Real-time imaging of metabolite deregulation in cancer

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Abstract: The goal of this project is to fundamentally change how we study cancer metabolism by using a unique technology to develop a suite of metabolite sensors that will reveal cancer metabolite dynamics in real time *in vitro* and *in vivo*. A major characteristic of cancer is altered metabolism, leading to changes in the levels of intracellular metabolites that drive cancer progression. Most studies use mass spectrometry to study these metabolic derangements. However, mass spectrometry cannot reveal the level of metabolites in individual cells and cannot reveal the temporal dynamics of metabolite fluxes in cancer cells. We recently developed a novel type of genetically encoded metabolite biosensor composed of RNA. These RNAs are expressed in cells and exhibit fluorescence in proportion to the level of specific target metabolites. Importantly, this approach allows rapid development of fluorescent biosensors that can detect metabolites with high sensitivity and specificity. Here we will use this approach to generate fluorescent biosensors that detect metabolites reflecting the levels of each of the major cancer metabolic pathways. We will use an innovative approach to express these RNA-based biosensors at high concentrations in mammalian cells, thus enabling real-time imaging of cancer metabolites in cancer cells and in xenograft cancer models. Lastly, we will use these sensors to study the dynamic metabolic response to p53 induction and to determine how serine metabolism can be therapeutically targeted in tumors in mice. Overall, the new technologies described in this proposal will markedly accelerate our ability to study and therapeutically target cancer metabolism.