

## **RAFFAELLA CHIARAMONTE - BIOGRAPHICAL SKETCH**

### **Education & Position**

1989 - Degree in Biological Sciences, University of Milano

1993 - Biotechnology Specialization School, University of Milano

1990-1998 - Research Associate, Laboratory of Molecular Pathology, Milano University Medical School

2002-2018 - Assistant Professor in Experimental medicine and Pathophysiology, Milano University.

2009-present – Director of Molecular Pathology laboratory at Dept. of Health Science

2018-present – Associate Professor in Experimental medicine and Pathophysiology at Milano University

**Research activity:** the interaction between cancer cell and tumor microenvironment. Role of Notch pathway in hematological malignancies.

The most relevant scientific contributions have led to the identification of molecular mechanisms mediated by Notch signaling that promote key aspects in the progression of multiple myeloma: i.e. bone marrow localization, bone destruction and the ability of myeloma to induce behavior pro-tumor by stromal cells through the release of IL6 and the induction of RNA editing activity of tumor cells.

These works laid the rational basis for the development of an anti-tumor therapeutic approach based on small molecules that inhibit the interaction between Notch and Jagged ligands with the intent of turning off the pathway.

More recently, the study was focused on the role of Notch ligands in the pathological communication mediated by tumor-derived extracellular vesicles with healthy cells of the surrounding microenvironment and the pre-metastatic niche.

### **Teaching (current)**

**Bachelor Degree in Medical Biotechnology:** course of General Pathology and Immunology – module of Oncology.

**Master Degree in Medical Biotechnology and Molecular Medicine:** Course of Tumor Epidemiology, Pathogenesis and Diagnosis and course of Onco-immunology.

**Degree in Physiotherapy:** Course in Physiology and Pathology

**Degree in Dietetics:** Course in general Pathology, Immunology and medical Genetics – module of Immunology.

**Doctoral School in Experimental Medicine:** member of the board, tutor and teacher in the practical course of Flow cytometry.

Mentoring: Advisor or co-advisor of ~30 thesis of Bachelor Degree in Medical Biotechnology, Master Degree in Medical Biotechnology and Molecular Medicine, PhD program in Molecular and Translational Medicine, PhD program of Experimental medicine, Specialization school in Medical Genetics.



Mentor of 4 post-doc collaborators.

### **Faculty Assignment**

2002-present: Member of the board of the PhD Program in Molecular and translational Medicine

2006-2012: Delegate to Internationalization for the Faculty of Medicine of Milano University.

2006-2012: Erasmus project coordination of the Bachelor and Master Degrees in Medical Biotechnology.

2009-2012: member of the Scientific Board at the dept. of Health Sciences

2012-2015: member of the board of the Specialization School in Medical Oncology.

2012-2018: member of the Academic Senate of the University of Milano.

Medicine.

2015-2017: member of the of the executive board of the PhD Program in Molecular and Translational Medicine.

2018-present: member of the board of the PhD Program in Experimental Medicine.

2018-present: Deputy director of the Department of Health Science.

**Scientific Societies membership:** European Society of Cell Proliferation, Italian Society of Pathology and Translational Medicine, European School of Hematology Virtual Network.

2018 Founding partner and member of EVIta the Italian Society of Extracellular Vesicles.

**Scientific Journal Reviewer:** Cancer Research, Experimental cell Research, Haematologica, Future Medicine, Cell Death and Disease, Cancer Letters, Oncotarget, Leukemia Research, BMC Cancer, Acta Haematologica, Leukemia & Lymphoma, Annals of Hematology, Acta Pharmacologica Sinica, Expert Review of Anticancer Therapy, Journal of Cutaneous Pathology, Pathology - Research and Practice, Clinical and Developmental Immunology.

**Grant Reviewer:** International Myeloma Foundation (IMF-USA), Swiss Cancer League, Leukemia and Lymphoma Research, Swiss National Science Foundation, Italian Ministry of Education University and Research, Serbian Ministry of Education and Science.

