KIRA GRITSMAN, M.D., Ph.D.

Positions:
Associate Professor, Departments of Medical Oncology and Cell Biology
Member, Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research
Albert Einstein College of Medicine

Research interests:

My lab studies the signal transduction pathways that affect the early fate decisions of adult hematopoietic stem cells (HSCs) as they progress from an undifferentiated multipotent state to the generation of differentiated blood cells. When early hematopoietic fate decisions go awry, this can lead to the development of leukemia. PI3 kinase (PI3K) is a lipid kinase that is important for the regulation of metabolism, the cell cycle, apoptosis, and protein synthesis. In hematopoietic cells, four isoforms of the catalytic subunit of PI3K (p110alpha, beta, delta, and gamma), can transduce growth factors, cytokines, and/or chemokines. Emerging evidence suggests that these isoforms have unique functions in normal and cancer cells, but may substitute for each other in some contexts. We have generated a series of mouse knockout models that allow us to study the roles of each of these isoforms, individually and together, in adult hematopoiesis, and also in mouse models of leukemia. We have uncovered important redundant roles for these PI3K isoforms in regulating HSC self-renewal, proliferation, and differentiation. We have also found that leukemic stem cells (LSC), which can be a source of relapse in AML patients, can depend upon individual PI3K isoforms. We are studying the mechanisms through which PI3K mediates LSC self renewal, including its effects on chromatin regulation and on recognition of LSCs by the immune system. We are also investigating new kinase targets in myeloid malignancies.

Current grant funding:

R01 CA196973-01A1 (Gritsman, K.) 04/01/16 – 03/31/22
(NIH/NCI) PI3K Isoform Dependence in Adult Hematopoiesis and Myeloid Leukemia

134154-RSG-19-130-01-DCC (Gritsman, K.) 01/01/20-12/31/23
(American Cancer Society) RON Kinase as a Therapeutic Target in Myeloproliferative Neoplasms

R56DK130895 (Gritsman, K.) 9/17/21-9/30/22
(NIH/NIDDK) Regulation of Autophagy by PI3 Kinase in Myelodysplastic Syndrome

Recent publications (selected):

Ames,K., Kaur, I., Shi, Y., Tong, M., Sinclair, T., Hemmati, S., Glushakow-Smith, S. G., Tein, E., Gurska, L., Dubin, R., Shan, J., Pradhan, K., Verma, A., Montagna, C., and **Gritsman, K.**, Deletion of PI3-Kinase Promotes Myelodysplasia Through Dysregulation of Autophagy in Hematopoietic Stem Cells, *BioRxiv* 2020, doi: https://doi.org/10.1101/2020.12.04.412593 (preprint)

Hemmati, S., Sinclair, T., Tong, M., Bartholdy, B., Okabe, R.O., Ames, K., Ostrodka, L., Haque, T., Kaur, I., Mills, T. S., Agarwal, A., Pietras, E.M., Zhao, J.J., Roberts, T.M., and **Gritsman, K.**, PI3 kinase alpha and delta promote hematopoietic stem cell activation, ***JCI Insight*** 2019 doi.org/10.1172/jci.insight.125832

Mitchell, K., Barreyro, L., Todorova, T., Taylor, S., Antony-Debre, I., Narayanagari, S., Carvajal, L., Leite, J., Piperdi, Z., Pendurti, G., Mantzaris, I., Paietta, E., Verma, A., **Gritsman, K.,**and Steidl, U. IL1RAP potentiates multiple oncogenic signaling pathways in AML, ***Journal of Experimental Medicine***. 2018 May 17. doi: 10.1084/jem.20180147, PMID: 29773641

Hemmati, S., Haque, T., and **Gritsman, K,** Inflammatory Signaling Pathways in Pre-leukemic and Leukemic Stem Cells, ***Frontiers in Oncology*** 2017 Nov 13;7:265. doi: 10.3389/fonc.2017.00265

Yuzugullu, H., Baitsch, L., Von, T., Steiner, A., Tong, H., Ni, J., Clayton, L., Bronson, R., Roberts, T., **Gritsman, K.**, and Zhao, J.J. A p110b-Rac signaling loop mediates Pten-loss-induced perturbation of hematopoiesis and leukemogenesis. ***Nature Communications*** October 7,2015, doi:10.1038/NCOMMS9501

Gritsman, K., Yuzugullu, H., Von, T., Yan, H., Clayton, L., Fritsch, C., Maira, S.-M., Hollingworth, G., Choi, C., Khandan, T., Paktinat, M., Okabe, R.O., Roberts, T.M., and Zhao, J.J. Hematopoiesis and RAS-driven myeloid leukemia differentially require PI3K isoform p110alpha**. *J Clin Invest*** 2014;124(4):1794-1809

Kharas, M.G., Okabe, R., Ganis, J.J., Gozo,M., Khandan,T., Paktinat, M., Gilliland, D.G., and **Gritsman, K.** Constitutively Active AKT Depletes Hematopoietic Stem Cells and Induces Leukemia in Mice. ***Blood*** 2010; 115(7): 1406-15 http://www.bloodjournal.org/content/115/7/1406