

Imaging and targeting glycolytically driven oxidative stress using ascorbate

Principal Investigator:

- Kayvan R. Keshari, PhD - Memorial Sloan Kettering Cancer Center

Co-Principal Investigators:

- Lewis C. Cantley, PhD - Weill Cornell Medicine
- Manish Shah, MD - Weill Cornell Medicine

Abstract: Compelling recent work from our labs revealed that glycolytic and redox metabolism is deregulated in colon and pancreatic cancer and this may provide new opportunities for targeted treatment. More specifically, we have demonstrated that glucose metabolism is reprogrammed in those cancers to facilitate survival and proliferation. This metabolic reprogramming is under control of KRAS mutations. We have demonstrated the feasibility and the efficiency of a new therapeutic strategy for pancreatic cancer treatment that uses ascorbate, a natural product highly tolerated in human body. The effectiveness of this treatment combines the enhanced glycolytic flux by KRAS-mutant cancer cells together with a disruption of redox homeostasis.

Here we propose to develop non-invasive methods to interrogate KRAS-mutant tumors, which could undergo ascorbate treatment, using molecular and metabolic imaging techniques. Specifically, we will combine hyperpolarized ^{13}C -MRI and ^{11}C -PET to characterize patient derived xenograft models of pancreatic cancer. In these same models we will fully elucidate the metabolic reprogramming that occurs with therapy and assess which metabolic imaging strategy reflects the biology of the tumor using mass spectrometry approaches. This will then be applied in a clinical trial of high dose ascorbate in patients with KRAS-mutant tumors. The overarching aim of this proposal is to characterize the biochemical mechanism of response to ascorbate therapy and assess the ability of these non-invasive translational tools as a platform to select patients for treatment. Ultimately, this approach will provide a means of treating KRAS driven cancers, annotate patients who will respond and provide a means of developing future novel therapeutics to exploit this mechanism.