Research Synopsis:

In our lab, we focus on quantitatively understanding the regulation and function of cellular stress responses. These responses are important for a wide range of biological processes, including the responses to DNA damage and oncogene activation. Our work focuses on understanding the tumor suppressor protein p53. p53 is upregulated in response to numerous cellular stresses, including various forms of DNA damage. When activated, it can regulate the expression of over a hundred genes, affecting a cell’s ability to repair damage, divide, or undergo programmed cell death if damage is too great. p53 is one of the most frequently mutated proteins in cancer, and mutations in the circuit regulating p53 are believed to occur in almost all cancers. More recently, we are studying interactions between p53 and the important oncogene c-Myc, which is an amplifier of all gene expression in cells. To study these important cellular components, we employ a variety of approaches:

- We use long-term time-lapse fluorescence microscopy to quantitatively measure dynamical changes in the concentration, localization, and activity of cellular components. These measurements are made at the level of single cells, providing a wealth of information not observable from traditional measurement methods that rely on population averaging of data.
- We use synthetic biology approaches to perturb biological circuits, such as interfering with existing network connections using small molecule inhibitors or RNAi, or creating new circuit feedbacks and feed-forwards through genetic perturbations.
- We complement our experimental studies with computational modeling of biological circuits. These models enable us to more formally synthesize our experimental observations, and they serve as a predictive tool to better understand the effects of perturbations.

Several areas of future investigation include:

- identifying and characterizing p53’s dynamical response to other forms of stress
- determining the functional consequences of p53 dynamics on p53’s regulation of target genes
- developing therapeutic strategies to manipulate p53 dynamics as a novel therapeutic strategy
- exploring other stress response circuits that show complex dynamical behaviors