**Super-enhancer landscapes reveal novel epigenomic patient subtypes and druggable dependencies in human AML**

Matthew L. Eaton*, M. Ryan Corces*, Michael R. McKeown†, Christopher Fiore‡, Jeremy T. Lopez*, Katarzyna Piotrowska*, Emily Lee*, Mei Wei Chen†, Darren Smith*, Steven M. Chan†, Julie L. Koenig‡, Sarah K. Knutson*, Kathryn Austgen†, Matthew G. Guenther†, David A. Orlando†, Jakob Lovén†, Christian Fritz‡, Ravindra Majeti*.  
*Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA, 02139, USA

**Abstract**

The bulk of translational cancer research to date has focused on somatic mutations in protein coding regions to identify putative oncogenic drivers. However, recent studies have shown that enhancer activity plays an important role in specifying and maintaining oncogenic cell states. Here, we present a mapping and analysis of the transcriptional cell state of acute myeloid leukemia (AML) via the H3K27ac landscape, gene expression, and somatic mutations from 62 AML patients. The goal of this work is to identify the recurrent enhancer landscapes of oncogenic cell states and translate that knowledge of the epigenome to discover novel therapeutic opportunities. Through a computational deconvolution of enhancer maps, we identify 6 epigenomically defined patient subtypes of AML. We demonstrate that while certain genetic lesions, such as MLL translocations and NPM1 mutations, do correlate with these subtypes, the epigenome provides a novel stratification of patients that is not fully specified by combinations of mutations. We develop a novel scoring of myeloid differentiation based on the enhancer landscape of healthy cells and use this score to show that enhancer subtypes are associated with the differentiation state of the underlying AML blasts. Enhancer subtypes are also clinically relevant as they are predictive of divergent overall survival, varying from a median overall survival of 9.2 months to a median overall survival that was not reached in our cohort. By using individual enhancer activity as a novel biomarker, we are able to predict the effect of existing therapies on cell line models. Finally, a network analysis of the super-enhancers underlying the patient subtypes suggests that one subtype of AML is specified in part by enhancer activation of the retinoic acid receptor alpha gene (RARA), and we demonstrate that RARA enhancer strength with the differentiation state of the underlying AML blasts. Enhancer subtypes are also clinically selective with the differentiation state of the underlying AML blasts. Enhancer subtypes are also clinically relevant as they are predictive of divergent overall survival, varying from a median overall survival of 9.2 months to a median overall survival that was not reached in our cohort. By using individual enhancer activity as a novel biomarker, we are able to predict the effect of existing therapies on cell line models. Finally, a network analysis of the super-enhancers underlying the patient subtypes suggests that one subtype of AML is specified in part by enhancer activation of the retinoic acid receptor alpha gene (RARA), and we demonstrate that RARA enhancer strength with the differentiation state of the underlying AML blasts. Enhancer subtypes are also clinically relevant as they are predictive of divergent overall survival, varying from a median overall survival of 9.2 months to a median overall survival that was not reached in our cohort. By using individual enhancer activity as a novel biomarker, we are able to predict the effect of existing therapies on cell line models. Finally, a network analysis of the super-enhancers underlying the patient subtypes suggests that one subtype of AML is specified in part by enhancer activation of the retinoic acid receptor alpha gene (RARA), and we demonstrate that RARA enhancer strength with the differentiation state of the underlying AML blasts. Enhancer subtypes are also clinically relevant as they are predictive of divergent overall survival, varying from a median overall survival of 9.2 months to a median overall survival that was not reached in our cohort. By using individual enhancer activity as a novel biomarker, we are able to predict the effect of existing therapies on cell line models. Finally, a network analysis of the super-enhancers underlying the patient subtypes suggests that one subtype of AML is specified in part by enhancer activation of the retinoic acid receptor alpha gene (RARA), and we demonstrate that RARA enhancer strength with the differentiation state of the underlying AML blasts.