Tang H, Mo T, Grunn A, Brahmachary M, Shen Q, Chadburn A, Rajewsky K, Tarakhovsky A, Pasqualucci L*, Dalla-Favera R*. Blimp1 is a tumor suppressor gene frequently disrupted in activated B-cell like diffuse large B cell lymphoma. ***Cancer Cell*** 18(6): 568-579, 2010. PMID: 21156281 (*equal contribution).
3. Zhang B, Calado DP, Wang Z, Fröhler S, Köchert K, Qian Y, Koralov SB, Schmidt-Supprian M, Sasaki Y, Unitt C, Rodig S, Chen W, Dalla-Favera R, Alt FW, Pasqualucci L*, Rajewsky K*. An oncogenic role for alternative NF-κB signaling in DLBCL revealed upon deregulated BCL6 expression. ***Cell Rep*** 11(5):715-726, 2015. PMID: 25921526 (*equal contribution).

Defining the genomic landscape of other mature B cell malignancies. My expertise in the genome-wide analysis of cancer has contributed to the characterization of the coding genome of other mature B cell malignancies, e.g. chronic lymphocytic leukemia, splenic marginal zone lymphoma, and hairy cell leukemia.

1. Fabbri G, Rasi S, Rossi D, Trifonov V, Bertoni F, Mullighan CG, Foá R, Pasqualucci L*, Rabadan R*, Dalla-Favera R*, Gaidano G*. Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. ***J Exp Med***, 208:1389-1401, 2011. PMID: 21670202. (*equal contribution)
2. Tiacci E, Trifonov V, Schiavoni G, et al, Pasqualucci L, Rabadan R, Falini B. BRAF mutations in hairy-cell leukemia. ***N Engl J Med*** 364:2305-2315, 2011. PMID:21663470.