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There is a critical need to develop new treatment options for the most diagnosed subtype of breast cancer, estrogen receptor positive (ER+). A common treatment is endocrine therapy that blocks ER signaling, which the tumor requires to grow. A strategy to increase effectiveness of cancer treatment is to use a combination of drugs that can enhance the effects of each other. Our lab previously analyzed biopsies from patients with ER+ breast cancer, before and after treatment with endocrine therapy, and found a significant increase in gene expression associated with the NF κ B pathway, a signaling pathway known to influence both tumor cell survival and tumor cell death. We also examined how gene expression changed in cultured ER+ breast cancer cells when deprived of estrogen and found increased NF κ B signaling. These results led us to ask if endocrine therapy that stimulates this pathway could synergize with Second Mitochondria-Derived Activator of Caspases (SMAC) mimetics that enhance NF κ B signaling and promote cell death. Using ER+ breast cancer cells and patient-derived xenograft (PDX) mouse models, we observed synergy between endocrine therapy and SMAC mimetics, resulting in tumor regression. Based on our initial studies, we will examine a broader range of selective estrogen receptor degraders (SERDs), a type of endocrine therapy, and SMAC mimetics, to determine efficacy and synergy across multiple models that represent ER+ breast cancers with heterogeneous genetic backgrounds. In addition, we will perform comprehensive analyses to determine the molecular effects of these combinations in ER+ breast cancer models that are either sensitive or resistant to SERD treatment. Together, these experiments will provide vital insights into the efficacy of SERD and SMAC mimetic combination, as well as the mechanism of action for synergy in ER+ breast cancer. Our results have the potential to be translated to the clinic, possibly leading to a new therapeutic approach to improve outcomes for patients with ER+ breast cancer.

Dr. Kuziel received her undergraduate degree from Reed College in Portland, Oregon and her graduate degree from the Cancer Biology PhD Program at the University of Wisconsin - Madison. She is currently a postdoctoral research fellow at Dana-Farber Cancer Institute in the Department of Medical Oncology. In the lab of Dr. Rinath Jeselsohn, Dr. Kuziel focuses on ER+ breast cancer, in particular, examination of a novel combination therapy that may improve ER+ breast cancer treatment.