BIOGRAPHICAL SKETCH

NAME:	POSITION TITLE:
Tiziana Vaisitti, Ph.D.	**Assistant Professor of Medical Genetics**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Torino, Italy	Post-Doc	2007-2014	Onco-Hematology
University of Torino, Italy	Ph.D.	2003-2006	Oncology
University of Torino, Italy	Master Degree	1998-2003	Biotechnology

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Personal Statement

After obtaining a PhD degree in Immunodiagnostic, I continued my training obtaining a 3-year fellowship from the Italian Association for Cancer Research (AIRC). During this period, I spent several periods in Italian and foreign laboratories as visiting scientist. Over these years, my research, in collaboration with other groups, was focused on the identification and functional characterization of recurrently mutated genes in chronic lymphoproliferative syndromes. These studies led to the recognition of mutations in NOTCH1, SF3B1 and BIRC3 in CLL patients and of NOTCH2 in SMZL patients. These mutations were subsequently functionally characterized. Current studies are dedicated to the understanding of the genetic, epigenetic and transcriptomic landscape of Richter's syndrome. From September 2014 to August 2016, I was Visiting Fellow at the Weill Cornell Medicine (New York, NY) working on the set-up of xenograft models of genetically characterized primary cells. These models allow for extensive genetic and molecular characterization of human diseases and can be used as pre-clinical tools to investigate the functional impact of novel drugs. A second topic of the research was the discovery and analysis of host micro-environmental conditions favoring leukemic development and progression, with attention focused on nucleotides/nucleosides and enzymes able to metabolize them, finally creating conditions for tumor progression and immune-escape.

In March 2017, I was appointed Assistant Professor of Medical Genetics at the University of Torino and, as part of the Immunogenetics and Transplant Biology Unit – Città della Salute e della Scienza, I'm part of a multidisciplinary team that works on the identification by NGS of genetic variants

responsible for diseases that can lead to organ failure and on the functional validation of some of these variants.

Positions and Employment

2002-2003: Internal student, Laboratory of Analytical Chemistry, Dept. of Chemistry, University of Torino, Italy. Supervisor: Prof. G. Giraudi

2003-2006: Ph.D. student, Laboratory of Immunogenetics, Dept. of Genetics, Biology and Biochemistry, University of Torino, Italy. Supervisor: Prof. F. Malavasi, M.D.

2004: Visiting scientist, Dept. of Evolutionary Biology, University of Siena, Italy. Reference: Prof. C.T. Baldari.

2007: Visiting scientist, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish, Manhasset, NY. Reference: Prof. N. Chiorazzi, M.D.

2009: Visiting scientist, Dept. of Medical Biochemistry and Immunology, School of Medicine, Cardiff University. Reference: Drs. C. Pepper, PhD e P. Brennan, PhD.

2007-2009: AIRC/FIRC Fellowship, Laboratory of Immunogenetics, Dept. of Genetics, Biology and Biochemistry, University of Torino, Italy. Supervisor: Prof. S. Deaglio, M.D., Ph.D.

2009-2014: Senior Post-Doc, Dept. of Medical Sciences and Human Genetics Foundation (HuGeF), University of Turin, Italy. Supervisor: Prof. S. Deaglio, M.D., Ph.D.

2014-2016: Visiting Fellow, Dept. of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY. Reference: Prof. D.M. Knowles

2017-2018: Assistant Professor of Medical Genetics (RTD A), Dept. of Medical Sciences, University of Torino, Torino, Italy

2018 -: Assistant Professor of Medical Genetics (RTD B), Dept. of Medical Sciences, University of Torino, Torino, Italy

2019 -: National professional qualification as Biologist

Mentoring activity:

- Training of 5 PhD students: PhD program in Biomedical Sciences and Human Oncology, Curriculum in Genetics and curriculum in Immunodiagnostic and PhD in Physiopathology
- Training of 1 MD/PhD student: MD/PhD program, University of Torino
- Training of 3 students: Biomedical Laboratory Technician, University of Torino
- Training of 6 students: Master Degree in Biotechnology, University of Torino

Teaching duties

2004-2006: Tutor in Human Genetics, Graduate programme in Medicine, University of Torino.

