Unique Highly Discrete Carbon Nanotubes (CNTs) for Tumor-Selective Delivery of Highly Potent Dual-Mechanistic Anticancer Agents

A key aspect in the development of effective anticancer agents centers on the ability to deliver these agents selectively to tumors or biological targets inherent to the tumor microenvironment, while leaving healthy cells intact. A long-standing program in our laboratory (and supported by numerous collaborations) has resulted in the discovery of several small-molecule anticancer agents that are highly potent against human cancer cell lines in vitro. A sub-set of these compounds is also effective at shutting down the blood supply to tumors, thus starving tumors of necessary nutrients and oxygen. Two delivery mechanisms will be investigated in order to increase selectivity of these anticancer agents for tumors and/or the tumor microenvironment. In one example these compounds will be chemically bonded to the inner core and outer surface of multi-walled carbon nanotubes (MWCNTs). A proprietary form of MWCNTs will be utilized (through a collaboration with Molecular Rebar Design, Austin TX) in which the tubes are clean, highly discrete, well dispersed (untangled), and functionalized in a controlled fashion. It is anticipated that these MWCNTs will function as excellent delivery vehicles by being of the right size and dimensions to escape through the holes in vasculature feeding tumors, which is known to be inherently leaky. This should release them site-specifically to the tumors that are fed by these vessels. In a second strategy several of these highly cytotoxic anticancer agents will be synthetically conjugated to linkers that are suitable to attach to antibodies. The antibodies will impart selectivity towards selected antigens in the tumor itself or in the tumor microenvironment. These antibody-drug conjugates (ADCs) are designed to home to the tumor, be cleaved from the linker by certain enzymes that are present in higher concentrations in the tumor (or tumor microenvironment), and then selectively release the potent anticancer agents through a fragmentation process. The actual antibody work will be done through collaboration (UTSW, Dallas, TX and others). In each example (MWCNTs and separately ADCs) the parent anticancer agent should be delivered selectively to the tumor and/or tumor microenvironment thus (ultimately) improving the overall treatment process (and potentially outcome) for the patient.