BIOGRAPHICAL SKETCH

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NAME: Valentina Lo Sardo

eRA COMMONS USER NAME: **VLOSARDO**

POSITION TITLE: Assistant Professor, Department of Cell and Regenerative Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Milan	B.S.-M.S.	11/2006	Biotechnology, Genetics
University of Milan	Ph.D.	12/2010	Biotechnology, Neuroscience, Genetics
University of Milan	Post-doc	2010/2011	Stem Cells, Neuroscience, Genetics
The Scripps Research Institute	Post-doc	2011/2018	Stem Cells, Cardiovascular disease, Genetics

A. Personal Statement

I began my position as an Assistant Professor at the University of Wisconsin-Madison in September 2020. *My research focuses on understanding the functional implications of common non-coding genetic variations associated with complex diseases, such as coronary artery disease (CAD) and cancer.* Using human induced pluripotent stem cells (iPSCs) and genome editing techniques, I investigate the role of human-specific genomic regions in disease susceptibility.

During my previous training, I gained extensive expertise in generating, culturing, differentiating, and manipulating mouse and human pluripotent stem cells. I also developed skills in molecular and cellular biology, biochemistry, microscopy, functional genomics, genome engineering, and transcriptomics. My **Ph.D. research**, explored rare genetic variants and their impact on neurological disease, particularly studying the Huntington Disease gene and uncovering a novel function of the huntingtin protein in regulating cell adhesion during early neuronal development (1). In **my postdoctoral studies** at the Scripps Research Institute, I expanded my research to investigate the influence of genetic variations on cell physiology. This involved studying the impact of aging and somatic mutations on the genetic and epigenetic stability of iPSCs (2). Additionally, I focused on the use of iPSCs and genome editing technologies to uncover the functional role of non-coding genomic regions linked to CAD (3). A significant part of my postdoctoral work involved investigating the 9p21.3 CAD risk locus, the strongest genetic risk factor for CAD. Despite being the first locus to be associated with CAD by Genome Wide Association Studies, its function was not defined. Using iPSC-isogenic lines and large-scale haplotype editing, I uncovered the causal role of the risk haplotype at 9p21.3 in altering the biology of vascular smooth muscle cells, an important cell type involved in early-stage CAD (3-4). This collaborative work involved renowned experts in cardiovascular disease, genomics, gene editing and bioengineering, Drs. Eric Topol, Ali Torkamani, Fyodor Urnov and Adam Engler. During my postdoctoral work, I have generated two collections of iPSCs: the "Wellderly Study Collection," the first collection including iPSCs from healthy donors at advanced ages (from 20 to 100 years old), and the "Coronary Artery Disease and Myocardial Infarction Collection," the first one including iPSCs from donors with myocardial infarction. These two collections are part of the Next Generation Genetic Association Studies (Next Gen) Program from NHLBI and banked at WiCell.

As an Assistant Professor at UW-Madison, my lab continues to study the link between common genetic variants and complex disease susceptibility, with emphasis on cardiovascular disease and cancer. I aim to uncover how these variants influence cell state, fate, and function to elucidate how they confer risk in carriers.

I serve on dissertation committees for PhD students of several graduate programs, including Genetics, Cell and Molecular Biology, Molecular and Cellular Pharmacology, Cell and Molecular Pathology and Comparative Biomedical Sciences. I lecture in two graduate level academic courses, *Fundamentals of stem cell and regenerative biology* and *Biology of heart disease and regeneration*, where I contribute with my expertise in somatic reprogramming, genetic manipulation of pluripotent stem cell as well as functional genomics of complex

diseases, iPSC disease modeling and stem cell therapeutics. Additionally, I am currently Course Director of the *Fundamentals of stem cell and regenerative biology* course.
I am an active member in several centers at UW-Madison, including the Stem Cell and Regenerative Medicine Center, Human Genomics and Precision Medicine Center, Genomic Science Innovation Center, Cardiovascular Research Center and the Cancer Center. I actively participate in seminars and research groups, fostering scientific discussions and collaborations and providing invaluable learning opportunity for my trainees.
My laboratory has currently 2 PhD students, 2 Research technicians, one Bioinformatic analyst and three undergraduate students.

1. **Lo Sardo V**.*, Zuccato C.*, Gaudenzi G., Vitali B., Ramos C., Tartari M., Myre M., Walker J., Pistocchi A., Conti L., Valenza M., Drung B., Schmidt B., Gusella J., Zeitlin S., Cotelli F. and Cattaneo E. *An evolutionary recent neuroepithelial cell adhesion function of huntingtin implicates ADAM10-Ncadherin*. ***Nature Neuroscience*** (2012). PMID: 22466506
2. **Lo Sardo V.,** Ferguson W., Erikson G.A., Topol E.J., Baldwin K.K., Torkamani A. Influence of donor age on induced pluripotent stem cells. ***Nature Biotechnology*** (2017). PMCID: PMC5505172
3. **Lo Sardo V.**, Chubukov P., Ferguson W., Kumar A., Teng E.L., Duran M., Zhang L., Cost G., Engler A.J., Urnov F., Topol E.J., Torkamani A., Baldwin K.K. Unveiling the Role of the Most Impactful Cardiovascular Risk Locus through Haplotype Editing. ***Cell*** (2018) PMCID: PMC6346426
4. Mayner J.M., Masutani E. M., Demeester E., Kumar A. Macapugay G., Ber P., **Lo Sardo V.** and Engler A.J. *Heterogeneous Expression of Alternatively Spliced lncRNA mediates Vascular Smooth Cell Plasticity*. **PNAS** (2023) PMID: 37276403

B. Positions, Scientific Appointments, and Honors

Positions

9/2020-	Assistant Professor, Department of Cell and Regenerative Biology, University of Wisconsin-Madison, School of Medicine and Public Health
2018- 2020	Staff Scientist, The Scripps Research Institute, La Jolla, CA.
2011-2018	Postdoctoral Research Associate,The Scripps Research Institute, La Jolla, CA
2010-2011	Postdoctoral Fellow, Department of Pharmacological Sciences, University of Milan, Italy
2007-2010	Ph.D. student, University of Milan, Italy
2006-2007	Telethon Research fellow, University of Milan, Italy
2005-2006	Research fellow, University of Milan, Italy

Scientific Appointment

2023-	Member, Editorial Board of Experimental and Molecular Pathology Journal, Elsevier
2023-	Director of the Fundamental of Stem Cell and Regenerative Biology graduate academic course
2022-	Member, American Society of Human Genetics (ASHG)
10/2022-	Member, UW Genomic Science Innovation Center
10/2020-	Member, UW Carbone Cancer Center, UW Stem Cell and Regenerative Medicine Center, UW Cardiovascular Research Center, UW Center for Human Genomics and Precision Medicine
2020-	Member, American Heart Association (AHA)
2013-	Member, International Society of Stem Cells Research (ISSCR)

Honors and Awards

2023	Panel moderator, International Society of Heart Research – North America Section Annual meeting 2023, Madison
2023	Invited speaker, Advancing Precision Medicine Symposium, Madison
2022	Invited speaker, UW 4th Cardiovascular Research Summit, Madison
2022	Invited speaker, UW Stem Cell and Regenerative Medicine Center Fall Conference, Madison
2021	Invited Speaker, University of Milan, Italy
2017	Invited Speaker, Cell and Gene Meeting on the Mesa 12th Annual Scientific Symposium, La Jolla (CA)
2012	The Scripps Research Institute Stem Cell Post-Doctoral Fellowship
2006	Telethon Foundation Fellowship

C. Contributions to Science

1. **Studying genetic risk for Coronary Artery Disease (CAD).** One of the most challenging problems in studying complex disease biology is understanding the causal effect of non-coding genetic variants, identified by Genome-Wide Association Studies, in increasing disease susceptibility. The 9p21.3 risk locus was the first genomic locus linked to cardiovascular disease, identified in 2007. Despite its strong association with coronary artery disease (CAD) and accounting for approximately 15% of cases, the underlying mechanisms and affected cell types of the 9p21.3 locus have remained largely elusive. During my postdoctoral training, I employed a functional genomics approach to elucidate, for the first time, the causal effect of the 9p21.3 risk locus on the maintenance of vascular cells. I integrated several powerful technologies to investigate its influence on cell functionality, including: 1) Induced pluripotent stem cell (iPSC) generation from genetically and clinically relevant subjects; 2) Large-scale haplotype editing and generation of isogenic cell lines; 3) Differentiation of iPSCs into disease-relevant cell types; 4) Transcriptomic and bioengineering approaches to evaluate disease phenotypes. This work resulted in the generation of the first knock-out model of the human 9p21.3 CAD locus and the first successful application of haplotype editing in donor-specific human cells. Through my study, I discovered novel molecular mechanisms driven by the risk form of the 9p21.3 locus in vascular smooth muscle cells (VSMCs), affecting adhesion, contraction, and proliferation. In addition to confirming alterations in previously identified CAD risk genes and pathways, I identified new phenotypes and key genes that represent potential therapeutic targets. My postdoctoral studies demonstrated the power of iPSCs for understanding the genetics of complex human diseases. Through successful collaborations with other groups in the field, my research provided also insights into other cell types.

   - **Lo Sardo V.**, Chubukov P., Ferguson W., Kumar A., Teng E.L., Duran M., Zhang L., Cost G., Engler A.J., Urnov F., Topol E.J., Torkamani A., Baldwin K.K. Unveiling the Role of the Most Impactful Cardiovascular Risk Locus through Haplotype Editing. ***Cell*** (2018) PMCID: PMC6346426
   - Kumar A., Thomas S.K., Wong K.C., **Lo Sardo V.**, Cheah D.S., Hou Y., Placone J.K., Tenerelli K.P., Ferguson W., Torkamani A., Topol E.J., Baldwin K.K, Engler A.J. *Mechanical activation of noncoding-RNA-mediated regulation of disease-associated phenotypes in human cardiomyocytes.* **Nature Biomedical Engineering** (2018) PMCID: PMC6430136
   - Teng E. L., Masutani E. M., Yeoman B., Fung J., Lian R., Ngo B., Kumar A., Placone J. K., **Lo Sardo V.** and Engler A. J. *High Shear Stress enhances Endothelial Permeability in the presence of the Risk Haplotype at 9p21.3*. **APL Bioengineering** (2021) PMCID: PMC8315817
   - Mayner J.M., Masutani E. M., Demeester E., Kumar A. Macapugay G., Ber P., **Lo Sardo V.** and Engler A.J. *Heterogeneous Expression of Alternatively Spliced lncRNA mediates Vascular Smooth Cell Plasticity*. **PNAS** (2023) PMID: 37276403

2. **Effect of Aging on iPSCs: insight into the genome and epigenome.** iPSCs are derived from somatic cells through a reprogramming process. Aging is a major contributor to somatic mutations, which naturally accumulate over time and are mosaic across cells in the body. Due to their clonal nature, iPSCs inherit the entire genomic repertoire of the donor cell, including rare somatic mutations that arise as a result of aging. To systematically investigate the impact of donor age on the genomic and epigenetic landscape of iPSCs, I generated and analyzed a large collection of iPSC lines (available at WiCell) derived from Peripheral Blood Mononuclear Cells (PBMCs) obtained from donors spanning different age groups (20-100 years old). My study revealed a linear increase in somatic mutations in blood cells with age. Consequently, iPSCs derived from older donors more frequently harbored these mutations, some of which affected disease-relevant genes. Interestingly, donors at advanced ages (>85 years old) exhibited fewer mutations than anticipated, indicating the presence of a protected hematopoietic stem cell population. The findings of my study highlighted the significance of tissue mosaicism in the cell sources for reprogramming. Additionally, the research provided valuable insights for establishing optimal study designs using iPSCs and guiding safety standards for the clinical application of iPSCs.

   - **Lo Sardo V.,** Ferguson W., Erikson G.A., Topol E.J., Baldwin K.K., Torkamani A. Influence of donor age on induced pluripotent stem cells. ***Nature Biotechnology*** (2017). PMCID: PMC5505172

3. **Neuronal cell fate induction in somatic cells.** In collaboration with other lab members at Scripps, I worked as a co-investigator, to generate iPSC-derived fibroblasts to study cell fate mechanisms driven my neurogenic transcription factors. This work described for the first time the conversion of fibroblasts into sensory neurons, by using exogenous expression of specific transcription factors.

