

BIOGRAPHICAL SKETCH

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Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Notarangelo, Luigi Daniele	POSITION TITLE Professor of Pediatrics		
eRA COMMONS USER NAME LNOTARANGELO			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Pavia, Italy	M.D.	1980	Medicine
University of Pavia, Italy	Residency	1984	Pediatrics
University of Pavia, Italy	Residency	1987	Allergy
University of Pavia, Italy	Residency	1993	Human Genetics

NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.

A. Positions and Honors.**Positions and Employment**

1986-1994 Senior Investigator, Dept. of Pediatrics, University of Brescia, Italy
 1994-1996 Associate Professor of Pediatrics, University of Brescia (Italy)
 1996-2000 Full Professor of Pediatrics, School of Dentistry, University of Brescia, Italy
 Head, Unit of Genetic Disorders of Childhood, University of Brescia, Italy
 2000-2006 Full Professor of Pediatrics, School of Medicine, University of Brescia, Italy
 Head, Department of Pediatrics, University of Brescia, Italy
 2006-todate Professor of Pediatrics, Harvard Medical School
 Director of the Research and Molecular Diagnosis Program on Primary Immunodeficiencies,
 Children's Hospital, Boston

Other experiences and Professional Memberships

1988-2006 Head, "Angelo Nocivelli Institute" of Molecular Medicine, Dept. of Pediatrics, University of Brescia
 1994-1997 Expert reviewer and Member of the panel for the 5-year-assessment report of the European Union Scientific Programme "Biomedicine"
 1994-1998 Secretary, European Society for Immune Deficiencies
 1996-todate Member of the W.H.O.-I.U.I.S. Committee for the classification of primary immune deficiencies
 2002-2006 President, European Society for Immune Deficiencies
 2003-todate Co-chairman, International Union of Immunological Societies, Committee on Immune Deficiencies

Honors

1987 N.A.T.O.-National Research Council Fellowship
 2004 International Querci Foundation Award for Research in Pediatrics
 2005 Finalist, 2005 "Descartes Prize for Research"
 2006 Member, Academia Leopoldina
 2007 Member, Kunkel Society

B. Selected peer-reviewed publications (in chronological order).

(out of 275 peer-reviewed publications – period 1993-2008)

