

BIOGRAPHICAL SKETCH

NAME: Luca Vago

eRA COMMONS USER NAME: VAGOLUCA

POSITION TITLE: Associate Professor, Research Group Leader

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Vita-Salute San Raffaele University, Milano, Italy	M.D.	2005	Medicine
Vita-Salute San Raffaele University, Milano, Italy	Ph.D.	2009	Molecular Medicine, Immunology
Experimental Hematology Unit, San Raffaele Scientific Institute, Milano, Italy	Postdoctoral Fellow	2011	Hematology, Gene Therapy
Vita-Salute San Raffaele University, Milano, Italy	Clinical Board	2014	Hematology

A. Personal**Statement**

I am a physician-scientist, and both my clinical and research activities are focused on elucidating the interplay between immune system and leukemia, especially in the model system of allogeneic HCT. In particular, my group's research focuses on understanding mechanism by which post-transplantation relapses occur, combining cutting-edge immunogenomic analysis of patient samples with the development of innovative humanized animal models. Our long-term aim is to develop personalized therapeutic approaches able to rewire a proficient graft-versus-tumor effect.

B. Positions**and****Honors****Positions and Employment**

2003-2009	Intern and Resident, Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milano, Italy
2004-2009	Research fellow and PhD student, Telethon Institute for Gene Therapy (TIGET), San Raffaele Scientific Institute, Milano, Italy
2008	Visiting scholar, Department of Structural Biology, Stanford University, Stanford (CA), USA
2009-2011	Post-Doctoral Fellow, Experimental Hematology Unit, San Raffaele Scientific Institute, Milano, Italy
2009-2014	Clinical Fellow in Hematology, Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milano, Italy
2011-2014	Research Project Leader, Unit of Molecular and Functional Immunogenetics, San Raffaele Scientific Institute, Milano, Italy
2014-2020	Assistant Professor of Immunogenetics and Hematology, Vita-Salute San Raffaele University, Milano, Italy
2015-present	Attending Physician, Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milano, Italy
2015-present	Group Leader, Unit of Immunogenetics, Leukemia Genomics and Immunobiology, San Raffaele Scientific Institute, Milano, Italy
2021-present	Associate Professor, Vita-Salute San Raffaele University, Milano, Italy

Other Experience and Professional Memberships

2009-	Member, European Federation for Immunogenetics (EFI)
2009-	Member, Associazione Italiana di Immunogenetica e Biologia dei Trapianti (AIBT)
2010-	Member, Società Italiana Ematologia Sperimentale
2014-	Member, European Hematology Association
2015-	Member, American Society of Hematology
2015-	Member, Grant Selection Scientific Committee, INCa and INSERM
2016-	HSCT Section Editor, "HLA" Journal (Wiley & Sons)
2016-	Scientific Committee Member, European Federation for Immunogenetics (EFI)
2018-2023	Subcommittee Leader, EBMT Cellular Therapy and Immunobiology WP
2018-	Associate Editor, Frontiers in Immunology
2020-2024	Member, ASH Scientific Committee on Immunology and Host Defense
2020-	Member, <i>Blood</i> Editorial Board
2021-	Chair, Scientific Committee, European Federation for Immunogenetics (EFI)
2021-2025	Member, CIBMTR Advisory Committee
2021-	Member, <i>Blood Advances</i> Editorial Board

Honors

2009	Julia Bodmer Award, European Federation for Immunogenetics (EFI)
2010	Riccardo Catalano Award, Associazione Italiana di Immunogenetica (AIBT)
2010	Jon van Rood Award, EBMT Immunobiology Working Party
2013	Jon van Rood Award, European Federation for Immunogenetics (EFI)
2014	American Society of Clinical Oncology Young Investigator Award
2015	"Silvia Fiocco" Award, Accademia Nazionale dei Lincei (Italian Academy of Sciences)
2015	Domenico Adorno Award, Associazione Italiana di Immunogenetica (AIBT)
2016	Van Bekkum Award, European Society for Blood and Marrow Transplantation (EBMT)
2020	Jon van Rood Award, EBMT Immunobiology Working Party

