Oxidative C-H Functionalization of Biological Membranes: The Chemical Basis of Ferroptosis

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Hydrogen-atom transfer (HAT) reactions are among the most fundamental processes in chemistry, underpinning phenomena ranging from combustion and polymer degradation to enzymatic catalysis and radical-mediated C–H functionalization. HAT likewise lies at the heart of ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation (LPO) of biological membranes that contributes to neurodegeneration and ischemia–reperfusion injury following stroke or organ transplantation. Unlike virtually every other regulated cell death pathway, ferroptosis is executed not by a protein signalling cascade but by a self-propagating radical chain reaction, making it uniquely amenable to chemical modulation.

This seminar will introduce the chemical basis of ferroptosis and describe how principles of physical organic chemistry can be applied to understand—and ultimately control—LPO in living cells. I will discuss the discovery and characterization of new classes of highly effective ferroptosis inhibitors that suppress LPO through both HAT-dependent and HAT-independent mechanisms, quantitative relationships between molecular structure and anti-LPO activity, and the unexpected finding that inhibitor localization within cells can outweigh intrinsic chemical reactivity in determining anti-ferroptotic activity and efficacy in animal models of disease, including acute kidney injury and neurodegeneration.