BIOGRAPHICAL SKETCH

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NAME: Roncarolo, Maria Grazia

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POSITION TITLE: Professor, Departments of Pediatrics and Medicine; Director, Center for Definitive and Curative Medicine; Co-Director, Institute for Stem Cell Biology and Regenerative Medicine

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Turin, Italy	M.D.	04/1982	Medicine
University of Turin, Italy	Natl. Board	07/1986	Pediatrics
University of Milan	Natl. Board	07/1990	Clinical Immunology

A. Personal Statement

I am a Pediatric Immunologist with a research focus on mechanisms and novel therapies for genetic and acquired diseases of the blood and immune system. My areas of expertise are Primary Immunodeficiencies, Immune Tolerance, T regulatory Cells and Gene Therapy. I discovered a new subset of human T cells with immune regulatory and suppressor functions, named Type 1 (Tr1) regulatory cells. My team established that Tr1 cells are responsible for induction and maintenance of tolerance to allo- and self-antigens and food- and environmental- antigens. I was the principal investigator of the first-in-human clinical trial using *in vitro* generated donor-derived Tr1 cells to favor immune reconstitution without severe graft-versus-host disease in cancer patients undergoing haploidentical hematopoietic stem cell transplantation. I recently initiated a new trial (IND#17292) to infuse *in vitro* generated Tr1 cell precursors specific for the host alloantigens to prevent graft-versus-host disease in children and young adults with hematological malignancies receiving HLA mismatched hematopoietic stem cell transplantation.
Parallel to the studies on immunological tolerance, I made major contributions to the design and execution of gene therapy trials for primary immunodeficiencies and other genetic diseases. I was the principal investigator for the first successful stem cell gene therapy trial for Severe Combined Immunodeficiency (SCID) patients lacking adenosine deaminase (ADA), a purine metabolism disorder that results in severe immunodeficiency and death. Based on the results from this trial, stem cell gene therapy for ADA-SCID has received European Commission approval to market under the name of Strimvelis.

B. Positions and Honors

Employment

1983-1984 Research Fellow, Division of Transplantation and Clinical Immunology, Hospital E. Herriot, University Claude Bernard, Lyon, France.
1984 Research Associate, Laboratory for Immunological Research, Schering-Plough, Lyon, France.
1985-07/86 Resident, Department of Pediatrics, Division of Immunology, School of Medicine, University of Turin, Italy.
08/86-01/88 Associate Senior Scientist (Chargée de Recherches), Laboratory for Immunological Research, Schering-Plouch, Lyon France.
Assistant Professor (Assistant Etranger), School of Medicine, University Claude Bernard, Lyon, France.
02/88-02/89 Assistant pediatrician (Médecin Résident Etranger des Hospices Civils de Lyon), Division of Transplantation and Clinical Immunology, Hospital E. Herriot, Lyon, France.
03/89-03/92 Staff Scientist, DNAX Research Institute for Molecular and Cellular Biology, Palo Alto, CA.

03/92-12/96 Senior Staff Scientist, DNAX Research Institute for Molecular and Cellular Biology, Palo Alto, CA.
11/94-11/01 Associate Professor of Pediatrics, School of Medicine, University of Turin, Turin, Italy.
11/01-02/07 Associate Professor of Pediatrics, School of Medicine, Vita-Salute San Raffaele University, Milan, Italy.
02/98-12/98 Director of Cellular Therapy Laboratory Telethon Institute for Gene Therapy (TIGET), San Raffaele Scientific Institute, Milan, Italy.
12/98-05/00 Co-Director of San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan, Italy.
06/00-09/08 Director of San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan, Italy.
03/08-09/13 Scientific Director of San Raffaele Scientific Institute, Milan, Italy.
02/98-06/14 Head of the Immune Tolerance Unit, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy.
07/03-06/14 Division Chief, Pediatric Immunology and Hematology, San Raffaele Hospital and San Raffaele Scientific Institute, Milan, Italy.
03/07-06/14 Professor of Pediatrics, School of Medicine, Vita-Salute San Raffaele University, Milan, Italy.
06/14-present George D. Smith Professor in Stem Cell and Regenerative Medicine,
Professor of Pediatrics and Medicine,
Director, Center for Definitive and Curative Medicine,
Co-Director, Institute for Stem Cell Biology and Regenerative Medicine
Stanford School of Medicine, Stanford University, Stanford, California, USA.