C. Contributions to Science

1. Discovering mechanisms of immune evasion and relapse after allogeneic HSCT

We demonstrated that up to one third of the cases of leukemia relapse following allogeneic HSCT from partially-incompatible family donors are due to disease variants characterized by genomic loss of the mismatched and patient-specific HLA haplotype, which confers to the leukemic clones a selective advantage in evading the graft-versus-leukemia effect. More recent studies have lead to the identification of additional non-genomic modalities of leukemia immune evasion leading to relapse, including the downmodulation of HLA class II molecules and the upregulation of ligands for T cell inhibitory checkpoints, to dissecting the underlying epigenetic mechanisms, and to propose new personalized option for treatment.

- a. **Vago L.**, Perna SK., Zanussi M., Mazzi B., Barlassina C., Stanghellini MT., Perrelli NF., Cosentino C., Torri F., Angius A., Forno B., Casucci M., Bernardi M., Peccatori J., Corti C., Bondanza A., Ferrari M., Rossini S., Roncarolo MG., Bordignon C., Bonini C., Ciceri F., and Fleischhauer K.: Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med*. 2009 Jul 30;361(5):478-88. PMID: 19641204
- b. Crucitti L., Crocchiolo R., Toffalori C., Mazzi B., Greco R., Signori A., Sizzano F., Chiesa L., Zino E., Lupo Stanghellini MT., Assanelli A., Carrabba MG., Markt S., Marcatti M., Bordignon C., Corti C., Bernardi M., Peccatori J., Bonini C., Fleischhauer K., Ciceri F., and **Vago L.***: Incidence, risk factors and clinical outcome of leukemia relapses with loss of the mismatched HLA after partially incompatible hematopoietic stem cell transplantation. *Leukemia*. 2015 May;29(5):1143-52. PMID: 25371177 (* equally contributing authors)
- c. Toffalori C., Zito L., Gambacorta V., Riba M., Oliveira G., Bucci G., Barcella M., Spinelli O., Greco R., Crucitti L., Cieri N., Noviello M., Manfredi F., Montaldo E., Ostuni R., Naldini M.M., Gentner B., Waterhouse M., Zeiser R., Finke J., Hanoun M., Beelen D., Gojo I., Luznik L., Onozawa M., Teshima T., Devillier R., Blaise D., Halkes C.J.M., Griffioen M., Carrabba M.G., Bernardi M., Peccatori J., Barlassina C., Stupka E., Lazarevic D., Tonon G., Rambaldi A., Cittaro D., Bonini

- C., Fleischhauer K., Ciceri F.*, and **Vago L.***: Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. *Nat Med.* 2019 Apr;25(4):603-611. PMID: 30911134 (* equally contributing authors)
- d. Gambacorta V., Beretta S., Ciccimarra M., Zito L., Giannetti K., Andrisani A., Gnani D., Zanolli L., Oliveira G., Carrabba MG., Cittaro D., Merelli I., Ciceri F., Di Micco R.*, **Vago L.***: Integrated Multiomic Profiling Identifies the Epigenetic Regulator PRC2 as a Therapeutic Target to Counteract Leukemia Immune Escape and Relapse. *Cancer Discov.* 2022 Jun 2;12(6):1449-1461. PMID: 35255120 (* equally contributing authors)
 - e. Apostolova P., Kreutmair S., Toffalori C., Punta M., Unger S., Burk AC., Wehr C., Maas-Bauer K., Melchinger W., Haring E., Hoefflin R., Shoumariyeh K., Hupfer V., Lauer E.M., Duquesne S., Lowinus T., Gonzalo Núñez N., Alberti C., da Costa Pereira S., Merten C.H., Power L., Weiss M., Böke C., Pfeifer D., Marks R., Bertz H., Wäsch R., Ihorst G., Gentner B., Duyster J., Boerries M., Andrieux G., Finke J., Becher B., **Vago L.***, Zeiser R.*: Phase II trial of hypomethylating agent combined with nivolumab for acute myeloid leukaemia relapse after allogeneic haematopoietic cell transplantation-Immune signature correlates with response. *Br J Haematol.* 2023 Oct;203(2):264-281. PMID: 37539479 (* equally contributing authors)

