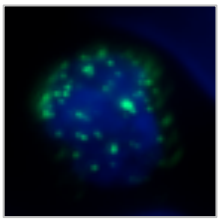
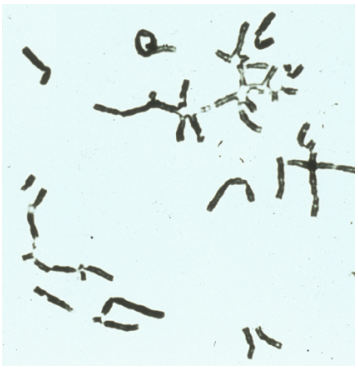
Kurre Laboratory - AVAILABLE RESEARCH PROJECTS

1) *Cell cycle Checkpoint Activation and Replication Stress in Fanconi Anemia (FA) Hematopoietic Stem Cells (HSC) – Impact on Long-term Fate and Function.*

Recent studies by our lab (Yoon et al.) and others have identified the origins of hematopoietic failure in FA during development. In a series of experiments we identified midgestation as a critical window for the onset of HSC deficits in FA mice, and replication stress as the underlying mechanism. In this project we will delve into the molecular and cellular underpinnings of our observation and focus on the functional implications of fetal HSC. Insight form these experiments will help us develop rational approaches to pharmacological reversal of the fetal block in HSC expansion. These studies will leverage new FA animal models, drug discovery and involve studies of genome stability.





2) *Transferable Endoplasmic Reticulum (ER) Stress and the Unfolded Protein Response (UPR) as Mechanisms of Niche Adaptation and Chemotherapy Resistance in Acute Myeloid Leukemia.*

Nearly half of all patients diagnosed with AML suffer disease recurrence after initially successful induction therapy. Persistent disease and clonal selection compromise subsequent treatment and patient survival. Mechanisms of resistance are diverse, ranging from cell intrinsic to those specified by adaptation of the leukemic microenvironment, i.e. extrinsic. We recently reported the involvement of extracellular vesicles (EVs) in the compartmental remodeling that accompanies AML invasion of the BM.

Our studies in mouse models and patient derived samples (Doron et al.) revealed widespread induction of ER stress in AML blast cells that was transferred to the stroma.

This project will pursue the observation of ER stress transmission to the BM stroma (already a known mechanism of drug resistance in the solid tumor microenvironment) and determine how ER stress transfer to stroma confers functional chemoresistance, and protects AML cells from eradication by chemotherapy. In addition, we will test a panel of candidate drugs for reversal of drug resistance.