
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME: Deaglio Silvia

POSITION TITLE: Associate Professor of Medical Genetics

eRA COMMONS USER NAME (credential, e.g., agency login)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary)*

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Torino, Italy	M.D.	1992-1998	Medicine
University of Torino, Italy	Board Certification	1998-2002	Oncology
University of Torino, Italy	Ph.D.	2002-2006	Genetics

A. Personal Statement

After obtaining an MD degree and training as a medical oncologist, I started a PhD program in Genetics at the University of Turin. My research interests were focused on enzymes that can synthesize and metabolize nucleotides, such as ATP and NAD, in the extracellular environment. During the PhD, I trained at the Beth Israel Deaconess Medical Center of Harvard University with Drs. Simon Robson and Terry Strom, where we identified an ATP-degrading pathway as an integral component of the suppressive machinery of regulatory T cells. After going back to Italy at the end of 2005, I obtained my first two grants as an independent investigator and studied nucleotide-nucleoside balance in the tumor microenvironment. In 2010 I started my own research group in the Laboratories of the Human Genetics Foundation in Turin, Italy. This group now comprises 12 researchers. In the past few years we have focused on NAD metabolism as a critical step in the regulation of leukemic cell homing and in the skewing of bystander cells towards a pro-survival phenotype. Furthermore, we participated in a joint effort to identify recurrently mutated genes in patients with chronic lymphocytic leukemia and splenic marginal zone lymphoma. Current studies are dedicated to the understanding of the role of these genes and their mutations in the biology of the disease. To do this, there is an urgent need of xenograft models that will allow expansion of genetically-typed primary cells. In order to implement these models in the lab, I spent two years as a visiting professor at Weill Cornell Medical College.

B. Positions and Honors

Positions and Employment:

- 1993-1998: Internal student, Laboratory of Cell Biology, Department of Genetics, Biology and Biochemistry, University of Torino.
- 1995: Visiting medical student, Sloan Kettering Cancer Center, New York, NY.
- 2001: Visiting scientist, Department of Cell Biology and Immunology, Instituto Parasitologia y Biomedicina, C.S.I.C., Granada, Spain.
- 1999-2002: Oncology fellow, Oncology Division, Molinette Hospital, Torino, Italy.
- 2002-2004: Clinical attending physician, Breast Cancer Clinic, Oncology Division, Molinette Hospital, Torino, Italy.
- 2002-2006: Ph.D. student (Genetics), Laboratory of Immunogenetics, Department of Genetics, Biology and Biochemistry, University of Torino.
- 2004-: 2005 Instructor in Medicine and (2005) Visiting Assistant Professor, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
- 2005-2011: Assistant Professor of Medical Genetics ("Ricercatore", "Confermato" since Jan 1, 2008), University of Torino Medical School, Torino, Italy.

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- Sept 2010-: Head of the Immunogenetics Research Unit of the Human Genetics Foundation (www.hugef-torino.org), Turin, Italy.**
- Oct 2011-: Associate Professor of Medical Genetics, University of Torino Medical School, Torino, Italy.**
- 2014-2016: Visiting Associate Professor, Department of Pathology and Laboratory Medicine, Weill Cornell Medical Center, Cornell University, New York, NY.
- Sept 2016-: Dirigente Medico, Servizio di Immunogenetica e Biologia dei Trapianti, Città della Salute e della Scienza Hospital, Turin, Italy.**

Honors and Professional Service:

- 1996: PBI international Prize for the best abstract presented at the 1996 Immunology Cooperation Group (GCI) meeting in L'Aquila, Italy.
- 1998: Telethon Foundation Prize for scientific research, Roma, Italy.
- 1999: Optime Prize for best-qualified students, Industrial Association of Torino. Torino, Italy.
- 2002: Cecilia Cioffrese prize for cancer research (Milano, Italy)
- 2004: Walter Knapp Young Investigator Award. Prize presented at the VIII HLDA Congress, December 10-14, 2004, Adelaide, Australia.
- 2006: Italian Cancer League Prize for translational researches in hematology (Asti, October 18, 2006)