2. Deciphering the immunobiology of Killer Cell Immunoglobulin-like Receptors and their role in haploidentical HSCT

The role of Natural Killer cells in allogeneic HSCT, and haploidentical HSCT in particular, is object of intense research and debate. In our studies, we provided novel insights on the phenotypical and functional features of NK cells reconstituting after haploidentical HSCT, and investigated by structural biology studies the fine determinants of NK cell target recognition.

- a. **Vago L.**, Forno B., Sormani MP., Crocchiolo R., Zino E., Di Terlizzi S., Lupo Stanghellini MT., Mazzi B., Perna SK., Bondanza A., Middleton D., Palini A., Bernardi M., Bacchetta R., Peccatori J., Rossini S., Roncarolo MG., Bordignon C., Bonini C., Ciceri F., and Fleischhauer K.: Temporal, quantitative, and functional characteristics of single-KIR-positive alloreactive natural killer cell recovery account for impaired graft-versus-leukemia activity after haploidentical hematopoietic stem cell transplantation. *Blood.* 2008 Oct 15;112(8):3488-99. PMID: 18645039
- b. Hilton HG.*, **Vago L.***, Older Aguilar AM., Moesta AK., Graef T., Abi-Rached L., Norman PJ., Guethlein LA., Fleischhauer K., and Parham P.: Mutation at positively selected positions in the binding site for HLA-C shows that KIR2DL1 is a more refined but less adaptable NK cell receptor than KIR2DL3. *J Immunol.* 2012 Aug 1;189(3):1418-30. PMID: 22772445 (* equally contributing authors)
- c. Russo A., Oliveira G., Berglund S., Greco R., Gambacorta V., Cieri N., Toffalori C., Zito L., Lorentino F., Piemontese S., Morelli M., Giglio F., Assanelli A., Lupo Stanghellini M.T., Bonini C., Peccatori J., Ciceri F., Luznik L, and **Vago L.**: NK cell recovery after haploidentical HSCT with posttransplant cyclophosphamide: dynamics and clinical implications. *Blood.* 2018 Jan 11;131(2):247-262. PMID: 28986344
- d. Ruggeri L., **Vago L.**, Eikema D.J., de Wreede L.C., Ciceri F., Diaz M.A., Locatelli F., Jindra P., Milone G., Diez-Martin J.L., Pérez-Simón J.A., Merluzzi M., Koster L., van der Werf S., van Biezen A., Toubert A., Nagler A., Chabannon C., Bonini C., Velardi A. Natural killer cell alloreactivity in HLA-haploidentical hematopoietic transplantation: a study on behalf of the CTIWP of the EBMT. *Bone Marrow Transplant.* 2021 Aug;56(8):1900-1907. PMID: 33767404

3. Developing innovative and sensitive molecular tools to improve the early detection of post-transplantation relapses

One of the major hurdles in devising effective treatments for post-transplantation relapses is that often they are diagnosed at a very late stage, when disease burden and patient condition render most treatment inefficacious or unfeasible. Over the years, our work has tackled this issues by to studies implementing quantitative and droplet digital PCR to track leukemia mutations over time after transplant and to facilitate the specific detection of HLA loss variants.