1. Korthauer U., Graf D., Mages H.W., Briere F., Padayachee M., Malcolm S., Ugazio A.G., Notarangelo L.D., Levinsky R.J., Kroczeck R.A.: Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. *Nature*, 1993, 361:539-541
2. Villa A., Notarangelo L.D., DiSanto J.P., Macchi P.P., Strina D., Frattini A., Lucchini F., Patrosso C.M., Giliani S., Mantuano E., Agosti S., Nocera G., Kroczeck R.A., Fischer A., Ugazio A.G., de Saint Basile G., Vezzoni P.: Organization of the human CD40L gene: implications for molecular defects in X chromosome-linked hyper-IgM syndrome and prenatal diagnosis. *Proc. Natl. Acad. Sci. USA* 1994, 91:2110-2114
3. Vihinen M., Vetrie D., Maniar H.S., Ochs H.D., Zhu Q., Vorechovsky I., Webster A.D.B., Notarangelo L.D., Nilsson L., Sowadski J.M., Smith C.I.E.: Structural basis for chromosome X-linked agammaglobulinemia: A tyrosine kinase disease. *Proc Natl Acad Sci USA* 1994, 91:12803-12807
4. Villa A., Notarangelo L.D., Macchi P., Mantuano E., Cavagni G., Brugnoli D., Strina D., Patrosso M.C., Ramenghi U., Sacco M.G., Ugazio A., Vezzoni P.: X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. *Nature Genetics* 1995, 9:414-417
5. Macchi P., Villa A, Giliani S., Sacco M.G., Frattini A., Porta F., Ugazio A.G., Johnston J.A., Candotti F., O'Shea J., Vezzoni P., Notarangelo L.D.: Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID). *Nature*, 1995, 377:65-68.
6. Wengler G.S., Notarangelo L.D., Berardelli S., Pollonni G., Mella P., Fasth A., Ugazio A.G., Parolini O.: High prevalence of nonsense, frame shift, and splice-site mutations in 16 patients with full-blown Wiskott-Aldrich syndrome. *Blood* 1995, 86:3648-3654.
7. Wengler G.S., Notarangelo L.D., Giliani S., Pirastru M.G., Ugazio A.G., Parolini O.: Mutation analysis in Wiskott-Aldrich syndrome on chorionic villus DNA. *Lancet* 1995, 346:641-642.
8. Bordignon C., Notarangelo L.D., Nobili N., Ferrari G., Casorati G., Panina P., Mazzolari E., Maggioni D., Rossi C., Servida P., Ugazio A.G., Mavilio F.: Gene therapy in peripheral blood lymphocytes and bone marrow for ADA-immunodeficient patients. *Science* 1995, 270:470-475.
9. Notarangelo L.D., Peitsch M.C. et al.: CD40Lbase: a database of CD40L mutations causing X-linked hyper-IgM syndrome. *Immunol Today*, 1996, 17:511-516.
10. Wengler G.S., Lanfranchi A., Frusca T., Verardi R., Neva A., Brugnoli D., Giliani S., Fiorini M., Mella P., Guandalini F., Mazzolari E., Pecorelli S., Notarangelo L.D., Porta F., Ugazio A.G.: In-utero transplantation of parental CD34 haematopoietic progenitor cells in a patient with X-linked severe combined immunodeficiency (SCIDX1). *Lancet* 1996, 348:1484-1487.
11. Bettinardi A., Brugnoli D., Quiròs-Roldan E., Malagoli A., La Grutta S., Correr A., Notarangelo L.D.: Missense mutations in the FAS gene resulting in autoimmune lymphoproliferative syndrome: A molecular and immunological analysis. *Blood*, 1997, 89:902-909.
12. Villa A., Santagata S., Bozzi F., Giliani S., Frattini A., Imberti L., Benerini Gatta L., Ochs H.D., Schwarz K., Notarangelo L.D., Vezzoni P., Spanopoulou E.: Partial V(D)J recombination activity leads to Omenn syndrome. *Cell* 1998, 93:885-896.
13. Badolato R., Sozzani S., Malacarne F., Bresciani S., Fiorini M., Borsatti A., Albertini A., Mantovani A., Ugazio A.G., Notarangelo L.D.: Monocytes from Wiskott-Aldrich patients display reduced chemotaxis and lack of cell-polarization in response to MCP-1 and fMLP. *J. Immunol.* 1998, 161:1026-1033.
14. Sayos, J. Wu C., Morra M., Wang N., Zhang X., Allen D., van Schaik S., Notarangelo L., Geha R., Roncarolo M.G., Oettgen H., De Vries J., Aversa G., Terhorst C.: The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM. *Nature* 1998, 395:462-469.
15. Notarangelo L.D., Villa A., Schwarz K.: Rag and Rag defects. *Curr Opin Immunol* 1999, 11:435-442.
16. Signorini S., Imberti L., Pirovano S., Villa A., Facchetti F., Ungari M., Bozzi F., Albertini A., Ugazio A.G., Vezzoni P., Notarangelo L.D.: Intrathymic restriction and peripheral expansion of the T cell repertoire in Omenn syndrome. *Blood* 1999, 94:3468-3478.
17. Frattini A., Orchard P.J., Sobacchi C., Giliani S., Abinun M., Mattsson J.P., Keeling D.J., Andersson A.-K., Wallbrandt P., Zecca L., Notarangelo L.D., Vezzoni P., Villa A.: Defects in the TCIRG1-encoded 116kD subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. *Nat. Genet.*, 2000, 25:343-346.

