
BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
VILLA Anna	Director of Research, Head of Unit at the Institute of Genetics and Biomedicine (IRGB) – National Research Council (CNR) Milano and Group Leader, Telethon Institute for Gene Therapy (San Raffaele,Milano)

EDUCATION/TRAINING

INSTITUTION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Milano Medical School	M.D.	1986	Medicine
University of Milano	Residency	1986 - 1990	Oncology
Institute of Advanced Biotechnology (ITBA)	Post-doctoral training	1990 - 1994	Molecular Biology

A. Personal Statement

I am Group Leader at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) and Director of Research at the Institute of Genetics and Biomedicine (IRGB), National Research Council (CNR) in Milan. My research has focused for over three decades on the genetic and molecular basis of primary immunodeficiencies, with particular emphasis on severe combined immunodeficiency (SCID) and Omenn syndrome (OS) caused by RAG gene defects. I contributed to the discovery of JAK3 and WAS mutations as causes of SCID and X-linked Thrombocytopenia, respectively, and identified hypomorphic mutations in RAG genes as responsible for Omenn syndrome (OS). My team has developed the *Rag2*^{R229Q} mouse model that has been instrumental in dissecting mechanisms of immune dysregulation in OS. My group has pioneered translational approaches to treat inborn errors of immunity, from ex vivo lentiviral gene therapy in Wiskott-Aldrich syndrome to more recent advances in homology-directed gene editing for RAG1 deficiency. In parallel, I have led international collaborations on osteopetrosis, identifying key genes (RANK, RANKL, CLCN7, OSTM1, TCIRG1) and developing preclinical gene- and cell-based therapies to treat TCIRG1 autosomal recessive osteopetrosis. I remain deeply committed to advancing gene therapy and genome editing as curative strategies for rare immune and bone diseases. My laboratory continues to integrate mechanistic insights with innovative therapeutic approaches, ensuring that discoveries in basic immunology can be rapidly translated toward clinical application.

B. Positions, Scientific Appointments, and Honors

1993-1998	Senior Investigator, Institute of Biomedical Technology, Segrate (Milan) Italy
1999-2001	Researcher at Consiglio Nazionale delle Ricerche, Institute of Biomedical Technology, Segrate (Milan) Italy
1998-2002	Professor of Biotechnology, University of Milan, Pharmacology Faculty.
2002—2006	Associate Professor, CNR, Institute of Biomedical Technology, Italy
2006- 2011	Director of Research at CNR Institute of Biomedical Technology, (Milan) Italy
2011-present	Director of Research at CNR, IRGB, Milan Unit
2019-2020	Acting Director of Institute for Genetics and Biomedical Research (IRGB), National Research Council
2006-2020	Head of Human Genome Unit, Istituto Clinico Humanitas, Milan Italy
2006-present	Group Leader of “Pathogenesis and Treatment of Immune and Bone Diseases

Unit" at Telethon Institute for Gene Therapy, San Raffaele, Milan, Italy

PROFESSIONAL ACTIVITIES

2000-2006 Responsible for data bank of Rag Defects and Osteopetrosis <http://www.uta.fi/bioinfo>
2000-2006 Head of the Genetic Working Party- European Society of Immunodeficiencies
2010-2014 Secretary of the European Society of Immunodeficiency (ESID)
2008-present Coordinator of the Retrospective Study on Osteopetrosis – Inborn Error Group (EBMT)
2014 National Academic Qualification as Full Professor of Pathology and Clinical Pathology Area 06/A2

Grant Reviewer:

Action Medical Research for Children (UK), Agence Nationale de la Recherche (ANR_AFM) (France); Fondation pour la Recherche Médicale Equipe FRM (France); Centre Hospitalier Régional Universitaire Montpellier (France); Deutsche Forschungsgemeinschaft (DFG) German Research Foundation; Member of Advanced ERC LS6 panel (2019-2020) and ad hoc Reviewer

Patents:

Genetic markers for bone mass. The University Court of the University Aberdeen (Scotland) -Patent N. 03737357.8-2402-GB0300470 Date of filing: 04.02.03

