# Peter Miller, MD, PhD

## Miller Laboratory

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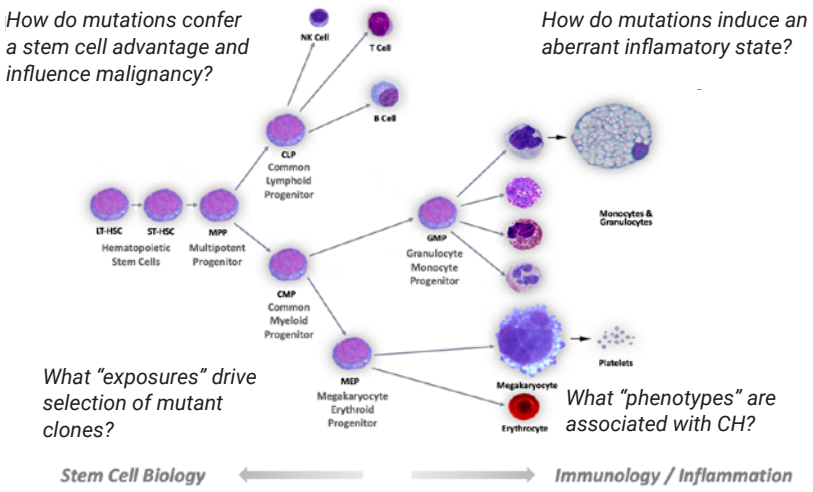
**The Miller laboratory** seeks to understand how somatic mutations in blood cells arise and drive abnormal cellular states including the development of blood cancers such as leukemia. We incorporate orthogonal tools including human genetics, mouse models, cellular assays, genetic screens, and molecular techniques to identify genes that are recurrently altered in blood disorders and determine how these alterations alter cellular programs such as self-renewal, response to DNA damage, and inflammation. We are particularly interested in using these tools to understand (1) the role of *PPM1D*, a gene that regulates the DNA Damage Response, in blood cell development (2) how mutations in *PPM1D* allow cells to be more resistant to chemotherapy and (3) how mutations in blood cells more generally influence inflammatory programs and pathophysiologic processes across multiple tissue-types. We seek to use our understanding of this biology to develop new therapies for the prevention and treatment of blood cancers.

Over the lifespan of an organism, somatic mutations arise in stem cells in many organs, some of which confer a competitive survival or growth advantage to the mutant cells. In such cases, a clonally selected population emerges in which additional mutational events can lead to malignant transformation and the development of cancer. This is particularly true in the blood system where mutations can drive selection of a non-malignant population, so called clonal hematopoiesis (CH), with subsequent mutational events leading to the development of blood cancers including myeloid neoplasms such as myeloproliferative neoplasms, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). We believe that understanding the molecular mechanisms by which mutations arise in hematopoietic cells and drive neoplastic transformation can highlight novel therapeutic opportunities for the treatment of blood cancers, particularly MDS and AML.

DNA sequencing studies have informed our understanding of the genetic landscape of many hematologic malignancies, including MDS and AML. Further efforts have catalogued the genes that are mutated in CH by identifying somatic alterations present in the peripheral blood of individuals without blood cancers. Taken together, these human genetic studies can inform the timing and context in which various mutations arise, and in so doing identify critical mediators of both normal hematopoiesis and malignancy. We utilize these studies to define testable hypotheses in the lab, the results of which can further inform clinical decision-making.

Our work has largely focused on mutations in the gene *PPM1D*. Using selected patient cohorts, we have found that individuals who have received cytotoxic therapy (chemotherapy or radiation) are significantly more likely to harbor activating mutations in *PPM1D*, in the form of CH or frank malignancy (MDS or AML). We now know that these mutations, which arise in hematopoietic stem cells, lead to increased levels of PPM1D protein via impaired proteasomal degradation. This in turn allows PPM1D to suppress the DNA damage response and P53 activation more effectively, thereby allowing *PPM1D*-mutant




*Framework for thinking about how somatic mutations arise in hematopoietic stem cells and drive aberrant stem cells processes including malignancy (left) and how these mutations influence aberrant inflammatory programs when present in mature immune cells and contribute to various disease phenotypes (right).*

cells to have a survival advantage relative to unmutated cells in the presence of cytotoxic stress. We now seek to more deeply characterize the biological processes driving these observations using novel genetically engineered mouse models, functional genetic techniques, and biochemical assays. We hypothesize that defining the role of PPM1D in normal and malignant hematopoiesis will both drive our efforts to therapeutically target PPM1D in numerous oncologic contexts, and more broadly inform our understanding of the DNA damage response in normal and cancerous cells. This is particularly important in individuals who have therapy-related cancers that tend to be highly resistant to our standard therapies and have very poor outcomes.

We also are interested in understanding how CH mutations drive aberrant inflammatory states. Numerous groups have shown that individuals with CH have a greater risk of adverse cardiovascular outcomes, via enhanced inflammatory programs within mature, mutant immune cells. Using analogous approaches, we found that individuals with CH are more likely to have chronic obstructive pulmonary disease (COPD), particularly severe forms, and that mice with hematopoietic loss of Tet2, a gene commonly mutated in CH, have enhanced pulmonary emphysema in numerous models, akin to what is seen in human COPD. We now seek to understand which mutant blood cell types and the specific molecular pathways that drive this enhanced lung inflammation. We believe that a deep understanding of the link between CH and COPD will define new therapeutic opportunities to treat inflammatory disease of the lung and beyond.

Taken together, our lab seeks to leverage observations from human genetic studies to make clinically meaningful biological insights with the goal of developing new therapies to improve the outcome of our patients with hematologic malignancies.

## Selected Publications:


**Miller PG**, Sperling AS, Mayerhofer C, McConkey M, Ellegast JM, Da Silva C, Cohen DN, Wang C, Sharda A, Yan N, Saha S, Schluter C, Schechter IA, Słabicki M, Sandoval B, Kahn J, Boettcher S, Gibson CJ, Scadden DT, Stegmaier K, Bhatt S, Lindsley RC, Ebert BL. PPM1D modulates hematopoietic cell fitness and response to DNA damage and is a therapeutic target in myeloid malignancy. *Blood.* 2023 Aug 18:blood.2023020331.

Gibson CJ, Fell G, Sella T, Sperling AS, Snow C, Rosenberg SM, Kirkner G, Patel A, Dillon D, Bick AG, Neuberg D, Partridge AH, **Miller PG**. Clonal Hematopoiesis in Young Women Treated for Breast Cancer. *Clin Cancer Res.* 2023 Jul 5;29(13):2551-2558.

Mayerhofer C,...**Miller PG**. Clonal Hematopoiesis in Older Patients with Breast Cancer Receiving Chemotherapy. *J National Cancer Institute*. 2023. Apr 12;djad05.

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Kahn JD, **Miller PG**,...Ebert BL. PPM1D truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. *Blood.* 132(11):1095-1105, 2018.

Miller PG, Al-Shahrour F,...Ebert BL. In Vivo RNAi screening identifies a leukemia-specific dependence on integrin beta 3 signaling. ***Cancer Cell***. 24(1):45-58, 2013.

Hartwell KA*, **Miller PG***,...Ebert BL, Golub TR. Niche-based screening identifies small-molecule inhibitors of leukemia stem cells. *Nat Chem Biol.* 9(12):840-8, 2013.