BIOGRAPHICAL SKETCH

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NAME: Roncarolo, Maria Grazia

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POSITION TITLE: Professor, Department of Pediatrics; Division Chief, Pediatric Stem Cell Transplantation and Regenerative Medicine; Co-Director, Institute for Stem Cell Biology and Regenerative Medicine; Co-Director, Bass Center for Childhood Cancer and Blood Diseases

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 physician scientist with a research focus on mechanisms of genetic and acquired diseases of blood and immune system. I am applying the knowledge I gain from these studies to develop novel cell and gene therapies for patients.

B. Positions and Honors

Positions

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, Turin, Italy.
08/86-01/88 Associate Senior Scientist (Chargée de Recherches), Laboratory for Immunological Research, Schering-Plough, 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, USA.
03/92-12/96 Senior Staff Scientist, DNAX Research Institute for Molecular and Cellular Biology, Palo Alto, CA, USA.
11/94-11/01 Associate Professor of Pediatrics, School of Medicine and Surgery, University of Turin, Turin. Italy.
11/01-02/07 Associate Professor of Pediatrics, School of Medicine and Surgery, 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 (HSR_TIGET), Milan, Italy.

07/03-06/14 Chief of Clinic, Pediatric Immunology and Hematology, San Raffaele Hospital and San Raffaele Scientific Institute, Milan, Italy.
03/07-06/14 Professor of Pediatrics, School of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy.
06/14-present Professor of Pediatrics and Medicine, Department of Pediatrics, Stanford School of Medicine, Division Chief, Pediatric Stem Cell Transplantation and Regenerative Medicine, Co-Director, Institute for Stem Cell Biology and Regenerative Medicine, Co-Director, Bass Center for Childhood Cancer and Blood Diseases, Stanford University, Stanford, CA, USA.

Other Experience and Professional Memberships

Professional experience:

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

Memberships:

American Association of Immunologists
American Pediatric Society
American Society of Gene and Cell Therapy
American Society of Hematology
American Society of Human Genetics
American Society for Blood and Marrow Transplantation
European Society for Immunodeficiencies
European Society for Gene and Cell Therapy

Honors

2000 Knighthood “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 Outstanding Achievement Award” from the European Society of Gene and Cell Therapy (ESGCT) for outstanding career and pioneering contributions to the field.
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.
2014 Knighthood “Commendatore dell’Ordine Al Merito della Repubblica Italiana” from the President of Italy for outstanding scientific contributions.
2017 Outstanding Achievement Award” from the American Society of Gene and Cell Therapy (ASGCT) for outstanding contributions to translational research to the field.

C. Contribution to Science

My academic career has emphasized 3 intersecting areas 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 with stable mixed chimerism 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 to allo- and self-antigens as well as to food- and environmental-antigens. Recently, I described a number of 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 clinical trial using these ex-vivo generated donor-derived Tr1 cells to prevent the occurrence of severe graft-versus-host disease in leukemia patients undergoing haploidentical hematopoietic stem cell transplantation. I discovered that Rapamycin favors expansion of human CD25+FOXP3+ T regulatory cell subset *in vivo* and also *in vitro*, in quantities that 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,
      A. 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 and demonstrated that SAP controls the cytolytic activity of $CD8^+$ T cells. 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 restores 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) Akbarpour M, Goudy KS, Cantore A, Russo F, Sanvito F, Naldini L, Annoni A, Roncarolo MG (2015). *Insulin B chain 9-23 gene transfer to hepatocytes protects from type 1 diabetes by inducing Ag-specific FoxP3+ Tregs.* Sci Transl Med. 27;7(289):289ra81.

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 in order to design novel stem cell and gene therapies for these patients. 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 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 resulting in a 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. Based on these results gene therapy for ADA-SCID has obtained an Orphan drug status from the FDA/EMEA, was licensed to GSK and recently has received European Commission approval to market under the name of Strimvelis. I participate 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.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/16GjfwR7DukAl/bibliography/47824779/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

Alex's Lemonade Stand — Roncarolo (PI) — 02/01/2016-01/31/2018
ALSF Reach Grant
Adoptive Immunotherapy of Tr 1 Cells to Improve Outcome of Allo-HSCT Treatment for Pediatric AML
The goal of this proposal is to improve pediatric AML outcome after allo-HSCT treatment by testing T regulatory cell subsets as effective therapeutics in minimizing GvHD without abrogating GvL.

Alex's Lemonade Stand — Roncarolo (PI) — 07/01/2015-06/30/2020
Phase I/II Infrastructure Grant
Expanding Innovative Pediatric Cancer Clinical Trial Access at Stanford
The goal of this proposal is to build an integrated translational and clinical research program in novel therapeutics for pediatric cancer patients.

California Institute for Regenerative Medicine — Porteus (PI) — 10/01/2015 - 03/31/2018
PC1-08111
Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1
The goal of this program is to develop a specific gene correction procedure that could be applied to almost every patient with SCID-X1 rather than to it naturally occur in an extremely rare lucky few.
Role: Co-PI

CureSearch/Rising Tide Foundation — Roncarolo (PI) — 01/01/2016 - 12/31/2018
CCR-15-800
Cell therapy methods to improve pediatric AML patient outcome post allogeneic HSCT
The goal of this proposal is to identify improved therapeutic options for the treatment of post allo-HSCT AML patients.

California Institute for Regenerative Medicine — Shizuru (PI) — 08/01/2013 - 07/31/2017
DR2A-05365
A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants
The goal of this project is to target blood forming stem cells in patients with a biologic agent, a monoclonal antibody (mAb), that binds the stem cell receptor, c-kit (CD117), to selectively deplete stem cells and create 'space' to permit engraftment of healthy purified donor blood stem cells.
Role: Co-PI

Emerson Collective — Roncarolo (PI) — 07/01/2016 – 06/30/2018
Emerson Collective Cancer Research Fund
Cell therapy with T regulatory cells to improve AML patient outcome post allogeneic-HSCT
The goals of this project are to test myeloid cell killing of Tr1(CD4IL-10) cells against primary leukemic cells and to understand the mechanisms of the anti-leukemic lytic activity. We will also determine whether Tr1-mediated killing is dependent on expression of specific markers on pediatric leukemic blasts. Our goal from these studies is to develop a strategy that ensures increased cure rates for AML patients.