C. Contribution to Science

1. Identification of a natural ligand for CD38. We raised a panel of monoclonal antibodies to perturb CD38-mediated adhesion to the endothelial cells. This led to the identification of CD31 as a ligand for CD38. CD31/CD38 interactions occur in the early phases of lymphocyte adhesion and mediate, activation, integrin expression and secretion of a number of cytokines and chemokines. The role of CD31-CD38 interactions was then dissected in different normal and pathological conditions. Most relevant publications:
 - a. Deaglio S, Dianzani U, Horenstein AL, Fernandez JE, van Kooten C, Bragardo M, Funaro A, Garbarino G, Di Virgilio F, Banchereau J, et al. Human CD38 ligand. A 120-KDA protein predominantly expressed on endothelial cells. *J Immunol.* 1996;156(2):727-34.
 - b. Deaglio S, Morra M, Mallone R, Ausiello CM, Prager E, Garbarino G, Dianzani U, Stockinger H, and Malavasi F. Human CD38 (ADP-ribosyl cyclase) is a counter-receptor of CD31, an Ig superfamily member. *J Immunol.* 1998;160(1):395-402.
 - c. Deaglio S, Mallone R, Baj G, Donati D, Giraudo G, Corno F, Bruzzone S, Geuna M, Ausiello C, and Malavasi F. Human CD38 and its ligand CD31 define a unique lamina propria T lymphocyte signaling pathway. *FASEB J.* 2001;15(3):580-2.
 - d. Malavasi F, Deaglio S, Funaro A, Ferrero E, Horenstein AL, Ortolan E, Vaisitti T, and Aydin S. Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology. *Physiol Rev.* 2008;88(3):841-86.

2. Identification of adenosine production as a non-redundant immunosuppressive mechanism of regulatory T cells. During this work, we discovered that regulatory T cells express CD39 and CD73, two key enzymes in the degradation of ATP and generation of adenosine. We also discovered that adenosine is an integral component of the suppressive mechanism of regulatory T cells, both in mice and in humans. We then hypothesized that tumor cells may hijack this mechanism, catalyzing the generation of adenosine in the tumor niche, limiting immune responses, Most relevant publications:
 - a. Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, Chen JF, Enjoji K, Linden J, Oukka M, et al. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med.* 2007;204(6):1257-65.
 - b. Sitkovsky M, Lukashev D, Deaglio S, Dwyer K, Robson SC, and Ohta A. Adenosine A2A receptor antagonists: blockade of adenosinergic effects and T regulatory cells. *Br J Pharmacol.* 2008;153 Suppl 1(S457-64).