18. Revy P., Muto T., Levy Y., Geissmann F., Plebani A., Sanal O., Catalan N., Forveille M., Dufourcq-Lagelouse R., Gennery A., Tezcan I., Ersoy F., Kayserili H., Ugazio A.G., Brousse N., Muramatsu M., Notarangelo L.D., Kinoshita K., Honjo T., Fischer A., Durandy A.: Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper-IgM syndrome (HIGM2). *Cell* 2000, 102:565-575.
19. Parolini S., Bottino C., Falco M., Augugliano R., Giliani S., Franceschini R., Ochs H.D., Wolf H., Bonnefoy J.-Y., Biassoni R., Moretta L., Notarangelo L.D., Moretta A.: X-linked lymphoproliferative disease: 2B4 molecules displaying inhibitory rather than activating function are responsible for the inability of Natural Killer cells to kill Epstein-Barr virus-infected cells. *J. Exp. Med.* 2000, 192:337-346.
20. Ferrari S, Giliani S, Insalaco A, Al-Ghonaïm A, Soresina AR, Loubser M, Avanzini MA, Marconi M, Badolato R, Ugazio AG, Levy Y, Catalan N, Durandy A, Tbakhi A, Notarangelo LD, Plebani A: Mutations of *CD40* gene cause a novel autosomal recessive form of hyper IgM. *Proc Natl Acad Sci U.S.A.*, 2001, 98:12614-12619.
21. Notarangelo LD, Mazza C, Giliani S, D'Aria C, Gandellini F, Ravelli C, Locatelli MG, Nelson DL, Ochs HD, Notarangelo LD: Missense mutations of the WASP gene cause intermittent X-linked thrombocytopenia. *Blood*, 2002, 99:2268-2269.
22. Aiuti A, Vai S, Mortellaro A, Casorati G, Ficara F, Andolfi G, Ferrari G, Tabucchi A, Carlucci F, Ochs HD, Notarangelo LD, Roncarolo MG, Bordignon C: Immune reconstitution in ADA-SCID after PBL gene therapy and discontinuation of enzyme replacement. *Nat Med* 2002, 8: 423-425.
23. Gulino AV, Moratto D, Cavadini P, Otero KI, Tassone L, Imberti L, Pirovano S, Notarangelo LD, Soresina R, Mazzolari E, Nelson DL, Sozzani S, Notarangelo LD, Badolato R: Altered leukocyte response to CXCL12 in patients with warts Hypogammaglobulinemia, Infections, Myelokathexis (WHIM) syndrome. *Blood*, 2004, 104:444-452.
24. Gismondi A, Cifaldi L, Mazza C, Giliani S, Parolini S, Morrone S, Jabobelli J, Bandiera E, Notarangelo L, Santoni A: Impaired natural and CD16-mediated NK cell cytotoxic function in WAS and XLT patients: ability of IL-2 to correct NK cell functional defect. *Blood*, 2004; 104:436-443
25. Jin Y, Mazza C, Christie JR, Giliani S, Fiorini M, Mella P, Gandellini F, Stewart DM, Zhu Q, Nelson DL, Notarangelo LD, Ochs HD: Mutations of the Wiskott-Aldrich Syndrome Protein (WASP): hot spots, effect on transcription and translation and phenotype/genotype correlation. *Blood* 2004, 104:4010-4019.
26. Cavadini P, Vermi W, Facchetti F, Fontana S, Nagafuchi S, Mazzolari E, Sediva A, Marrella V, Villa A, Fischer A, Notarangelo LD, Badolato R: AIRE deficiency in thymus of 2 patients with Omenn syndrome. *J Clin Invest* 2005, 115:728-732.
27. Mazzolari E, Moshous D, Forino C, De Martiis D, Offer C, Lanfranchi A, Giliani S, Imberti L, Pasic S, Ugazio AG, Porta F, Notarangelo LD: Hematopoietic stem cell transplantation in Omenn syndrome: a single center experience. *Bone Marrow Transplantation*, 2005, 36:107-114.
28. Grunebaum E, Mazzolari E, Porta F, Dalleria D, Atkinson A, Reid B, Notarangelo LD, Roifman CM: Bone marrow transplantation for Severe Combined Immune Deficiency. *JAMA*, 2006, 295:508-518.
29. Notarangelo LD, Gambineri E, Badolato R: Immunodeficiencies with autoimmune consequences. *Adv Immunol* 2006; 89:319-368
30. Fontana S, Parolini S, Vermi W, Booth S, Gallo F, Donini M, Benassi M, Gentili F, Ferrari D, Notarangelo L, Cavadini P, Mercenaro E, Dusi S, Cassatella M, Facchetti F, Griffiths GM, Moretta A, Notarangelo LD, Badolato R: Innate immunity defects in Hermansky-Pudlak type 2 syndrome *Blood*, 2006; 107:4857-4864.
31. Mazzolari E, Lanzi G, Forino C, Lanfranchi A, Aksu G, Ozturk C, Giliani, Notarangelo LD, Kutukculer N. First report of successful stem cell transplantation in a child with CD40 deficiency. *Bone Marrow Transplant* 2007;40:279-281.
32. Marrella V, Poliani PL, Casati A, Rucci F, Frascoli L, Gougeon ML, Lemercier B, Bosticardo M, Ravanini M, Battaglia M, Roncarolo MG, Cavazzana-Calvo M, Facchetti F, Notarangelo LD, Vezzoni P, Grassi F, Villa A. A hypomorphic R229Q Rag2 mouse mutant recapitulates human Omenn syndrome. *J Clin Invest.* 2007, 117:1260-1269.
33. Marangoni F, Trifari S, Scaramuzza S, Panaroni C, Martino S, Notarangelo LD, Baz Z, Metin A, Cattaneo F, Villa A, Aiuti A, Battaglia M, Roncarolo MG, Dupre L. WASP regulates suppressor activity of human and murine CD4+CD25+FOXP3+natural regulatory T cells. *J Exp Med.* 2007;204(2):369-380.
34. Marodi L, Notarangelo, LD. Education and worldwide collaboration pays off. *Nat Immunol.* 2007;8(4):323-324.
35. Marodi L, Notarangelo LDN. Immunological and genetic bases of new primary immunodeficiencies, *Nature Review Immunology*, 2007, 7:851-861.

