



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP160440

Project Title:  
Targeting the undruggable: a first-in-class inhibitor of the HIF-2  
transcription factor

Award Mechanism:  
Individual Investigator

Principal Investigator:  
Brugarolas, James

Entity:  
The University of Texas Southwestern Medical Center

### Lay Summary:

Kidney cancer is particularly prevalent in Texas. One third of patients present with metastasis and another third will develop metastases. In the metastatic setting, kidney cancer is incurable. Recent discoveries about the biology of kidney cancer have led to 7 new drugs. These drugs extend life expectancy, but do not cure. The drugs target two classes of kidney cancer drivers, growth factors and kinases. However, suitable drug targets have been exhausted and there are no good strategies to target proteins in other classes. The most important driver of kidney cancer, the HIF-2 complex, belongs to a class of proteins, transcription factors, that have traditionally been considered "undruggable." However, pioneering research at UT Southwestern (UTSW) led to a strategy to block HIF-2 function. This strategy builds on the discovery of a cavity within one of the two proteins that make up the HIF-2 complex that provides a foothold for a drug to change the shape of the protein and block HIF-2. In collaboration with Peloton Therapeutics, a company founded by UTSW faculty, a so called "first-in-class" drug was developed, which is now in clinical trials at UTSW to treat kidney cancer. We have been interested in 3 important questions: (1) will all kidney cancers respond and if not, which kidney cancers will respond; (2) will combinations with other drugs approved for kidney cancer treatment be more effective; and (3) as for other drugs, will resistance develop. We have evaluated these questions using mice that have been implanted with human kidney cancer. In previous studies we showed that human kidney cancer grows just as well in mice as in humans and that it is the same. Using this platform, we have identified 3 subtypes of kidney cancer that vary in their responsiveness to the drug. We have also identified a mechanism of resistance. In this proposal, we will evaluate the significance of the subtypes we have identified, explore drug combinations and tackle resistance.