- c. Longhi MS, Robson SC, Bernstein SH, Serra S, and Deaglio S. Biological functions of ecto-enzymes in regulating extracellular adenosine levels in neoplastic and inflammatory disease states. *Journal of molecular medicine*. 2013;91(2):165-72.
 - d. Serra S, Horenstein AL, Vaisitti T, Brusa D, Rossi D, Laurenti L, D'Arena G, Coscia M, Tripodo C, Inghirami G, et al. CD73-generated extracellular adenosine in chronic lymphocytic leukemia creates local conditions counteracting drug-induced cell death. *Blood*. 2011;118(23):6141-52.
3. Identification of the role of CD38 in the chronic lymphocytic leukemia niche. Clinical observations indicate that CD38 may be expressed by a subset of CLL patients, generally those with an inferior clinical outcome. We built on this observation, identifying CD38 as a critical “molecular drift”, guiding CLL cells from the blood to privileged niches within the lymph nodes and the bone marrow. We then used and enzymatically dead CD38 mutant to show that its enzymatic activities lead to the production of second messengers that increase cytoplasmic Ca²⁺ levels, facilitating signals regulating cell movement. Most relevant publications:
- a. Deaglio S, Capobianco A, Bergui L, Durig J, Morabito F, Duhrsen U, and Malavasi F. CD38 is a signaling molecule in B-cell chronic lymphocytic leukemia cells. *Blood*. 2003;102(6):2146-55.
 - b. Deaglio S, Vaisitti T, Aydin S, Bergui L, D'Arena G, Bonello L, Omede P, Scatolini M, Jaksic O, Chiorino G, et al. CD38 and ZAP-70 are functionally linked and mark CLL cells with high migratory potential. *Blood*. 2007;110(12):4012-21.
 - c. Vaisitti T, Aydin S, Rossi D, Cottino F, Bergui L, D'Arena G, Bonello L, Horenstein AL, Brennan P, Pepper C, et al. CD38 increases CXCL12-mediated signals and homing of chronic lymphocytic leukemia cells. *Leukemia*. 2010;24(5):958-69.
 - d. Vaisitti T, Audrito V, Serra S, Buonincontri R, Sociali G, Mannino E, Pagnani A, Zucchetto A, Tissino E, Vitale C, et al. The enzymatic activities of CD38 enhance CLL growth and trafficking: implications for therapeutic targeting. *Leukemia*. 2015;29(2):356-68.
4. Identification of the role of the NAD-biosynthetic enzyme nicotinamide phosphoribosyl transferase (NAMPT), also known as visfatin or pre-B colony enhancing factor (PBEF) in the tumor microenvironment. Our data indicate that NAMPT is secreted in the extracellular compartment by activated tumor cells. Here, NAMPT induces differentiation of monocytes into alternatively activated monocytes, which then skew T cell responses and promote leukemic growth.
- a. Audrito V, Vaisitti T, Rossi D, Gottardi D, D'Arena G, Laurenti L, Gaidano G, Malavasi F, and Deaglio S. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT1 tumor suppressor network. *Cancer research*. 2011;71(13):4473-83.
 - b. Audrito V, Serra S, Brusa D, Mazzola F, Arruga F, Vaisitti T, Coscia M, Maffei R, Rossi D, Wang T, et al. Extracellular nicotinamide phosphoribosyltransferase (NAMPT) promotes M2 macrophage polarization in chronic lymphocytic leukemia. *Blood*. 2015;125(1):111-23.
5. Identification recurrently mutated genes in fludarabine-resistant CLL cells. This project originated as a multicentric collaboration, aimed at sequencing the exome of CLL cells obtained from fludarabine-resistant patients. It led to the identification of mutations in NOTCH1, SF3B1 and BIRC3 genes. We then went on to analyze the functional role of NOTCH1 in CLL cells. The same approach was also used to study the genomic landscape of patients with splenic marginal zone lymphoma (SMZL), with the identification of mutations in NOTCH2 and KLF2 and a preliminary evaluation of their function in these cells.
- a. Rossi D, Deaglio S, Dominguez-Sola D, Rasi S, Vaisitti T, Agostinelli C, Spina V, Brusca A, Monti S, Cerri M, et al. Alteration of BIRC3 and multiple other NF-kappaB pathway genes in splenic marginal zone lymphoma. *Blood*. 2011;118(18):4930-4.

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- b. Rossi D, Trifonov V, Fangazio M, Bruscaggin A, Rasi S, Spina V, Monti S, Vaisitti T, Arruga F, Fama R, et al. The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development. *J Exp Med*. 2012;209(9):1537-51.
- c. Arruga F, Gizdic B, Serra S, Vaisitti T, Ciardullo C, Coscia M, Laurenti L, D'Arena G, Jaksic O, Inghirami G, et al. Functional impact of NOTCH1 mutations in chronic lymphocytic leukemia. *Leukemia*. 2014;28(5):1060-70.
- d. Piva R, Deaglio S, Fama R, Buonincontri R, Scarfo I, Bruscaggin A, Mereu E, Serra S, Spina V, Brusa D, et al. The Kruppel-like factor 2 transcription factor gene is recurrently mutated in splenic marginal zone lymphoma. *Leukemia*. 2015;29(2):503-7.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/48168277/?reload=addfrompubmed&sortby=date&groupby=citation_type

Metrics: Total IF: 834
Mean IF: 6.52
H index: 42

D. RESEARCH SUPPORT

Ongoing Research Support

Sponsor/Italian Association for Cancer Research

Grant Number 17314 Deaglio (PI) 01/01/2016 - 12/31/2018
Title: "Understanding tumor-host interactions and therapy resistance in chronic lymphocytic leukemia: moving up a NOTCH?"
Objective: Mechanistic project to understand the function of NOTCH1 and the role of its mutations in CLL

Sponsor/ Italian Ministry of Health, Young Investigator call 2011

Grant Number GR-2011-02346826 Deaglio (co-PI) 11/15/2014 - 11/15/2017
Title: "Pleiotropic transcriptional control mechanisms of CD49d expression in trisomy 12 chronic lymphocytic leukemia: implications for novel therapeutic approaches".

