"Identification and Clinical Assessment of Genes that Regulate the Response of Cancers to Rapamycin"

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Funding Category: A

Abstract: Basic and pre-clinical studies suggest that the mTOR inhibitor rapamycin has great promise as an anti-tumor agent, but so far oncology clinical trails have yielded mixed results, with some patients showing tumor regression but most deriving no benefit. The long-term goals of our proposed project are to understand why cancer cells and tumors exhibit varied cellular and molecular responses to rapamycin and to exploit this information to inform the clinical use of this drug and to spur the development of new therapies that potentiate the anti-tumor properties of rapamycin. We propose the following specific aims: (1) to identify genes that determine the molecular and cellular responses to rapamycin in candidate and unbiased RNAi screens; (2) to use oncogenomic data and tumor samples from patients treated with rapamycin to prioritize for follow up study the candidate genes from Aim 1 with the greatest likelihood of being relevant to the response to rapamycin of real human tumors; (3) to validate in mouse models of cancer the genes from Aim 2 that modulate the anti-tumor effects of rapamycin in vivo; and (4) to understand at a mechanistic level why the genes validated in Aim 3 modulate the anti-tumor properties of rapamycin. Sabatini and Sawyers have already assembled a team, including a shared MSKCC-MIT MD-PhD student and former technical member of the Sabatini lab, to jump start the project and incorporated new members (Rosen and Rubin) to enhance the impact of our findings in clinical material relevant to the use of rapamycin in oncology.