Replacement of RAG1 for Use in Therapy. International Application No.PCT/EP2021/078222; International Filing Date 12.10.2021

International Application No.PCT/EP2022/078298; International Filing Date 11.10.2022
Polynucleotides Useful for correcting mutations in the RAG1 gene

Honors

2005 Winner, 2005 "Descartes Prize for Research"
2008 Member of Kunkel Society of Immunology

International Journal Reviewer:

Associate Editor of Journal of Allergy and Clinical Immunology, Frontiers in Immunology, Physiology
Ad hoc reviewer for Journal of Allergy and Clinical Immunology, Nature Medicine, Journal of Clinical Immunology, Journal of Leukocyte Biology, Blood, Blood Advances, Molecular Therapy, Journal of Bone and Mineral Research, Molecular Therapy.

C. Contributions to Science

Dr Villa has published 251 papers in international scientific journals for total citations of 13107 and Scopus "h" index of 63. Orcid number: <https://orcid.org/0000-0003-4428-9013>. A complete list is available: <https://pubmed.ncbi.nlm.nih.gov/?term=villa+anna&sort=date>

1. Discovery of genetic causes of severe combined immunodeficiency (SCID)

Early in my career, I contributed to the identification of fundamental genetic lesions underlying severe combined immunodeficiency (SCID) and related inborn errors of immunity. My group was among the first to demonstrate that mutations in the *JAK3* gene cause autosomal recessive SCID, a landmark discovery that defined a new signaling pathway essential for T- and NK-cell development. This work established *JAK3* as the first non-receptor tyrosine kinase associated with a human primary immunodeficiency, provided mechanistic insight into cytokine signaling via the common gamma chain receptor, and rapidly translated into improved diagnostic and therapeutic approaches. In parallel, I contributed to the characterization of mutations in the *WAS* gene, clarifying the molecular basis of X-linked thrombocytopenia and Wiskott–Aldrich syndrome. These studies not only provided critical tools for accurate genetic diagnosis and genetic counseling but also enabled refined genotype–phenotype correlations that continue to guide clinical management and hematopoietic

stem cell transplantation outcomes. Through subsequent collaborations, I extended these investigations to additional rare immunodeficiencies, including contributions to the elucidation of genetic defects in Omenn Syndrome and osteopetrosis, broadening the molecular taxonomy of primary immunodeficiencies and autosomal recessive osteopetrosis. Collectively, these discoveries laid the groundwork for mechanistic studies, animal modeling, and ultimately therapeutic innovations such as gene therapy and genome editing.

- a. Macchi P*, **Villa A***, et al.). Nature 1995;377(6544):65–8.
- b. **Villa A**, Notarangelo LD, Macchi P et al.. Nat Genet. 1995; 9 ;414-417
- c. **Villa A**, Santagata S, et al. Cell 1998; 93(5):885-96.
- d. Sobacchi C ... **Villa A**. Nat Genet. 2007 Aug;39(8):960–962.

2. Development of animal models to study RAG deficiency and Omenn Syndrome

My laboratory established the *Rag2R229Q* hypomorphic mouse, which faithfully recapitulates the combined immunodeficiency and immune dysregulation observed in patients with Omenn Syndrome (OS). This model was the first to demonstrate how partial loss-of-function mutations in the RAG complex could simultaneously impair V(D)J recombination and drive aberrant immune activation. Using this model, we uncovered that the persistence of oligoclonal, autoreactive T cells drive tissue infiltration, inflammation, and elevated Th2 cytokine production, thereby explaining the paradoxical coexistence of immunodeficiency with severe autoimmunity. This model became widely adopted as the international standard for mechanistic studies of OS, facilitating investigations into thymic selection, central tolerance, and the interplay between lymphopenia and immune activation. It has also provided a preclinical platform to test gene therapy vectors, immunomodulatory drugs, and stem cell transplantation strategies. Importantly, our work has informed the refinement of clinical conditioning regimens and guided the design of novel therapeutic interventions for patients with RAG hypomorphic mutations.

