MICROENVIRONMENTAL REGULATION OF HEMATOPOIESIS

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SUMMARY & MISSION STATEMENT

Our laboratory is interested in understanding how stromal cells of the bone marrow microenvironment regulate healthy and malignant hematopoiesis, as well as immune cell trafficking and activation in marrow tissues. Our ultimate goal is to find new ways in which dysfunctional stromal-hematopoietic crosstalk maybe targeted in hematologic malignancies.

OVERVIEW

High throughput, continuous blood cell production is the end result of an extraordinarily complex and tightly regulated set of cellular interactions that take place within the ecosystem of bone marrow tissues. In my research group we investigate how the non-hematopoietic cells - that form the stromal backbone of bone marrow - assemble into highly organized three dimensional infrastructures, which host and critically control hematopoiesis. In particular, we focus in defining the specialized niche cell types that maintain hematopoietic stem cells. We aim to further dissect the cellular and molecular make-up of the stromal microenvironment, and the ways in which stromal regulation is subverted in pathological hematopoiesis. We have a special interest in the inflammatory signals that trigger alterations in stromal cell function, which promote the initiation and development of malignant transformation of hematopoietic progenitors. We are further interested in studying the mechanisms driving immune cell trafficking in and out of marrow tissues in the context of infections and neoplasias. Our research largely relies on the use of state of the art imaging technologies implemented in our laboratory, which enable the three-dimensional reconstruction, visualization and quantitative analysis of large volumes of hematopoietic tissues with unprecedented resolution.

SELECTED CANCER RELATED PUBLICATIONS

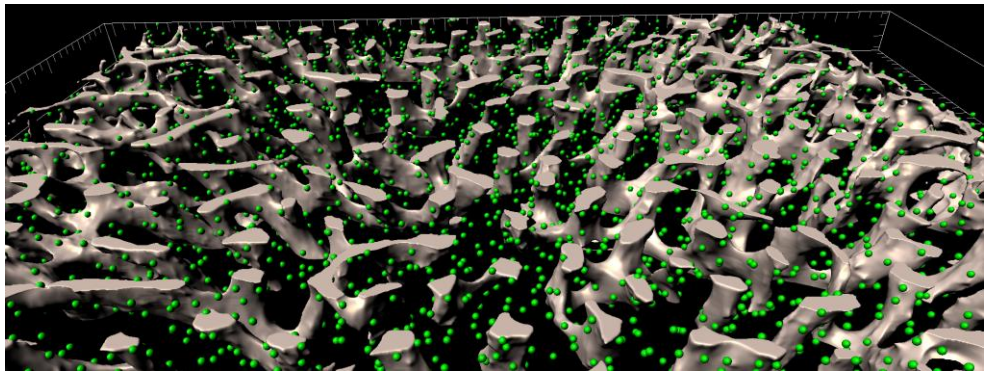
Quantitative spatial analysis of hematopoiesis-regulating stromal cells in the bone marrow microenvironment by multiscale 3D microscopy. Gomariz A, Helbling, Isringhausen S, Suessbier U, Becker A, Boss A, Nagasawa T, Paul G, Goksel O, Székely G, Stoma S, Nørrelykke SF, Manz MG, Nombela-Arrieta C. **Nature Communications** (Accepted for publication May 2018)

Pathogen-Induced TLR4-TRIF Innate Immune Signaling in Hematopoietic Stem Cells Promotes Proliferation but Reduces Competitive Fitness. Takizawa H, Fritsch K, Kovtonyuk LV, Saito Y, Yakkala C, Jacobs K, Ahuja AK, Lopes M, Hausmann A, Hardt WD, Gomariz Á, Nombela-Arrieta C, Manz MG. **Cell Stem Cell.** 2017 Jul 19. Aug 3;21(2):225-240.e5

Quantitative Imaging of Hematopoietic Stem and Progenitor Cell localization and hypoxic status in the Bone Marrow microenvironment. Nombela-Arrieta C*, Pivarnik G, Winkel B, Canty KJ, Harley B, Mahoney JE; Park SY, Lu J, Protopopov A, Silberstein LE* (2013). **Nat Cell Biol**, 15(5):533-43. * co-corresponding author

The elusive nature of Mesenchymal Stem Cells. Nombela-Arrieta C; Ritz J; Silberstein LE (2011). **Nat Rev Mol Cell Biol**, 12(2):126-31

Nombela-Arrieta C*; Mempel TR*, Soriano SF, Mazo I, Wymann MP; Hirsch E, Martínez-A C, Fukui Y, von Andrian UH, Stein JV (2007). A central role for DOCK2 during interstitial lymphocyte motility and sphingosine-1-phosphate-mediated egress. **J Exp Med**, 204(3):497-510. * Shared authorship



Processed 3D digital reconstruction of the sinusoidal vascular system (grey) and mesenchymal stromal cells (green) in murine bone marrow for the study of vascular-cellular interactions.