2004-2017: Teaching Assistant in Human Genetics, Graduate programme in Biomedical Laboratory Technicians, University of Torino.

2018-: Chair of Human Genetics, Graduate programme in Biomedical Laboratory Technicians, University of Torino.

2018-: Chair of Medical Genetics, Speciality programme in Geriatrics, University of Torino

2018-: Chair of Medical Genetics, Speciality programme in Orthodontics, University of Torino

2018-: Chair of Medical Genetics, Speciality programme in Pediatrics Odontology, University of Torino
2018-: Teaching Member of the Master in "Immunogenetics and transplant biology", University of Torino
2018-: Teaching Member of the PhD School in Biomedical Sciences and Oncology, University of Torino
2019-: Chair of Medical Genetics, Graduate Programme in Nursing (Aosta), University of Torino

Professional Memberships

2006- : SIC Società Italiana di Cancerologia
2006- : EACR European Association for Cancer Research
2009- : EHA European Hematology Association
2012- : ASH American Society of Hematology
2017- : ERIC European Research Initiative on CLL
2019- : SIGU Società Italiana di Genetica Umana

Honors:

2005: Prize for the best graduate student in Biotechnology from the University of Turin
2007: Travel grant by the Società Italiana di Cancerologia, 49° Congress of the Society
2009: Travel grant by the European Hematology Association, 14th Congress of the Society
2011: Mediterranean School of Oncology (MSO) Young Investigator Award (short listed)
2011: AACR-SIC Scholar in Training award from American association for Cancer Research - Società Italiana di Cancerologia
2017: Best abstract presented at the XVII International Workshop on Chronic Lymphocytic Leukemia (iwCLL), May 2017, New York, NY.

Selected lectures and seminars:

2005: Speaker at the Congress "Chronic Lymphocytic Leukemia", Reggio Calabria, Italy
2009: Invited seminar: "Human CD38: from disease marker to therapeutic target"; Dept. of Medical Biochemistry and Immunology, School of Medicine, Cardiff University.
2009: Speaker at the 2nd European Congress of Immunology (ECI) 2009, Berlin, Germany.
2010: Speaker at 9th International Conference on Human Leukocyte Differentiation Antigens HLDA9, Barcelona, Spain.
2010: Speaker at the 97th Annual Meeting of the American Association of Immunology (AAI), Baltimore, USA.
2010: Speaker at the XI National Meeting of the Italian Society of Experimental Hematology (SIES) 2010, Torino, Italy.
2012: Speaker at the XII National Meeting of the Italian Society of Experimental Hematology (SIES), Roma, Italy.
2013: Speaker at the 4th National Workshop of the Italian Society of Experimental Hematology (SIES), Bologna, Italy.

2016: Speaker at the 58th American Society of Hematology (ASH) Annual meeting, San Diego (CA).
2017: Speaker at the iwCLL 2017 17th International Workshop on Chronic Lymphocytic Leukemia, New York (NY).
2018: Invited Seminar: "Richter's syndrome: an orphan disease in search of identity" University of Genoa, Genoa, Italy.
2018: Speaker at the 60th American Society of Hematology (ASH) Annual meeting, San Diego (CA).
2019: Invited Seminar: "Richter's syndrome: looking for culprit(s)" Azienda USL-IRCCS di Reggio Emilia, Italy

Contribution to Science

1. Identification by clinical exome sequencing of variants relevant for the diagnosis of genetic diseases responsible for organ failure. The aim of this research and diagnostic area of interest is the identification of variants responsible for genetic diseases resulting in organ failure. The focus is on kidney, liver and cardiac diseases to provide clinicians and patients a genetic diagnosis and confirmation of the clinical phenotype. To this aim we're expoliting next-generation sequencing based on Illumina platforms, using a clinical exome kit (focused on 6700 genes) or a targeted panel (174 genes related to cardiac diseases). This diagnostic service is part of the Regional Transplantation Center (Torino) and is recruiting samples from different regional hospitals. Dr. Vaisitti is responsible for the DNA sequencing and bio-informatic analysis of data.
Moreover, we're looking for genetic variants and polymorphisms that can be involved in chronic organ rejection. These clinical phenomena are mainly due to minor histocompatibility antigens capable of inducing antibodies production in recipient patients. The identification of these variants/polymorphisms in a pre-transplant step should significantly improve the donor-recipient matching, enhancing the compatibility and reducing the risk of organ rejection.

