Title: The Iron Core of Cancer: Clues and Opportunities

The iron metabolism of malignant cells, which is altered to ensure higher acquisition and utilization, motivates the investigation of iron-binding strategies in cancer treatment. Several iron scavengers are employed clinically to treat iron overload disorders; however, these systems are not designed specifically to target intracellular iron in malignant cells and currently no iron chelator has been approved for clinical use with a cancer indication. In this context, we seek to engineer contemporary iron-binding approaches in cancer research, particularly to improve our control of intracellular delivery and tumor selectivity as well as our understanding of the parameters correlated to iron deprivation in cell proliferation and malignancy. In a prochelation approach aimed at increasing intracellular specificity, disulfide reduction/activation switches are incorporated on iron-binding scaffolds resulting in intracellularly activated scavengers. We have applied this strategy to several tridentate donor sets including thiosemicarbazones, aroylhydrazones and semicarbazones. The resulting prochelator systems are antiproliferative in several cancer cell lines and do not result in the intracellular generation of oxidative stress. Consistent with iron deprivation, the tested prochelators lead to cell-cycle arrest at the G1/S interface and induction of apoptosis. Broadening the focus of our research to include not only cancer cells but also other tumor-associated cells, we are assessing the effects of our prochelators on macrophages, namely immune cells that are important components of the tumor microenvironment and primarily responsible for iron recycling in the human body.