### **Recent Financial Awards (lest 10 years)**

01-01-2018 al 31-12-2022 AIRC Investigator Grant - IG 2017 "Impact of Notch signaling on extracellular vesicles-mediated tumor progression in multiple myeloma". Project code: 20614. Role: PI

Dal 01-12-2017 al 30-11-2018 Project for University research - Linea 2 azione B: Investigating the role of Jag ligands in multiple myeloma. Role: PI

2016: Transition Grant 2015/2017 – Horizon 2020 Linea 1A. Progetto "Unimi Partenariati H2020". Role: PI

2015-2017: R21 grant from the National Cancer Institute (NCI/NIH-USA): "Niche-responsive RNA editing by ADAR1 in dormant multiple myeloma initiating cell maintenance". N° 20144986 NIH. Role: Co-PI.

2014 Transition Grant, Linea A1-B Progetto Italia per l'Europa. Role: PI

2010-2012 Grant from Ministry of Education, University and Research (PRIN 2008): “Effects of Notch activation on the hematopoietic reconstitutive potential of CD34+ cells collected through different mobilization regimens. Role: PI

2009-2011 Grant from Ministry of Health - Research on specific issues (finalizzata) – Ordinary project (IRCCS): “Investigations on molecular pathways involved in mammary gland morphogenesis and role of their functional subversion in human breast carcinogenesis” Role: Collaborator.

2008-2010 Grant from Ministry of Health - Oncological Research – Ordinary project (IRCCS): “Biological and molecular characterization of cancer stem cells” Role: Collaborator.

2008-2009 Grant University Program for Research (PUR) “The oncogene Notch1 regulates chemokine receptors expression in acute leukemia: characterization of molecular mechanism” Role: PI.

2008-2009 CARIPLO Foundation Grant "Characterization of the roles of Numb and Notch in normal mammary gland development and in breast carcinogenesis" Role: Collaborator.

## **Publications**

Colombo M, Platonova N, Giannandrea D, Palano MT, Basile A, **Chiaramonte R**. Re-establishing Apoptosis Competence in Bone Associated Cancers via Communicative Reprogramming Induced Through Notch Signaling Inhibition. *Front Pharmacol*. 2019 Feb 27;10:145. doi: 10.3389/fphar.2019.00145

Saltarella I, Frassanito MA, Lamanuzzi A, Brevi A, Leone P, Desantis V, Di Marzo L, Bellone M, Derudas D, Ribatti D, **Chiaramonte R**, Palano MT, Neri A, Mariggiò MA, Fumarulo R, Dammacco F, Racanelli V, Vacca A, Ria R. Homotypic and Heterotypic Activation of the Notch Pathway in Multiple Myeloma-Enhanced Angiogenesis: A Novel Therapeutic Target? *Neoplasia*. 2019 Jan;21(1):93-105. doi: 10.1016/j.neo.2018.10.011.

Zulueta A., Colombo M, Peli V, Falleni M, Tosi D, Baisi A, **Chiaramonte R**, Caretti A. Lung mesenchymal stem cells-derived extracellular vesicles attenuate the inflammatory profile of Cystic Fibrosis epithelial cells. *Cell Signal*. 2018 Nov;51:110-118. doi: 10.1016/j.cellsig.2018.07.015.

Colombo M, Mirandola L, Chiriva-Internati M, Basile A, Locati M, Lesma E, **Chiaramonte R\*** and Platonova N\*, published. Cancer Cells Exploit Notch Signaling To Redefine A Tumor Supportive Cytokine Milieu. *Front Immunol*. 2018 Aug 14;9:1823. doi: 10.3389/fimmu.2018.01823. eCollection 2018.

### **\* co-last authors**

Lazzari E, Santos ND, Miller AC, Mondala FK, Pineda G, Jiang Q, Leu H, Ali SH, Ganesan AP, Wu CN, Costello C, Minden M, **Chiaramonte R**, Stewart AK, Crews LA, and Jamieson CH. Alu-dependent RNA Editing of GLI1 Promotes Malignant Regeneration in Multiple Myeloma. *Nat Commun*. 2017 Dec 4;8(1):1922.

Platonova N, Parravicini C, Sensi C, Paoli A, Colombo M, Neri A, Eberini I and Chiaramonte R. Identification of small molecules uncoupling the Notch::Jagged interaction through an integrated high-throughput screening. *PLoS ONE* 12(11): e0182640.

Mirandola L, Pedretti E, Figueroa JA, **Chiaramonte R**, Colombo M, Chapman C, Grizzi F, Patrinicola F, Kast WM, Nguyen DD, Rahman RL, Daver N, Ruvolo P, Post SM, Bresalier RS and Chiriva-Internati M. Cancer testis antigen Sperm Protein 17 as a new target for triple negative breast cancer immunotherapy. *Oncotarget* 2017; 8:74378-74390.