1. Vaisitti T et al., *Clinical exome sequencing is a powerful tool in the diagnostic flow of monogenic kidney diseases: an Italian experience.* Submitted May 2020
2. Amoroso A et al., *HLA and AB0 polymorphisms influence SARS-CoV-2 infection and COVID-19 severity.* Transplantation Nov 2020

2. Set-up and genetic/trasncriptome analysis of patient-derived xenograft models of Richter's syndrome. In the last years, attention has been focused on the set-up of patient-derived xenograft (PDX) models of RS. Once established, PDXs were genetically characterized by whole-exome sequencing or targeted sequencing to identify chromosomal abnormalities and gene mutations. Expression profiling of PDXs were perfomed by RNA sequencing to identify detrimental pathway contributing to disease pathogenesis. These models represent useful tools for pre-clinical testing of novel drugs.

3. Vaisitti T. et al., *Targeting metabolism and survival in chronic lymphocytic leukemia and Richter syndrome cells by a novel NF-kB inhibitor*. Haematologica. 2017 Nov;102(11):1878-1889

4. Vaisitti T et al., *Novel Richter's syndrome xenograft models to study genetic architecture, biology and therapy responses*. Cancer Res. 2018 Jul 1;78(13):3413-3420.

3. Identification and functional characterization of novel genetic lesions in chronic lymphoproliferative diseases. The third main topic of my research is the identification of novel genetic lesions characterizing CLL patients and driving the transformation to Richter syndrome, the acute and more aggressive form of CLL. As part of a network of collaborators, we identified several recurrent mutations in CLL patients, characterizing the more aggressive subset of patients. The open question now is to understand the functional impact of these mutations, trying to dissect the signaling pathway and identifying the main players. This topic is quite important in a translational perspective due to the poor responsiveness to conventional chemotherapy and drugs of this subset of patients.

5. Arruga, F., et al., *Functional impact of NOTCH1 mutations in chronic lymphocytic leukemia.* Leukemia, 2014. **28**(5): p. 1060-70.
6. Rossi, D., et al., *The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development.* The Journal of experimental medicine, 2012. **209**(9): p. 1537-51.
7. Rossi, D., et al., *Disruption of BIRC3 associates with fludarabine chemorefractoriness in TP53 wild-type chronic lymphocytic leukemia.* Blood, 2012. **119**(12): p. 2854-62.
8. Rossi, D., et al., *Mutations of the SF3B1 splicing factor in chronic lymphocytic leukemia: association with progression and fludarabine-refractoriness.* Blood, 2011. **118**(26): p. 6904-8.

4. Role of nucleotides and nucleotide-metabolizing enzymes in shaping the tumor niche. In addition to the contributions described above, I'm part of a team interested in studying the role of nucleotides and nucleotides-metabolizing enzymes as modifier of the tumor microenvironment. The final aim of this topic is to analyze the expression and understand the role played by nucleotides and their relative enzymes in generating the favorable conditions for the tumor growth, by modifying the host environment and controlling the immune system. This project led to the identification of NAMPT and adenosine as key players in the tumor-host cross-talk and elements favoring the establishment of growth favorable niches.

9. Arruga, F., et al., *Targeting of the A2A adenosine receptor counteracts immunosuppression in vivo in a mouse model of chronic lymphocytic leukemia*. Haematologica, 2020.
10. Audrito, V., et al., *Extracellular nicotinamide phosphoribosyltransferase (NAMPT) promotes M2 macrophage polarization in chronic lymphocytic leukemia.* Blood, 2015. 125(1): p. 111-23.
11. Serra, S., et al., *CD73-generated extracellular adenosine in chronic lymphocytic leukemia creates local conditions counteracting drug-induced cell death.* Blood, 2011. 118(23): p. 6141-52.
12. Vaisitti, T., et al., *NAD+-metabolizing ecto-enzymes shape tumor-host interactions: the chronic lymphocytic leukemia model.* FEBS letters, 2011. 585(11): p. 1514-20.

