"Comparative oncogenomics to discover oncogene synthetic lethality"

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Funding Category: B

Abstract: The identification of oncogenes causally implicated in carcinogenesis has, in a few select instances, led to the implementation of molecularly targeted therapies. However, most known oncogenes and tumor suppressors have proven to be challenging therapeutic targets. An alternative approach to direct targeting of known cancer alleles is to exploit the genetic concept of synthetic lethality, in which gene products are identified that, when suppressed or inhibited, result in cell death only in the presence of another non-lethal mutation – such as addictive oncogenic alleles. In theory, this strategy provides a means to target currently "undruggable" proteins while simultaneously reducing the potential for side effects. Although synthetic phenotype screens in model organisms have provided insights into a broad spectrum of biological processes, the technology to perform such screens in mammals has only recently been realized.
We propose to identify genes that exhibit synthetic lethality when suppressed in the setting of oncogenic MYC or K-RAS alleles by using the Broad Institute and CSHL RNAi libraries in genetically defined human and murine cancer models. Although MYC and K-RAS are amplified or mutated in a wide diversity of human cancers and unequivocally play essential roles in cancer development, these oncogenes have proven difficult to target using traditional approaches. By using a cross-species comparative genetic approach, we will identify true synthetic lethal interactions of clinical relevance and ultimately validate these interactions in vivo.