CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130135

Project Title:
Comprehensive identification of all human Ras effectors to define mechanisms of Ras-induced malignancy and potential drug targets

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

The Ras proteins are key switches to relay signals from the growth factors. Genes encoding these proteins are among the most frequently mutated in cancer. About 30% of human cancers contain an oncogenic mutant Ras that forces growth, and in pancreatic and colon cancer, the mutation rates can be >50%. Activated Ras proteins directly activate one or more of a large, partially unidentified class of effector proteins. Ras proteins can control more than one effector at a given time, and the same Ras protein can control different effectors during different stages of tumor development. Identifying all the Ras effectors would not only reveal all of the potential pathways by which Ras proteins could dysregulate growth and cause tumors, but could provide biomarkers and possible therapeutic targets for many cancers. Until now, full identification of Ras effectors has been hindered by sensitivity issues due to relatively low affinity of effector-Ras binding, and by the difficulty of sorting through all of the 19,000 or so human gene products to find the remaining effectors. But we propose to apply a new combination of methods that is more sensitive than the conventional methods and allows for use of modern robotic technology to efficiently sort through all of these gene products to identify potential Ras effectors – we have already proved the capability of our method in preliminary experiments. We will test each of the identified potential effectors to determine that it indeed receives and relays signals from one or more of the Ras proteins to control growth in a panel of cancer cell lines. Our success will greatly extend knowledge of how tumors occur, as well as identifying biomarkers indicating which pathways are driving individual tumors and which members of that network could be targets for effective therapy. Furthermore, because Ras dysregulation is involved in a great many common tumor types, these benefits would have wide-ranging application in cancer treatment.