Other Professional Experience

2018-present President of the Federation of Clinical Immunology Societies (FOCIS).
2008-present Board Member (and Chair 2017-2019) of the Eureka Institute for Translational Medicine.
2008-present Board Member of Cosmo Pharmaceuticals.
2016-2018 Co-Chair of the Scientific Advisory Board of Glaxo Smith Kline Cell and Gene Therapy (CGT).
2015-2017 Member of the Spark Therapeutics Scientific Advisory Board.
2014-2017 Member of the Scientific Advisory Board of the Child and Family Research Institute, BC Children Hospital.
2015-2016 Member of the External Immunology Board of the Glaxo Smith Kline Immunology Network.
2012-2014 Member of the Scientific Advisory Board of the French Rare Diseases Foundation.
2011-2014 Member of the Scientific Advisory Board of the Global Health Institute (GHI) Lausanne.
2007-2012 Member of the External Scientific Advisory Board of the Tumorzentrum L. Heilmeyer, Comprehensive Cancer Center Freiburg.
1999-2002 President Genethon Scientific Advisory Board of the Association Française contre les Myopathies.
1997-2002 Consultant for Novartis Pharmaceutical in the areas of Immunology, Transplantation and Gene Therapy.
1997-2000 Member of the Scientific Advisory Board of Kinetix Pharmaceutical.
1993-1996 Member of Schering-Plough's "Cytokine Team" for developing cytokines for clinical applications.

Honors

2000 Nominated “Ufficiale dell’Ordine Al Merito della Repubblica Italiana” from the President of Italy for outstanding scientific contributions.
2005 Elected Member of the Academia Europaea of Sciences.
2010 “The outstanding Achievement Award” from the European Society of Gene and Cell Therapy (ESGCT) for outstanding career and pioneering contributions to the field of cell and gene therapy.
2012 Eurordis Scientific Award 2012 for outstanding contributions to the cure of genetic diseases.
2012 Elected Member of the Austrian Academy of Sciences.
2013 Gold Apple prize, awarded by the Marisa Bellisario Foundation, for outstanding contribution to science.
2013 Knighthood “Commendatore dell’Ordine Al Merito della Repubblica Italiana” from the President of Italy for outstanding scientific contributions.
2017 “The outstanding Achievement Award” from the American Society of Gene and Cell Therapy (ASGCT) for a lifetime of significant scientific contributions to the field of gene and cell therapy.

C. Contributions to Science

My academic career has emphasized 3 intersecting area of inquiry:

1. **Understanding the mechanisms of immunological tolerance**

I have made significant contributions to the discovery of the mechanisms underlying the induction and breaking of tolerance in bone marrow/organ transplantation and autoimmune diseases. Specifically, I contributed to the discovery and biological characterization of human T cells with immune regulatory and suppressor functions. I discovered a novel subset of inducible suppressor T cells, designated as T regulatory type 1 (Tr1) cells and determined their biological functions. I established that these cells were present in tolerant patients after hematopoietic stem cell transplantation. Subsequently I isolated these cells from man and mice and demonstrated that they are responsible for induction and maintenance of tolerance. Recently, I described genes preferentially expressed by Tr1 cells and I discovered that the surface molecules CD49b and LAG3 are specific biomarkers for this subset of T regulatory cells. This allows for their isolation for therapeutic purposes and *in vivo* tracking in patients. I developed a GMP grade protocol to generate Tr1 cells for clinical use. I was the principal investigator of the first-in-human clinical trial using these ex-vivo generated donor-derived Tr1 cells in cancer patients undergoing haploidentical hematopoietic stem cell transplantation. I discovered that Rapamycin favors expansion of human CD25+FOXP3+ T regulatory cells *in vivo* and *in vitro* in quantities, which allow their use for therapeutic purposes.