- a. Marrella V **Villa A**.. J Clin Invest. 2007;117(5):1260–1269.
- b. Rigoni R..... **Villa A***, Cassani B.. J Exp Med. 2016 Mar 7;213(3):355–375. doi:10.1084/jem.20151116. *Corresponding author
- c. Rigoni R., **Villa A***, Cassani B*. J Allergy Clin Immunol. 2020 S0091-6749(20)30492-9. doi:10.1016/j.jaci.2020.04.005. *Co-senior authors
- d. Cassani B... **Villa A**.. J Exp Med. 2010 Jul 5;207(7):1525-40. doi: 10.1084/jem.20091928. Epub 2010 Jun 14.

3. Advancing gene therapy for inborn errors of immunity

Building on the molecular and mechanistic discoveries, I have led translational efforts to develop gene therapy for severe inborn errors of immunity. Our group contributed to pioneering lentiviral vector-mediated gene therapy for Wiskott–Aldrich syndrome (WAS), moving from preclinical studies to first-in-human trials. In addition, we explored gene-based strategies for osteopetrosis, identifying and targeting mutations in *TCIRG1*. By combining mechanistic understanding with vector design and stem cell approaches and testing novel non genotoxic conditioning, we advanced proof-of-concept studies that opened the door to correcting disorders previously deemed untreatable. Most recently, my group has extended gene therapy platforms into the era of precise genome editing. We have developed CRISPR/Cas9-mediated strategies to repair pathogenic mutations in the *RAG1* gene in hematopoietic stem and progenitor cells.

- a. Capo V.... **Villa A**.. Haematologica. 2021;106(1):74-86. doi: 10.3324/haematol.2019.238261.PMID: 31949009
- b. Castiello MC...**Villa A**, Notarangelo LD. J Allergy Clin Immunol. 2021 Jan;147(1):309-320.e6. doi: 10.1016/j.jaci.2020.04.033. Epub 2020 May 6.PMID: 32387109

c. Castiello MC ... **Villa A***, Capo V*. Front Immunol. 2023 Nov 13;14:1268620. doi: 10.3389/fimmu.2023.1268620. eCollection 2023.PMID: 38022635

d. Castiello MC.. **Villa A**. Sci Transl Med. 2024;16(733):eadh8162.

SELECTED GRANTS

2019-2024 Horizon GRANT AGREEMENT NO 755170: "Stem-cell based gene therapy for recombination deficient SCID (RECOMB)". Unit Responsible

2021-2024 Ricerca Finalizzata 2019 RF-2019-12369703 Ministry of Health "IPSCs from Duchenne Muscular Dystrophy: perfect genetic correction by chromosome transplantation and generation of 3D cell culture for drug investigation" Responsible for Unit 2

2023-2025 PRIN 2022 Education and Research Ministry-P20223MF7X "Toward understanding and treatment of skeletal disease in lysosomal storage disorder". Responsible for Unit 2

2023-2025 PRIN 2022 Education and Research Ministry Prot. 2022R7PMJP " Targeting the overlapping mechanisms inducing immune cell dysfunctions and autoimmunity in the pathophysiology of Thymic Epithelial Tumors". Responsible for Unit 2

2021-2026 Fondazione Telethon Core Grant: Elucidating the significance of osteopetrotic bone marrow niche in hematopoietic stem and progenitor cells and its implications for stem cell therapy. PI

Book Chapters

1. Stiehm's Immune Deficiencies. Edited by: E.R Stiehm & K.E Sullivan. Chapter 4: T Cell Defects page 88-126. Elsevier, 2014
2. Primary Immunodeficiency Diseases. A molecular and genetic approach. Third Edition. Edited by H.D Ochs, E. Smith, JM Puck. Chapter 13: V(D)J Recombination Defects. Page 168-187. Oxford, 2014
3. Primary Immunodeficiency Diseases: Definition, Diagnosis and Management. Second Edition. Edited by N. Rezaei, A. Aghamahammadi, LD Notarangelo. Springer, 2015
4. Encyclopedia of Immunobiology. Edited by Elsevier. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED).