BIOGRAPHICAL SKETCH

NAME: Alessandra Balduini

POSITION TITLE: Full Professor, University of Pavia

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pavia, Pavia, Italy	MD (cum laude)	07/1994	Medicine
Université Joseph *Fourier*, *Grenoble*, *France*	Extèrne des Hôpitaux	09/1993	Medicine
University of Indiana, Indianapolis, USA	Post-doc	12/1996	Stem Cell Biology
University of Pavia, Pavia, Italy	Specialization (cum laude)	10/2000	Clinical Biochemistry
IUSS-SAFI, University of Pavia, Pavia, Italy	M.S.	10/2000	Art and Science

A. Personal Statement

I have a broad background in haematology, with specific training and expertise in the research of haematopoietic stem cell biology and clinical aspects of platelet related disorders. Before creating my research group in 2007, I was a staff physician in the laboratory of Clinical Biochemistry, IRCCS San Matteo Foundation, and University of Pavia, Italy. In 2005-2006 I was Visiting Professor at Dana Farber Cancer Institute at Harvard Medical School. Since 2007 I have led a research group based in the Department of Molecular Medicine - University of Pavia, Italy. The goal is to establish a cross-sectional program that integrates biological with bioengineering approaches to the study of haematopoiesis and bone marrow environment. My research focuses on how the different components of the bone marrow microenvironment regulate platelet production. I developed the groundwork for modeling human bone marrow by bioengineering a 3D model made of porous silk that fully recreates the physiology of the living bone marrow niche environment. This system can generate functional platelets *ex vivo*, offering new opportunities for producing blood components for clinical applications. Recently, we proved that this superior tissue system also represents a new tool for studying pathologic mechanisms of human platelet production and testing drug efficiency.

B. Positions and Honors

Positions and Employment

2001-2005: Staff Physician, Clinical Biochemistry Laboratory, Policlinico San Matteo Foundation, Pavia, Italy.
2001- 2011: Assistant Professor of Medicine, Department of Biochemistry-University of Pavia, Italy.
2011-2021: Associate Professor, Department of Molecular Medicine, University of Pavia, Italy.
2021-present: Full Professor, Department of Molecular Medicine, University of Pavia, Italy.

Other Experience and Professional Memberships

2005-2006: Visiting Professor, Dana Farber Cancer Institute-Harvard Medical School, Boston, USA
2011: Visiting Professor, Universidad de Buenos Aires, Buenos Aires, Argentina
2007-present: Visiting Scientist, Department of Biomedical Engineering, Tufts University, Boston, USA.
2007-present: member of the International Society of Thrombosis and Hemostasis (ISTH), the American Society of Hematology (ASH), the Società Italiana di Biochimica (SIB), the European Hematology Association (EHA)

Honors

2005: Award-Progetto Professionalità, Fondazione Banca Regionale Europea
2011: Award-International Society of Thrombosis and Haemostasis, Reach the World Education Program
2015: Award-European Haematology Association-Japanese Society of Hematology
2017: Award-Ministero degli Affari Esteri e Cooperazione Internazionale (MAECI) Progetti di Grande Rilevanza

2019: Elected Chair of the 2023 Gordon Research Conference "Cell Biology of Megakaryocytes and Platelets"
2021: Elected member of the American Society of Hematology Scientific Committee on Megakaryocytes and Platelets (2021-2025). Elected Chair of this Committee for 2025.

Academic activities

1. Professor of Clinical Biochemistry: Medical School, Biotechnology, University of Pavia
2. Professor of Clinical Biochemistry: Specialization in Clinical Biochemistry and Pathology, Internal Medicine, Pulmonology, Microbiology, Surgery, Neurosurgery, Hematology, Endocrinology, Geriatrics, Ophthalmology, University of Pavia
3. Member of the Board of Doctorate in Bioengineering and Bioinformatics, University of Pavia (2013-2017)
4. Member of the Board of Doctorate in Translational Medicine, University of Pavia (2017-present)
5. In the last 10 years 30 undergraduate students wrote their final thesis and 5 obtained their PhD in my lab
6. In the last 10 years I supported 10 post-doc positions (3 to 6 year each)
7. PhD thesis external reviewer INSERM Paris, University of Strasbourg, University of Toulouse, Cambridge University

International Academic Programs

2011: International Society of Thrombosis and Hemostasis Reach the World Education Program
2012-2013: Whitaker International Program
2013: American Society of Haematology, Visitor Training Program
2014: European Haematology Association-Japanese Society of Hematology Fellowship Exchange Program
2015: EMBO International Student Exchange Program
2016: Japanese Society of Haematology and European Haematology Association program
2017-2019: Progetti di Grande Rilevanza Ministero degli Esteri

C. Contribution to Science

1. Megakaryopoiesis in platelet diseases: After several years as a clinician, I resumed my research career in 2005, focusing on the development of protocols for cultivating megakaryocytes (Mks) from human cord blood, investigating the intricate mechanisms of hematopoiesis, Megakaryocyte differentiation, and platelet release. During 2005-2006, I held the position of Visiting Professor at the Dana Farber Cancer Institute, at Harvard Medical School in Boston, USA. My research focused on the exploration of platelet production mechanisms in mouse embryonic stem cells. The outcomes of these investigations significantly contributed to our understanding of Megakaryocyte differentiation regulation.

In 2007, I established my personal research laboratory at the Department of Molecular Medicine, University of Pavia, Italy. In collaboration with my newly formed research team, I investigated the mechanisms of megakaryocyte differentiation in physiological and pathological conditions. A notable achievement was our contribution to revealing the pathogenetic mechanisms governing a novel form of inherited thrombocytopenia, which was correlated with mutations in the ANKRD26 gene. More recently we explored the pathogenetic mechanisms of platelet defects in other inherited thrombocytopenia as well as myopathies.

1.Chen Z, Naveiras O*, Balduini A*, Mammoto A, Conti MA, Hosoya H, Adelstein R, Ingber D, Daley GQ, Shivdasani R. The May-Hegglin anomaly gene Myh9 is a negative regulator of platelet biogenesis modulated by the Rho-ROCK pathway (2007) **Blood** 110:171-9.
2. Bluteau D*, Balduini A*, Balayn N, Currao M, Nurden P, Deswarte C, Leverger G, Noris P, Perrotta S, Solary E, Vainchenker W, Debili N, Favier R, Raslova H. Thrombocytopenia-associated mutations in the ANKRD26 regulatory region induce MAPK hyperactivation. (2014) **J Clin Invest**. 124: 580-91.
3. Abbonante V, Gruppi C, Battiston M, Zulian A, Di Buduo CA, Chrisam M, Sereni L, Laurent PA, Semplicini C, Lombardi E, Mazzucato M, Moccia F, Petronilli V, Villa A, Bello L, Pegoraro E, Bernardi P, Braghetta P, De Marco L, Bonaldo P, Balduini A. Ablation of collagen VI leads to the release of platelets with altered function. (2021) **Blood Adv**. Dec 14;5(23):5150-5163.
4. Marín-Quílez A, Di Buduo CA, Díaz-Ajenjo L, Abbonante V, Vuelta E, Soprano PM, Miguel-García C, Santos-Mínguez S, Serramito-Gómez I, Ruiz-Sala P, Peñarrubia MJ, Pardal E, Hernández-Rivas JM, González-Porras JR, García-Tuñón I, Benito R, Rivera J, Balduini A, Bastida JM. Novel variants in GALE cause syndromic macrothrombocytopenia by disrupting glycosylation and thrombopoiesis. (2023) **Blood** Jan 26;141(4):406-421.

2. Haematopietic Stem Cells and Megakaryocyte Differentiation in myeloproliferative neoplasms: In 2014, my research team achieved a groundbreaking milestone by demonstrating the pivotal role of calcium as a fundamental regulator in the process of platelet production. Furthermore, we extended our investigations to delve into the influence of calcium on megakaryocyte development, particularly in the context of CALR-mutant Myeloproliferative Neoplasms. Additionally, we collaborated on studies that yielded crucial insights into the significance of galactosylation to normal platelet development and to Myeloproliferative Neoplasms.

1. Di Buduo C, Moccia F, Battiston M, De Marco L, Mazzucato M, Moratti R, Tanzi F, Balduini A. The importance of calcium in the regulation of megakaryocyte function. (2014) **Haematologica** 99: 769-78.
2. Di Buduo CA, Abbonante V, Marty C, Moccia F, Rumi E, Pietra D, Soprano PM, Lim D, Cattaneo D, Iurlo A, Gianelli U, Barosi G, Rosti V, Plo I, Cazzola M, Balduini A. Defective interaction of mutant calreticulin and SOCE in megakaryocytes from patients with myeloproliferative neoplasms. (2020) **Blood** ;135(2):133-144.
3. Giannini S, Lee-Sundlov MM, Rivadeneyra L, Di Buduo CA, Burns R, Lau JT, Falet H, Balduini A, Hoffmeister KM. β4GALT1 controls β1 integrin function to govern thrombopoiesis and hematopoietic stem cell homeostasis. (2020) **Nat Commun.** Jan 17;11(1):356
4. Di Buduo A, Giannini S, Abbonante V, Rosti V, Hoffmeister K, Balduini A. Increased β4GALT1 expression associates with platelet surface galactosylation and thrombopoietin plasma levels in MPNs. (2021) **Blood** 137(15):2085-2089.

3. Bone marrow environment: I've focused my research towards unraveling the mechanisms governing interactions between type I collagen and megakaryocytes in the bone marrow milieu. This has resulted in two publications in the Blood Journal, spotlighting the significance of fibronectin in modulating Megakaryocyte function amid the bone marrow matrix environment. Our exploration extended to the expression and function of the novel collagen receptor Discoidin Domain Receptor I (DDR1) on human megakaryocytes, revealing the mechanisms underlying extracellular matrix component-megakaryocyte interactions. We validated these findings through *in vivo* mouse models, which facilitated a comprehensive understanding of these interactions in bone marrow. This research culminated in the detailed characterization of megakaryocytes in the context of Myeloproliferative Neoplasms. Using this methodological approach, we successfully identified the pivotal role of the fibronectin isoform EIIIA in regulating hemopoiesis within the bone marrow, particularly in the context of myeloproliferative neoplasms. More recently, our focus has shifted to investigating the role of autophagy, both in vivo and in vitro, further broadening our understanding of the dynamics at play within this complex environment.

1. Malara A, Gruppi C, Rebuzzini P, Visai L, Perotti C, Moratti R, Balduini C, Tira ME, Balduini A. Megakaryocyte-matrix interaction within bone marrow: new roles for fibronectin and factor XIII-A. (2011) **Blood** 117(8): 2476-83.
2. Abbonante V, Gruppi C, Rubel D, Gross O, Moratti R, Balduini A. Discoidin Domain Receptor 1 is a novel modulator of megakaryocyte-collagen interactions. (2013) **J Biol Chem**. 288: 16738-46.
3. Malara A, Gruppi C, Abbonante V, Cattaneo D, De Marco L, Massa M, Iurlo A, Gianelli U, Balduini CL, Tira ME, Muro AF, Chauhan AK, Rosti V, Barosi G, Balduini A. EDA fibronectin-TLR4 axis sustains megakaryocyte expansion and inflammation in bone marrow fibrosis. (2019) **J Exp Med** 216(3):587-604.
4. Abbonante V, Malara A, Chrisam M, Metti S, Soprano P, Semplicini C, Bello L, Bozzi V, Battiston M, Pecci A, Pegoraro E, De Marco L, Braghetta P, Bonaldo P, Balduini A. Lack of COL6/collagen VI causes megakaryocyte dysfunction by impairing autophagy and inducing apoptosis. (2022) **Autophagy** Jul 20;1-16

4. Mechano-sensors and megakaryocyte function: In addition to researching the chemical attributes of extracellular matrix components in bone marrow, we analyzed the impact of their elasticity on governing megakaryocyte function. Our latest efforts have been directed towards understanding the role of mechano-sensors in orchestrating platelet production, both in normal physiological conditions and during disease states.

1. Malara A, Gruppi C, Pallotta I, Spedden E, Tenni R, Raspanti M, Kaplan DL, Tira ME, Stai C, Balduini A. Extracellular matrix nano-mechanics determine megakaryocyte function. (2011) **Blood** 118(16): 4449-53
2. Malara A, Currao M, Gruppi C, Celesti G, Viarengo G, Buracchi C, Laghi L, Kaplan DL, Balduini A. Megakaryocytes Contribute to the Bone Marrow-Matrix Environment by Expressing Fibronectin, Type IV Collagen and Laminin. (2014) **Stem Cells**. 32: 926-37

3. Abbonante V, Di Buduo CA, Gruppi C, De Maria C, Spedden E, De Acutis A, Staii C, Raspanti M, Vozzi G, Kaplan DL, Moccia F, Ravid K, Balduini A. A new path to platelet production through matrix sensing. (2017) **Haematologica** 102: 1150-1160
4. Abbonante V, Karkempetzaki A, Leon C, Krishnan A, Huang N, Di Buduo CA, Cattaneo D, Ward C, Matsuura S, Guinard I, Weber J, De Acutis A, Vozzi G, Iurlo A, Ravid K, Balduini A. Newly Identified Roles for PIEZO1 Mechanosensor in Controlling Normal Megakaryocyte Development and in Primary Myelofibrosis. (2024) **Am J Hematol** Jan 2. Online ahead of print

5. Human Bone Marrow Niche Environment modeling: In 2007, my research journey led me to use silk protein as a biomaterial for developing a 3D bioreactor model that successfully reproduces the intricacies of the bone marrow environment, transforming the study of platelet formation. Thanks to this ingenious model, functional platelets are generated *ex vivo*, and the inclusion of endothelial cell co-cultures has remarkably increased the number of released platelets. The extraordinary biocompatibility, non-thrombogenic characteristics, and adjustable mechanical properties inherent in silk have paved the way for this system's exceptional capabilities. It enables the binding of cytokines, extracellular matrix components, and endothelial-derived proteins. This multifaceted approach opens a fresh path for the production *ex vivo* of blood components with direct clinical applications. Furthermore, our advanced tissue system serves as a unique tool for the exploration of pathologic mechanisms affecting platelet production and provides a direct platform for assessing drug efficiency using patient blood samples. This marks a giant stride for personalized medicine and the advancement of clinical practice.

1. Di Buduo CA, Wray LS, Tozzi L, Malara A, Chen Y, Ghezzi CE, Smoot D, Sfara C, Antonelli A, Spedden E, Bruni G, Staii C, De Marco L, Magnani M, Kaplan DL, Balduini A. Programmable 3D silk bone marrow niche for platelet generation ex vivo and modeling of megakaryopoiesis pathologies. (2015) **Blood** 125(14): 2254-64.
2.Di Buduo CA, Soprano PM, Tozzi L, Marconi S, Auricchio F, Kaplan DL, Balduini A. Modular flow chamber for engineering bone marrow architecture and function. (2017) **Biomaterials** 146:60-71
3. Di Buduo CA, Laurent PA, Zaninetti C, Lordier L, Soprano PM, Ntai A, Barozzi S, La Spada A, Biunno I, Raslova H, Bussel JB, Kaplan DL, Balduini CL, Pecci A, Balduini A. Miniaturized 3D bone marrow tissue model to assess response to Thrombopoietin-receptor agonists in patients. (2021) **Elife**;10: e58775.
4. Di Buduo CA, Lunghi M, Kuzmenko V, et al. Bioprinting Soft 3D Models of Hematopoiesis using Natural Silk Fibroin-Based Bioink Efficiently Supports Platelet Differentiation. (2024) ***Adv Sci (Weinh)***: e2308276.

Complete List of Published Work in My Bibliography:
www.ncbi.nlm.nih.gov/pubmed/?term=balduini+a