   - Blanchard J.W., Eade K.T., Szücs A., **Lo Sardo V.**, Tsunemoto R.K, Williams D., Sanna P.P., Baldwin K.K. Selective conversion of fibroblasts into peripheral sensory neurons. ***Nature Neuroscience*** (2015). PMCID: PMC4466122

4. **Identification of a new function of the huntingtin gene and insights into HD.** Huntingtin is a ubiquitously expressed protein, with a particularly important function in the nervous system. This gene has been described in most multicellular species. In humans, the expansion of a polyQ stretch in the N-terminus of huntingtin is the genetic cause of Huntington Disease, an autosomal dominant neurological disorder. In my initial research, I cloned the huntingtin homologue in sea urchins, which represent one of the oldest species with a rudimentary nervous system. By comparing the sequences of multiple known huntingtin homologues, I reconstructed the evolutionary history of the protein and discovered the first evidence of a polyQ sequence in sea urchin huntingtin. This investigation provided insights into the evolutionary conservation of huntingtin across species. To gain a deeper understanding of the role of huntingtin in the nervous system, I utilized mouse embryonic stem cells (ESCs) knockout for the huntingtin gene. Through neuronal differentiation of wild-type and knockout ESCs, I uncovered a novel function of huntingtin in regulating the formation of neural rosettes—an *in vitro* model for neural tube formation. Importantly, defective neural tube formation was confirmed *in vivo* in zebrafish embryos. My study revealed that these defects were mediated by the interaction of huntingtin with N-cadherin and ADAM10, a disintegrin and metalloproteinase. Importantly, the knock-out defects were rescued by introducing the N-terminal portion of the huntingtin protein. By using a complementation approach with huntingtin homologues from different species, I demonstrated that only homologues from species with a complex nervous system could successfully rescue the knockout defects.

   - Tartari M., Gissi C., **Lo Sardo V.**, Pesole G., Cattaneo E. *Phylogenetic comparison of huntingtin homologues reveals the appearance of a primitive polyQ in sea urchin*. ***Mol Biol Evol.*** (2008). PMID: 18048403
   - **Lo Sardo V**.*, Zuccato C.*, Gaudenzi G., Vitali B., Ramos C., Tartari M., Myre M., Walker J., Pistocchi A., Conti L., Valenza M., Drung B., Schmidt B., Gusella J., Zeitlin S., Cotelli F. and Cattaneo E. *An evolutionary recent neuroepithelial cell adhesion function of huntingtin implicates ADAM10-Ncadherin*. ***Nature Neuroscience*** (2012). PMID: 22466506

Additional Contributions

1. Generation of ***NHLBI NEXT GEN cell lines collections – "CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION" and "WELLDERLY STUDY"***
   These collections of iPSCs were generated from PBMCs as part of the Next Generation Genetic Association Studies (Next Gen) Program from NHLBI. The entire cell collections are banked at WiCell https://www.wicell.org/home/stem-cells/catalog-of-stem-cell-lines/collections/wellderly-study-collection.cmsx
   https://www.wicell.org/home/stem-cells/catalog-of-stem-cell-lines/collections/nhlbi-next-gen-topol.cmsx
   Cell stem cell volume 20 issue 4, April 6, 2017. https://www.cell.com/consortium/NextGen

2. ***"STEM CELLS AND REPROGRAMMING METHODS FOR NEUROSCIENCE"*** Online Training Series by the Society for Neuroscience (Online August 7, 2019). This online training series on demand has the goal to create a set of lasting foundational, educational, and technical training resources about iPSC methods and their applications. The training has been developed for a broad audience of neuroscientists. I lectured the first module of the series, presenting ***"Generating and genome editing iPSCs".***
   https://neuronline.sfn.org/Collections/Stem-Cells-and-Reprogramming-Methods-for-Neuroscience

3. **Introduction to the community: early-career researchers in the time of Covid-19**

Takayama K, Weaver LN, Lummertz da Rocha E, **Lo Sardo V**, Gehart H, Vu LP.Cell Stem Cell. 2020 Dec 3;27(6):853-855. doi: 10.1016/j.stem.2020.11.011. PMID: 33275897

4. **Preventing Anthracycline-Induced cardiotoxicity using functional genomics and human-induced pluripotent setm cell-derived cardiomyocytes**
   Lo Sardo V and Kamp T J. Editorial in *Circulation*, 2022 doi: 10.1161/CIRCULATIONAHA.121.058128

Complete List of Publications in MyBibliography
https://pubmed.ncbi.nlm.nih.gov/?term=lo+sardo+v&sort=date