Sponsor/ Fondazione Italiana Ematologi Oncologi Pediatrici

Deaglio (co-PI) 05/01/2016 - 04/30/2019
Title: "Functional genomics applied to pediatric cancers: from mutations, to function, to therapy".
Objective: Identification and functional analysis of recurrently mutated genes in pediatric sarcomas

Sponsor: Halozyme Therapeutics

Deaglio (PI) 06/01/2016 - 05/31/2017
Title: Analysis of the therapeutic potential of pegylated-ADA in chronic lymphocytic leukemia

Sponsor: Immune Target, Inc.

Deaglio (PI) 09/01/2016 - 08/31/2017
Title: Evaluation of the effects of a novel NF-kB inhibitor in chronic lymphocytic leukemia and Richter Syndrome models

Completed Research Support

Sponsor: Italian Association for Cancer Research Deaglio (PI) 1/1/2013-12/31/2015
Grant Number 89259

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Title: **“Cooperation between adenosinergic and hypoxic signals in the organization of the leukemic niche”**

Aims:

Aim 1: To determine the effects of hypoxia on the adenosinergic axis in CLL and in bystander cells

Aim 2: To determine whether adenosine signaling may activate an hypoxic signature

Aim 3: To determine the effects of adenosine signaling under hypoxic conditions in T lymphocytes from CLL patients

Aim 4: To test the impact of pharmacological targeting of adenosine receptors in CLL

Sponsor: **Italian Ministry of Health** Deaglio (PI)

11/15/2010-11/15/2014

Grant Number Young Investigator Call 2008, 1138053

Title: **Identification of novel prognostic factors and therapeutic targets for Richter’s Syndrome**

Aim 1: To define the role of extracellular nucleotides in favoring transformation of CLL to Richter Syndrome

Aim 2: To discover the role the host genetic polymorphism in predisposing to Richter Syndrome

Aim 3: To determine the role of immune checkpoint inhibitors in favoring transformation of CLL to Richter Syndrome

Aim 4: To set-up animal models of Richter’s syndrome

Sponsor: **Italian Ministry of Education**

Deaglio (PI)

01/01/2011-5/31/2014

Grant number: Progetto Giovani Ricercatori, call 2008, RBFR08ATLH

Title: **Soluble factors, membrane receptors and genetic regulation in tumor/host interactions**

Aim 1: evaluate whether the signals mediated by extracellular nucleotides collaborate with the chemokine network in directing neoplastic cells towards growth-permissive microenvironments, while at the same time protecting against the action of the immune system

Aim 2: to analyze the expression of HLA-G, a non-classical histocompatibility molecule, in a wide cohort of CLL patients and to evaluate its role in the regulation of the interactions between leukemic cells and the host immune system.

Aim 2: To analyze the influence of the interactions between the genetic background of the host and tumor cell biology on the phenotypic heterogeneity of CLL

Sponsor/ Italian Ministry of Health, Young Investigator call 2010

Grant Number GR-2010-2317594

Deaglio (co-PI)

11/15/2013 - 11/15/2015

Title: “New genetic lesions characterizing high risk chronic lymphocytic leukemia: clinical and functional implications”

Objective: Multitask program designed to understand the functional role of the main genetic lesions characterizing chemotherapy-resistant CLL cases.

Sponsor/Cariplo Foundation – Biomedical Research Grants

Grant Number Deaglio (co-PI)

01/01/2014 - 4/30/2016

Title: “Deciphering the molecular basis of splenic marginal zone lymphoma by whole exome sequencing and functional genomics”.

Objective: Functional genomics studies to characterize the most common genetic mutations in SMZL patients

Sponsor/ Italian Ministry of Education, Futuro in ricerca 2012 grant

Grant Number RBFR12D1CB

Deaglio (co-PI)

03/31/2014 - 03/31/2016

Title: “Identification and functional characterization of genomic lesions in lymphoid malignancies”

Objective: Multitask program designed to characterize the molecular event leading to transformation of chronic lymphocytic leukemia and splenic marginal zone lymphoma.