Professor Lockett’s research group is interested in developing model systems, new materials, and new analytical tools to study reactions on surfaces (chemical and biological) and the behavior of enzymes and cells in tissue-like environments. His research interests are broad, and researchers utilize a large number of analytical techniques to better understand the following areas: 3D Cell culture and oxygen’s role in tumor progression; in vitro drug metabolism models; adapting 3D culture system to support liver-like structures to perform metabolic stability, induction, and cytotoxicity screens in a high-throughput manner; and chemically modified surfaces for electrochemical sensors, catalyst supports, and photo-electrodes.

Professor Lockett received his bachelor’s degree in chemistry from University of Pittsburgh, his doctorate in chemistry from the University of Wisconsin-Madison, and was a post-doctoral fellow at George M. Whitesides.

For additional information, visit his website.

Oxygen is a master regulator of a number of cellular processes. In tissues, gradients of oxygen and nutrients extend radially from blood vessels. The gradients in these diffusion-dominated environments increase greatly when a blood vessel is occluded, or in the case of the tumors, when the rate of proliferation outpaces the rate of vascularization. The extent of hypoxia in tumors has been correlated with cancer aggressiveness, drug resistance, and invasiveness. Gradients of oxygen are also believed to direct cellular invasion from the solid tumor mass to neighboring healthy tissue.

Despite the pivotal role that oxygen plays in tumor biology, there are a limited number of in vitro assays able to quantify cellular morphology, gene- and protein-expression, or drug sensitivities in well-defined oxygen gradients. Due to the lack of experimental tools, many studies compare cellular differences at a single normoxic (21% O₂) and hypoxic (~0.2% O₂) condition. Monolayer cultures are also commonly used in these normoxia-hypoxia comparisons. These experiments provide a simplified view of oxygen-mediated regulation, overlooking the importance of gradients by exposing cells to a single oxygen and nutrient concentration. Evaluating a limited number of oxygen tensions has led to the inadequate interpretation that cellular responses to oxygen are a binary phenomenon, eliciting a particular hypoxic phenotype or not.

We are developing a 3D culture platform utilizing paper-based scaffolds to prepare tissue- or organ-like structures. We are able to engineer extracellular environments with specific oxygen or nutrient gradients, and to tease apart the nuanced responses of cells in gradients of different steepness and shape. In this talk, I will highlight the paper-based culture platform as well as other technologies we are developing to address three long-standing questions in tumor biology. First is the role that oxygen gradients play in directing cellular movement. We have recently shown that oxygen is a chemo-attractant in diffusion-dominated environments, and are exploring what additional extracellular conditions (e.g., gradient steepness, presence of overlapping nutrient gradients) promote this directed invasion. Second is the oxygen-mediated mechanisms through which hypoxic cells become drug resistant. In particular, we use invasion assays and tumor-like structures to evaluate the relationship between oxygen tension, active resistance (upregulation of drug efflux pumps), and passive resistance (altered metabolism or halted proliferation). Third is the relationship between hypoxia and hormone responsiveness in estrogen receptor alpha positive (ER+) breast cancers.