a) H. Groux, A. O'Garra, M. Bigler, M. Rouleau, S. Antonenko, J.E. de Vries and **M. G. Roncarolo** (1997). *A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis*. Nature 389:737-742.
b) M. Battaglia, A. Stabilini, B. Migliavacca, J. Horejs-Hoeck, T. Kaupper, and **M.G. Roncarolo** (2006). *Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and Type 1 diabetic patients.* J Immunol 177: 8338-8347.
c) N. Gagliani, C.F. Magnani, S. Huber, M.E. Gianolini, M. Pala, P. Licona-Limon, B. Guo, D.R.Herbert, Bulfone, F. Trentini, C. Di Serio, R. Bacchetta, M. Andreani, L.Brockmann, S. Gregori, R. Flavell, and **M.G. Roncarolo** (2013). *Co-expression of CD49b and LAG-3 identifies human and murine Tr1 cells*. Nat Med 19: 739-746.
d) R. Bacchetta, B. Lucarelli, C. Sartirana, S. Gregori, M.T. Lupo Stanghellini, P. Miqueu, S. Tomiuk, M. Hernandez-Fuentes, M.E. Gianolini, R. Greco, M. Bernardi, E. Zappone, S. Rossini, U. Janssen, A. Ambrosi, M. Salomoni, J. Peccatori, F. Ciceri, and **M.G. Roncarolo** (2014). *Immunological outcome in haploidentical-HSC transplanted patients treated with IL-10-anergized donor T cells.* Front Immunol 5: 16.1-13.

2. Investigating the mechanisms of immune mediated diseases

I investigated the mechanisms underlying the pathology of genetic immune diseases such as Severe Combined Immune Deficiency (SCID), SAP deficiency, Wiskott Aldrich Syndrome (WAS), IPEX, and of acquired immune diseases such as type 1 diabetes and celiac disease. I contributed to the identification of SAP as the gene responsible for the genetic X-linked lymphoproliferative disease defined as Duncan's syndrome. I discovered that patients with WASP deficiency have a defect in the immunological synapse and an impaired differentiation of CD25+FOXP3+ T regulatory cells. I led the studies on IPEX patients showing defective regulatory and effector functions in patients with different FOXP3 mutations. I demonstrated that treatment with rapamycin and IL-10 can restore tolerance in preclinical models of type 1 diabetes and pancreatic islet transplantation by inducing expansion of CD25+FOXP3+ regulatory cells in the tissue and promoting differentiation of Tr1 cells in the spleen. I established a preclinical in vivo gene therapy protocol using hepatocyte lentiviral vector targeted deliver of insulin peptides, to protect and reverse type 1 diabetes.

a) L. Dupré, A. Aiuti, S. Trifari, S. Martino, P. Saracco, C. Bordignon and **M.G. Roncarolo** (2002). *Wiskott-Aldrich syndrome protein regulates lipid raft dynamics during immunological synapse formation.* Immunity 17: 157-166.
b) R. Bacchetta, L. Passerini, E.Gambineri, M. Dai, S.E.Allan, L. Perroni, F. Dagna-Bricarelli, C. Sartirana, S. Matthes-Martin, A. Lawitschka, C. Azzari, S.F. Ziegler, M.K. Levings, and **M.G. Roncarolo** (2006). *Defective regulatory and effector T cell functions in patients with FOXP3 mutations.* J Clin. Invest 116:1713-1722.
c) M. Battaglia , A. Stabilini , E. Draghici , B. Migliavacca, S. Gregori , E. Bonifacio, and **M.G. Roncarolo** (2006). *Induction of tolerance in type I diabetes via both CD4+CD25+ T regulatory cells and T regulatory type I cells.* Diabetes 55: 1571-1580.
d) M. Akbarpour, K.S. Goudy, A. Cantore, F. Russo, F. Sanvito. L. Naldini, A. Annoni, M.G. **Roncarolo** (2015). *Insulin chain 9-23 gene transfer to hepatocytes protects from type 1 diabetes by inducing Ag-specific FOXP3+ Tregs*. Sci Transl Med 7: 289-300.