5. Analysis of the functional role of CD38 in Chronic lymphocytic leukemia. One of the main focus of my research was the understanding of the role played by CD38, an ectoenzyme of the cell surface, in chronic lymphocytic leukemia (CLL). CD38 is not only a negative prognosticator of the disease, but a pathogenetic element. We deeply analyzed and dissected the signaling pathway driven by CD38 and we identified the molecular partners of this molecule. Indeed, in leukemic cells, CD38 is able to work in association with CXCR4, a chemokine receptor, and CD49d, an integrin, controlling the homing process of neoplastic cells to growth-favorable niches. These effects are mediated by its enzymatic properties.

13. Zucchetto A*, Vaisitti T*****, et al., *The CD49d/CD29 complex is physically and functionally associated with CD38 in B-cell chronic lymphocytic leukemia cells* Leukemia. 2012 Jun;**26**(6):1301-12 *These authors equally contributed to the work.
14. Vaisitti, T., et al., *The enzymatic activities of CD38 enhance CLL growth and trafficking: implications for therapeutic targeting.* Leukemia, 2015. **29**(2): p. 356-68.
15. Vaisitti, T., et al., *CD38 signals upregulate expression and functions of matrix metalloproteinase-9 in chronic lymphocytic leukemia cells.* Leukemia, 2013. **27**(5): p. 1177-81.
16. Vaisitti, T., et al., *CD38 increases CXCL12-mediated signals and homing of chronic lymphocytic leukemia cells.* Leukemia, 2010. **24**(5): p. 958-69.

RESEARCH SUPPORT

Completed research support:

2007 - 2009: 3-year fellowship from the Italian Association for Cancer Research (AIRC/FIRC), "Role of CD38 in the pathogenesis of chronic lymphocytic leukemia (B-CLL)"

2009: Regione Piemonte Ricerca Sanitaria Finalizzata "Pre-clinical evaluation of the use of anti-CD38 antibodies in chronic lymphocytic leukemia (B-CLL)"
Role: PI

2014-2017: Italian Ministry of Health, Young Investigator Grant #GR-2011-02349282 "Analysis of the *in vitro* and *in vivo* role of ET-1/ETAR and CD38/CD31 axes in chronic lymphocytic leukemia: prognostic, functional and therapeutic implications" Role: PI of one Unit

2016-2017: Institutional grant by Human Genetics Foundation (HuGeF),. "Design and set-up of novel therapeutic approaches to target B cell malignancies". Role: PI

2017-2018: Fondazione CRT Fondazione CRT, Erogazioni Ordinarie 2017 - I tornata (Ricerca e Istruzione). "Messa a punto di monitoraggi molecolari tramite digitalPCR per valutare evoluzione clonale e risposta terapeutica della leucemia linfatica cronica". Role: PI

Ongoing Research support:

2018-2021: Italian Ministry of Health, Young Investigator Grant #GR-2016-02364298 "Highlighting the tumorigenic role of long non coding RNA in patients with Anaplastic Large cell Lymphoma". Role: PI of one Unit.

2018-2019: Ricerca Locale ex-60%, University of Torino "Next Generation sequencing (NGS) to screen for inherited cardiac conditions leading to organ failure". Role: PI

2017-2019: Funds from VelosBio, Inc. “Genetic regulation and functional study of ROR1 in Richter’s syndrome patients”. Role: Co-PI
2018-2019: Funds from Verastem Oncology, Inc. “Mechanisms of action of PI3K inhibitors in Richter’s syndrome”. Role: Co-PI
2019-2020: Ricerca Locale ex-60%, University of Torino “Next Generation sequencing (NGS) to screen for inherited cardiac conditions leading to organ failure”. Role: PI
2020-2025: Italian Association for Cancer Research (AIRC) – My First AIRC Grant "Probing Richter's syndrome by multiple "omics" approaches to find its Achille's heel". Ruolo: PI

Peer-reviewed publications.
A complete list of publications is available at: https://pubmed.ncbi.nlm.nih.gov/?term=vaisitti+t

Publication with Impact Factor (2005-2020): 45
Total IF: 383,683
Mean IF: 8.526
H-Index (Scopus): 24
Total citations: 2815

Publication without Impact Factor: 1
Chapter in a book: 1