Natalia Platonova, Lesma Elena, Basile Andrea, Bignotto Monica, Garavelli S, Palano MT, Moschini Ad, Neri A, Colombo M and **Chiaramonte R**. Targeting Notch as a therapeutic approach for human malignancies. *Current Pharmaceutical Design*, 2017, 23, 1-27.

Colombo M, Galletti S, Bulfamante G, Falleni M, Tosi D, Todoerti K, Lazzari E, Crews LA, Jamieson CH, Ravaioli S, Baccianti F, Garavelli S, Platonova N, Neri A, **Chiaramonte R**. Multiple myeloma-derived Jagged ligands increases autocrine and paracrine interleukin-6 expression in bone marrow niche. *Oncotarget*. 2016; 7: 56013-29

**Chiaramonte R**, Colombo M, Bulfamante G, Falleni M, Tosi D, Garavelli S, De Simone D, Vigolo E, Todoerti K, Neri A, Platonova N. Notch pathway promotes ovarian cancer growth and migration via CXCR4/SDF1 $\alpha$  chemokine system. *Int J Biochem Cell Biol*. 2015; 66:134-40.

Colombo M, Galletti S, Garavelli S, Platonova N, Paoli A, Basile A, Taiana E, Neri A, **Chiaramonte R**. Notch signaling deregulation in Multiple Myeloma: a rational molecular target. *Oncotarget* 2015; 6: 26826–40.

Platonova N, Manzo T, Mirandola L, Colombo M, Vigolo E, Cermisoni GC, De Simone D, Garavelli S, Cecchinato V, Lazzari E, Neri A and **Chiaramonte R**. PI3K/AKT Signaling Inhibits NOTCH1 Lysosome-mediated Degradation. *Genes, Chromosomes and Cancer*, 2015; 54: 516–526

Colombo M, Mirandola L, Reidy A, Suvorava N, Konala V, **Chiaramonte R**, Grizzi F, Rahman RL, Jenkins MR, Nugyen DD, Dalhbeck S, Cobos E, Figueroa JA, Chiriva-Internati M. Targeting Tumor Initiating Cells through Inhibition of Cancer Testis Antigens and Notch Signaling: A Hypothesis. *International Reviews of Immunology*, 2015;34(2):188-99.

Colombo M, Thümmel K, Mirandola L, Garavelli S, Todoerti K, Apicella L, Lazzari E, Lancellotti M, Platonova N, Akbar M, Chiriva-Internati M, Soutar R, Neri A, Goodyear CS, **Chiaramonte R**. Notch signaling drives multiple myeloma induced osteoclastogenesis. *Oncotarget* 2014, 5(21): 10393-406.

Verdelli D, Nobili L, Todoerti K, Mosca L, Fabris S, D'Anca M, Pellegrino E, Piva R, Inghirami G, Capelli C, Introna M, Baldini L, **Chiaramonte R**, Lombardi L, Neri A. Molecular events underlying interleukin-6 independence in a subclone of the CMA-03 multiple myeloma cell line. *Genes Chromosomes Cancer*. 2014;53(2):154-67.

Mirandola L, Apicella L, Colombo M, Yuefei Yu, Berta DG, Platonova N, Lazzari E, Lancellotti M, Bulfamante G, Cobos E, Chiriva-Internati M, **Chiaramonte R**. Anti-Notch treatment prevents multiple myeloma cells localization to the bone marrow via the chemokine system CXCR4/SDF-1. *Leukemia* 2013, 27(7):1558-66 doi: 10.1038/leu.2013.27.

Colombo M, Mirandola L, Platonova N, Apicella L, Basile A, Figueroa AJ, Cobos E, Chiriva-Internati M, **Chiaramonte R**. Notch-directed microenvironment reprogramming in myeloma: a single path to multiple outcomes. *Leukemia* 2013, 27(5):1009-18. doi: 10.1038/leu.2013.6.