36. Matangkasombut P, Pichavant M, Saez DE, Giliani S, Mazzolari E, Finocchi A, Villa A, Sobacchi C, Cortes P, Umetsu DT, Notarangelo LD. Lack of iNKT cell in patients with combined immune deficiency due to hypomorphic RAG mutations. *Blood*, 2008;111:271-274.
37. Ozsahin H, Cavazzana-Calvo M, Notarangelo LD, Schulz A, Thrasher AJ, Mazzolari E, Slatter MA, Le Deist F, Blanche S, Veys P, Fasth A, Bredius R, Sedlacek P, Wulffraat N, Ortega J, Heilmann C, O'Meara A, Wachowiak J, Kalwak K, Matthes-Martin S, Gungor T, Ikinciogullari A, Landais P, Cant AJ, Friedrich W, Fischer A. Long-term outcome following hematopoietic stem cell transplantation in Wiskott-Aldrich Syndrome: collaborative study of ESID/EGBMT. *Blood* 2008; 111:439-445.
38. Castriconi R, Dondero A, Cantoni C, Della Chiesa M, Prato C, Nanni M, Fiorini M, Notarangelo L, Parolini S, Moretta L, Notarangelo L, Moretta A, Bottino C. Functional characterization of natural killer cells in type I leukocyte adhesion deficiency. *Blood*. 2007;109:4873-81.

C. Research Support.

Ongoing Research Support

European Union EURO-POLICY-PID-006411 Notarangelo (CoI) 12/01/2004-01/31/2008
Policy-oriented and harmonising research activities in the field of Primary Immune Deficiency Diseases (EURO-POLICY-PID)

This study focuses on understanding the pathophysiology of PID, carrying out epidemiological studies in different European Countries, establishing diagnostic and therapeutic guidelines, and increasing the awareness of PID.

Role: Co-PI

PRIN 2006 2006061378_002 Notarangelo (PI) 010/01/2007-31/12/2009

Cytotoxicity defects in hemophagocytic syndromes of childhood

This project aims at defining the molecular and cellular mechanisms involved in hemophagocytic syndrome of childhood

Role: PI

Completed Research Support

European Union QLG1-2001-01395 Notarangelo (Co-I) 11/04/2001-11/30/2004

The European Initiative for Primary Immune Deficiencies (EURO-PID)

This study has focused on the identification of novel genetic defects in Primary Immune Deficiencies (PID), as well as on development of diagnostic guidelines and exploitation of novel therapeutic approaches

Role: Co-PI

FIRB RBNE0189JJ_003 Notarangelo (PI) 01/01/2002-12/31/2006

Molecular mechanisms of signal transduction involved in control of hematopoietic cells differentiation and proliferation

This study investigates cytokine-mediated signal transduction in lymphoid development, with particular regard to the role played by γ c- and IL-7-mediated signaling and their contribution to SCID.

Role: PI

FIRB RBNE0189JJ_004 Notarangelo (PI) 01/01/2002-12/31/2006

Novel receptors and mediators in innate immunity

This study investigates the role of innate immunity in selected primary immune deficiencies, such as WHIM syndrome, congenital neutropenia, Hermansky-Pudlak syndrome, and APECED.

Role: PI

AFM-Telethon GAT0203 Notarangelo (PI) 01/12/2003 – 30/11/2006

Correction of Severe Combined Immuno-deficiencies due to V(D)J recombination defects by gene therapy

This project is aimed at identifying novel gene defects associated with impaired V(D)J recombination and at developing novel forms of treatment for these disorders, based on gene therapy

Role: PI