“Discovery of Prostate Cancer Tumor Suppressors and Treatment Biomarkers through *in vivo* RNA Interference Screens”

Principal Investigator:

- Charles Sawyers, MD, Memorial Sloan-Kettering Cancer Center

Co-Principal Investigators:

- Gregory Hannon, PhD, Cold Spring Harbor Laboratory

Funding Category: A

Abstract: Over the past several years, our understanding of prostate cancer has grown enormously. From a treatment perspective, it has become that clear castration-resistant prostate cancer (CRPC) mainly owes this property to reactivation of androgen receptor signaling pathways. This has led to new targeted therapies, which are nearing FDA approval, but these have substantial shortcomings. Roughly half of the candidates for treatment present with therapy-resistant disease and most of those who initially respond acquire resistance over time. Thus, CRPC is a prime candidate for the use of RNAi-based approaches to understanding genetic alterations that promote tumor progression and that contribute to therapy resistance. A considerable difficulty is that castration-resistance phenotypes can only be effectively measured *in vivo*, necessitating the use of *in vivo* RNAi screening approaches that remain on the cutting edge for that technology. Fortunately, work by the Sawyers lab, characterizing the prostate cancer genome, has yielded candidate tumor suppressors and genomic biomarkers of therapy resistance, permitting a focused effort on ~800 genes. Here, we propose a collaboration to use mouse and human models of CRPC to identify new prostate tumor suppressors and to identify determinants of therapy response. *In vivo* screening paradigms will be executed in two models, the mouse Myc-CaP prostate cancer xenograft and the LNCaP/AR human prostate cancer xenograft. In the latter case, we will specifically address mechanisms of resistance to a novel antiandrogen that was developed by the Sawyers lab and that is about to enter widespread clinical use.