Pandey, A. Kurup, A. Shrivastava, S. Rahdi, D. Nguyen, C.Arentz, N.s D'Chuna, F. Hardwick, M. D'Sousa, **R. Chiaramonte**, N. Platonova, M. Jenkins, W. M. Kast, E. Cobos, R. Rahman & M. Chiriva-Internati *Cancer testes antigens in breast cancer: biological role, regulation and therapeutic applicability*, *International Reviews of Immunology*, 2012, 31: 302 – 320.

M. Chiriva-Internati, A. Pandey, R. Saba, M. Kim, C. Saadeh, T. Lukman, **R. Chiaramonte**, M. Jenkins, E. Cobos, C. Jumper & R. Alawi. *Cancer Testis Antigens: a Novel Target in Lung Cancer*, *International Reviews of Immunology*, 2012; 31: 321 – 343.

Mirandola L, Chiriva-Internati M, Montagna D, Locatelli F, Zecca M, Ranzani M, Basile A, Locati M, Cobos E, Kast WM, Asselta R, Paraboschi EM, Comi P, **Chiaramonte R**. Notch1 regulates chemotaxis and proliferation by controlling the chemokine receptors 5 and 9 in T-cell acute lymphoblastic leukemia. *J Pathol.*, 2012, 226(5):713-22.

Mirandola L, Yu Y, Jenkins MR, **Chiaramonte R**, Cobos E, John CM and Chiriva-Internati M. Tracking human multiple myeloma xenografts in NOD-Rag-1/IL-2 receptor gamma chain-null mice with the novel biomarker AKAP-4. *BMC Cancer*. 2011 Sep 16;11:394.

Mirandola L, Comi P, Cobos E, Kast WM, Chiriva-Internati M, **Chiaramonte R**. Notch-ing from T-cell to B-cell lymphoid malignancies. *Cancer Lett*. 2011 Sep 1;308(1):1-13.

Chiriva Internati M, Yu Y., Mirandola L, Jenkins M R, Gornati R, Bernardini G, Gioia M, **Chiaramonte R**, Cannon MJ, Kast WM, Cobos E. The Cancer Testis Antigen, Ropporin, is a Potential Target for Multiple Myeloma Immunotherapy. *J Immunother*. 2011 Jul-Aug;34(6):490-9.

Mirandola L, Larocca S, Rea K, Palma G, Comi P, **Chiaramonte R**. Notch: from fly wings to human hematological tumors. *Archive of Oncology* 17(vol.3-4) (2009). ISSN: 1450-9520

Hesson LB, Dunwell TL, Cooper WN, Catchpoole D, Brini AT, **Chiaromonte R**, Griffiths M, Chalmers AD, Maher ER, Latif F. The novel *RASSF6* and *RASSF10* candidate tumour suppressor genes are frequently epigenetically inactivated in childhood leukaemias. *Mol. Cancer* 8:42-51 (2009)

Dunwell TL, Hesson LB, Pavlova T, Zabarovska V, Kashuba V, Catchpoole D, **Chiaromonte R**, Brini AT, Griffiths M, Maher ER, Zabarovsky E, Latif F. Epigenetic analysis of childhood acute lymphoblastic leukemia. *Epigenetics*;4:185-93 (2009).

Mirandola L, Basile A, Comi P, **Chiaromonte R**. Burkitt lymphoma translocation turns Notch over to the dark side. *Leuk Res.* 2009 Jun;33(6):750-1.

Pizzimenti S., Barrera G., Calzavara E., Mirandola L., Toaldo C., Dianzani M.U., Comi P., **Chiaromonte R**. Down-regulation of Notch1 expression is involved in HL-60 cell growth inhibition induced by 4-hydroxynonenal, a product of lipid peroxidation. *Medicinal Chemistry*, 2008;4:551-7.

Calzavara E, **Chiaromonte R**, Cesana D, Basile A, Sherbet GV, Comi P. Reciprocal regulation of Notch and PI3K/Akt signalling in T-ALL cells in vitro. *J Cell Biochem.* 2008, 103:1405–1412.

Cecchinato V., Basile A., Scarpati B., Fazi C., Brando B, Erba E. , Comi P. and **Chiaromonte R**. Hexamethylene bisacetamide inhibits malignant phenotype in T-ALL cell lines. *Leukemia Research.* *Leuk Res.* 2008 May; 32(5):791-7.

Cecchinato V, **Chiaromonte R** , Nizzardo M, Cristofaro B, Calzavara E, Sherbet GV, Comi P (2007). Resveratrol-induced apoptosis in human T- cell acute lymphoblastic leukemia MOLT-4 cells. *Biochem Pharmacol.* 2007 Dec 3;74(11):1568-74.