- a. Xue E., Tresoldi C., Sala E., Crippa A., Mazzi B., Greco R., Messina C., Carrabba MG., Lupo Stanghellini MT., Markt S., Corti C., Peccatori J., Bernardi M., Ciceri F., and **Vago L.**: Longitudinal qPCR monitoring of nucleophosmin 1 mutations after allogeneic hematopoietic

stem cell transplantation to predict AML relapse. *Bone Marrow Transplant*. 2016 Mar;51(3):466-9. PMID: 26642331

- b. Brambati C., Galbiati S., Xue E., Toffalori C., Crucitti L., Greco R., Sala E., Crippa A., Chiesa L., Soriani N., Mazzi B., Tresoldi C., Stanghellini MT., Peccatori J., Carrabba MG., Bernardi M., Ferrari M., Lampasona V., Ciceri F., and **Vago L.**: Droplet digital polymerase chain reaction for DNMT3A and IDH1/2 mutations to improve early detection of acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation. *Haematologica*. 2016 Apr;101(4):e157-61. PMID: 26703962
- c. Ahci M., Toffalori C., Bouwmans E., Crivello P., Brambati C., Pultrone C., Stempelmann K., Bost D., Mazzi B., Beelen D.W., Ciceri F., Mulder W., Fleischhauer K., and **Vago L.**: A New Tool for Rapid and Reliable Diagnosis of HLA Loss Relapses after HSCT. *Blood*. 2017 Sep 7;130(10):1270-1273
- d. Gambacorta V., Parolini R., Xue E., Greco R., Bouwmans E.E., Toffalori C., Giglio F., Assanelli A., Lupo Stanghellini M.T., Ambrosi A., Mazzi B., Mulder W., Corti C., Peccatori J., Ciceri F., **Vago L.** Quantitative PCR-based chimerism in bone marrow or peripheral blood to predict acute myeloid leukemia relapse in high-risk patients: results from the KIM-PB prospective study. *Haematologica*. 2020 Sep 10;106(5):1480-1483. PMID: 33054102

4. Characterizing mechanisms and clinico-biological correlates of immune reconstitution after haploidentical HSCT and T cell suicide gene therapy.

Infusion of T cells genetically engineered to express suicide genes represent one of the most advanced and elegant approaches to provide immune protection to transplanted patient while avoiding the risk of uncontrollable graft-versus-host disease. Over the years, we conducted clinical trials employing the Herpes Simplex Virus Thymidin Kinase gene, elucidated how the infused gene-modified prompt immune recovery, and which are the determinants of their long-term persistence in vivo.

- a. Ciceri F., Bonini C., Stanghellini MT., Bondanza A., Traversari C., Salomoni M., Turchetto L., Colombi S., Bernardi M., Peccatori J., Pescarollo A., Servida P., Magnani Z., Perna SK., Valtolina V., Crippa F., Callegaro L., Spoldi E., Crocchiolo R., Fleischhauer K., Ponzoni M., **Vago L.**, Rossini S., Santoro A., Todisco E., Apperley J., Olavarria E., Slavin S., Weissinger EM., Ganser A., Stadler M., Yannaki E., Fassas A., Anagnostopoulos A., Bregni M., Stampino CG., Bruzzi P., and Bordignon C.: Infusion of suicide-gene-engineered donor lymphocytes after family haploidentical haemopoietic stem-cell transplantation for leukaemia (the TK007 trial): a non-randomised phase I-II study. *Lancet Oncol*. 2009 May;10(5):489-500. PMID: 19345145
- b. **Vago L.**, Oliveira G., Bondanza A., Noviello M., Soldati C., Ghio D., Brigida I., Greco R., Lupo Stanghellini MT., Peccatori J., Fracchia S., Del Fiacco M., Traversari C., Aiuti A., Del Maschio A., Bordignon C., Ciceri F., and Bonini C.: High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus host disease. *Blood*. 2012 Aug 30;120(9):1820-30. PMID: 22709689
- c. Oliveira G., Ruggiero E., Stanghellini MT., Cieri N., D'Agostino M., Fronza R., Lulay C., Dionisio F., Mastaglio S., Greco R., Peccatori J., Aiuti A., Ambrosi A., Biasco L., Bondanza A., Lambiase A., Traversari C., **Vago L.**, von Kalle C., Schmidt M., Bordignon C., Ciceri F., and Bonini C.: Tracking genetically engineered lymphocytes long-term reveals the dynamics of T cell immunological memory. *Sci Transl Med*. 2015 Dec 9;7(317):317ra198. PMID: 26659572

