Mechanism-Based Targeting of RNA Binding Protein Networks for Chemo-Sensitization in Non-Small Cell Lung Cancer (NSCLC)

Principal Investigator:

- Michael B. Yaffe, MD, PhD – The Broad Institute of MIT & Harvard

Co-Principal Investigators:

- Robert B. Darnell, MD, PhD – The Rockefeller University
- Michael T. Hemann, PhD – The Broad Institute of MIT & Harvard

Abstract: Most frontline chemotherapeutics exert their effects by causing DNA damage but what governs sensitivity or resistance to these agents in order to predict which patients will benefit from a specific treatment is lacking. Countless genome wide analyses for modifiers of the response of cultured tumor cells to DNA damage have converged on RNA binding proteins as the most important and under-appreciated class of proteins that influence DNA damage-triggered cell death. However, the relative importance of each of these candidate DNA damage regulating RNA-BPs *in vivo* and their feasibility as *bona-fide* therapeutic targets remains unknown. Here we propose to systematically prioritize candidate RNA-BPs for their effects on platinum-based chemotherapy response by performing an *in vivo* RNAi screen in a transplantable non-small cell lung cancer (NSCLC) mouse model that is intrinsically resistant to the frontline chemotherapeutic cisplatin to identify RNA-BPs whose loss induces chemo-sensitization. RNA-BPs that have profound effects on chemotherapy-induced cell death will have their target RNAs identified under basal conditions and in response to chemotherapy using revolutionary CLIP-Seq technology. These studies will define mechanisms of action and will be used to inform the rational design of next-generation RNA-based nano-particle encapsulated drugs that will be tested as chemo-sensitizing agent*s in vivo*. Together this work will define novel mechanisms of resistance to frontline chemotherapy and establish the targeting of RNA-BPs as a new paradigm for combination chemotherapy for treatment of human malignancies.