**Chiaromonte R.** (2006) Still puzzling Notch signaling in B-cell malignancies. *Leukemia Research* vol.30 pp. 1331–1332.

**Chiaromonte R.**, Calzavara E, Basile A, Comi P (2005). Notch Signalling in Cancer. A chapter of the book “Molecular and Cellular Pathology of Cancer Progression”.pp. 275-326. Research Signpost Collection - Editor G.V. Sherbet - ISBN: 81-7736-283-6.

**Chiaromonte R.**, Basile A, Tassi E, Calzavara E, Cecchinato V, Rossi V, Biondi A, Comi P (2005). A wide role for Notch1 signaling in acute leukemia. *CANCER LETTERS.* vol. 219 pp. 113-120

**Chiaromonte R.**, Calzavara E., Balordi F., Sabbadini M., Capello D., Gaidano G., Serra A., Comi P. And Sherbet G.V. (2003). Differential regulation of Notch signal transduction in leukemia and lymphoma cell in culture. *Journal of Cellular Biochemistry.* vol. 88 pp. 569-577.

**Chiaromonte R.**, Calzavara E., Basile A., Comi P. And Sherbet G.V. (2002). Notch Signal Transduction Is Not Regulated by Sel1L In Leukemia and Lymphoma Cells In Culture. *Anticancer Research.* vol. 22 pp. 4211-4214 .

**Chiaromonte R.**, Sabbadini M., Comi P. and Sherbet G.V. (2002). Allele frequency of two intragenic microsatellite loci of SEL1L gene in Northern Italy population. *Molecular and Cellular Biochemistry.* vol. 232 pp. 159-161.

**Chiaromonte R.**, Bartolini E.Riso P., Calzavara E., Erba D., Testolin G., Comi P. And Sherbet G.V. (2001). Oxidative stress signalling in the apoptosis of Jurkat T lymphocytes. *Journal of Cell Biochem.* vol. 82 pp.437-444.

Pociot F., Larsen Z.M., Zavattari P., Deidda E., Nerup J., Cattaneo M., **Chiaromonte R.**, Comi P., Sabbadini M., Zollo M., Biunno I., Cucca F. (2001). No evidence for SEL1L as a candidate gene for IDDM11-conferred susceptibility. *Diabetes-Metabolism Research and Reviews.* vol. 17 pp. 292-295.

**Chiaromonte R.**, Bartolini E, Testolin C, Comi P (1998). Regulation of the human glut4 gene expression in tumor RD18 cell line. *Pathobiology.* vol. 66 pp. 191-195.

**Chiaromonte R.**, Fasola S, Lollini PI, De Giovanni C Comi P (1998). Is mts1(S100A4) gene involved in the metastatic process modulated by gamma-interferon?. *Pathobiology.* vol. 66 pp. 38-40.

Petroni D, Bartolini E, **Chiaromonte R.**, Ottolenghi S, Comi P (1998). computer sequence analysis of highly conserved zinc fingers modules. *Dna Sequence.* vol. 9 pp. 163-169.

**Chiaromonte R.**, Polizzi D, Bartolini E, Petroni D, Comi P (1997). PlGF-saporin fusion protein: a potential anti-angiogenic agent. *Anti-Cancer Drug Design.* (incorporato in *Oncology Research*) vol. 12 pp. 649-657.

Comi P, **Chiaromonte R.**, Maier Jam (1995). Senescence-dependent regulation of type 1 plasminogen activator in human vascular endothelial cells. *Experimental Cell Research.* vol. 219 pp. 304-308.

**Chiaromonte R.**, Comi P (1993). VEGF: ruolo nell'angiogenesi. *Biotec.* vol. 8(3) pp. 17-18.

**Chiaromonte R.**, Martini R, Taramelli, R Comi P (1993). Identification of the 5' end of the gene encoding a human insulin responsive glucose transporter. *Gene*. vol. 130 pp. 307-308.

Ghisotti D, **Chiaromonte R.**, Forti F, Zangrossi S, Sironi G, Deho' G (1992). Genetic analysis of the immunity region of phage-plasmid P4. *Molecular Microbiology*. vol. 6 pp. 3405-3413.