5. Elucidating the role of HLA-DPB1 incompatibility in the outcome of allogeneic HSCT

By combining molecular modelling, functional immunological assays, and retrospective analysis of large cohorts of transplanted patients, we demonstrated that incompatibilities at the HLA-DPB1 locus play a relevant role in determining the outcome of allogeneic HSCT, and developed novel donor selection algorithms based on our findings.

- a. Zino E., **Vago L.**, Di Terlizzi S., Mazzi B., Zito L., Sironi E., Rossini S., Bonini C., Ciceri F., Roncarolo MG., Bordignon C., Fleischhauer K.: Frequency and targeted detection of HLA-DPB1 T cell epitope disparities relevant in unrelated hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007 Sep;13(9):1031-40. PMID: 17697965
- b. Crocchiolo R., Zino E., **Vago L.**, Oneto R., Bruno B., Pollichieni S., Sacchi N., Sormani MP., Marcon J., Lamparelli T., Fanin R., Garbarino L., Miotti V., Bandini G., Bosi A., Ciceri F.,

- Bacigalupo A., and Fleischhauer K.; Gruppo Italiano Trapianto di Midollo Osseo, Cellule Staminali Ematopoietiche (CSE) e Terapia Cellulare; Italian Bone Marrow Donor Registry.: Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation. *Blood*. 2009 Aug 13;114(7):1437-44. PMID: 19515726
- c. Sizzano F., Zito L., Crivello P., Crocchiolo R., **Vago L.**, Zino E., and Fleischhauer K.: Significantly higher frequencies of alloreactive CD4+ T cells responding to nonpermissive than to permissive HLA-DPB1 T-cell epitope disparities. *Blood*. 2010 Sep 16;116(11):1991-2. PMID: 20847212
 - d. Lorentino F., Sacchi N., Oldani E., Miotti V., Picardi A., Gallina A.M., Crivello P., Bernasconi P., Saccardi R., Farina L., Benedetti F., Cerno M., Grassi A., Bruno B., Patriarca F., Ciceri F., Fleischhauer K.*, **Vago L.***, Bonifazi F.* Comparative evaluation of biological HLA-DPB1 mismatch models for survival and graft versus host disease prediction after unrelated donor hematopoietic cell transplantation. *Haematologica*. Apr;105(4):e186-e189. PMID: 31471374

Complete List of Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/luca.vago.1/bibliography/public/>

D. Additional Information: Research Support and/or Scholastic Performance

Active Grants

AIRC Investigator Grant # 25131 01/01/21 – 12/31/25
 Associazione Italiana Ricerca sul Cancro (AIRC)
 Translating the immunobiology of post-transplantation relapses into consensus guidelines and personalized therapies
 Role: co-PI
 Direct costs: 120'000 EUR/year (60'000 EUR/year to LV)
 Overlap with present proposal: absent

ERA-NET-JTC2021 TRANSCAN-3 01/10/22 – 30/09/25
 European Commission (EC)
 Profiling and functional analysis of the Immune environment of eXtramedullary leukemia rELapses (PIXEL)
 Role: Coordinator, PI of WP1
 Direct costs: 435'000 EUR/year (84'000 EUR/year to LV)
 Overlap with present proposal: absent

AIRC Investigator Grant # 28953 01/01/24 – 12/31/28
 Associazione Italiana Ricerca sul Cancro (AIRC)
 Deciphering the Interplay Between Epigenetics, Metabolism and Stroma in Leukemia Post-Transplant Immune Escape
 Role: PI
 Direct costs: 130'000 EUR/year
 Overlap with present proposal: minimal (15%, technologies to analyze leukemia epigenetics and metabolism are shared)