3. Stem cell and gene therapy

I focused my studies on severe inherited blood and metabolic diseases, including severe combined immunodeficiency (SCID), lysosomal storage diseases and hemoglobinopaties to design novel stem cell and gene therapies. I was a key member of the first team to carry out fetal stem cell transplants given before birth to treat these genetic diseases. I made major contributions to the design, execution and follow up of haploidentical transplantation in utero using maternal haploidentical hematopoietic stem cells to cure SCID-X1 deficient patients. I have also characterized the *in vitro* and *in vivo* proliferative and differentiation capacity of fetal liver lymphoid and myeloid progenitors and I contributed to define the biological activities of FLK27FLT-3 ligand on these cells. I successfully led the first stem cell-based gene therapy trail for SCID patients lacking adenosine deaminase (ADA), a severe life-threatening disorder due to defects in the purine metabolism that results in severe immunodeficiency and death. The trial, combining gene corrected blood stem cells with low-dose chemotherapy, is now considered the gold standard for gene therapy in inherited immune diseases. Gene therapy for ADA-SCID has obtained an Orphan drug status from the FDA/EMEA and European Commission approval to market under the name of Strimvelis. I participated in the design and implementation of a lentiviral based gene therapy trial for metachromatic leukodistrophy. I was the principal investigator in a successful gene therapy trial for Wiskott Aldrich Syndrome using lentiviral vectors.

a) A.W. Flake, **M.G. Roncarolo**, J. Puck, G. Almeida-Porada, M. Evans, M. Johnson, E. Abella, D. Harrison, and E. Zanjani (1996). *Treatment of X-linked severe combined immunodeficiency by in utero transplantation of paternal bone marrow.* New Engl J Med 335:1806-1810.

b) A. Aiuti, F. Cattaneo, S. Galimberti, U. Benninghoff, B. Cassani, L. Callegaro, S. Scaramuzza, G. Andolfi, M. Mirolo, I. Brigida, A. Tabucchi, F. Carlucci, M. Eibl, M.Aker, S. Slavin, H. Al-Mousa, A. Al Ghonaium, A. Ferster, A. Duppenthaler, L. Notarangelo, R. Buckley, M. Bregni, S. Marktel, M.G.Valsecchi, P. Rossi, F. Ciceri, R. Miniero, C. Bordignon, and **M.G. Roncarolo** (2009). *Gene Therapy for immunodeficiency due to adenosine deaminase deficiency.* N Engl J Med 360: 447-458.

c) A. Biffi, E. Montini, L. Lorioli, M. Cesani, F. Fumagalli, T. Plati, C. Baldoli, S. Martino, A. Calabria, S. Canale, F. Benedicenti, G. Vallanti, L. Biasco, S. Leo, N. Kabbara, G. Zanetti, W.B. Rizzo, N.A. Mehta, M.P. Cicalese, M. Casiraghi, J.J. Boelens, U. Del Carro, D.J. Dow, M. Schmidt, A. Assanelli, V. Neduva, C. Di Serio, E. Stupka, J. Gardner, C. von Kalle, C. Bordignon, F. Ciceri, A. Rovelli, **M.G. Roncarolo**, A. Aiuti, M. Sessa, and L. Naldini (2013). *Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy.* Science 341: 1233158.

d) A. Aiuti, L. Biasco, S. Scaramuzza, F. Ferrua, M.P. Cicalese, C. Baricordi, F. Dionisio, A. Calabria,S. Giannelli, M.C. Castiello, M. Bosticardo, C. Evangelio, A. Assanelli, M. Casiraghi, S. Di Nunzio,L. Callegaro, C. Benati, P. Rizzardi, D. Pellin, C. Di Serio, M. Schmidt, C. von Kalle, J. Gardner, N. Mehta, V. Neduva, D.J. Dow, A. Galy, R. Miniero, A. Finocchi, A. Metin, P. Banerjee, J.S. Orange,S. Galimberti, M.G. Valsecchi, A. Biffi, E. Montini, A. Villa, F. Ciceri, **M.G. Roncarolo***, and L. Naldini* (2013). *Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich Syndrome.* Science 341: 1233151. *Equal contribution.

Published more than 300 papers in international scientific peer review journals and contributed 23 chapters to books. Publications have been cited > 40,000 times, “h “index: 101 (according to Web of Science) **Complete List of Published Work in MyBibliography:** http://www.ncbi.nlm.nih.gov/sites/myncbi/16GjfwR7DukAl/bibliography/47824779/public/?sort=date&direction=ascending.