The Development of Deoxynyboquinone as a Personalized Anticancer Compound

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The major challenge in cancer therapy is to selectively destroy cancer cells in the presence of healthy tissue. One viable strategy relies on targeting the function of an enzyme which is overexpressed in cancer cells relative to healthy cells. NQO1 is a cytoprotective enzyme which is overexpressed in most solid tumors and which detoxifies quinone-containing substrates. However, a few quinones are rendered more toxic by the action of NQO1. We have discovered that deoxynyboquinone (DNQ) is a potent cytotoxin and generates toxic levels of reactive oxygen species (ROS) selectively in cancer cells through a bioreduction/oxidation process mediated exclusively by NQO1. Excitingly, DNQ is effective at reducing the size of tumors in a mouse model of cancer. Unfortunately, DNQ must be delivered at concentrations near the maximum tolerated dose in mice to achieve maximal efficacy. In addition, the poor aqueous solubility of DNQ necessitated the use of a formulation containing a high concentration of 2-hydroxypropyl-β-cyclodextrin (HPβCD) which would complicate treatment in human patients. Thus, we set out to discover derivatives of DNQ which are more soluble than, and equipotent to, the parent compound.

We report the synthesis and evaluation of a library of DNQ derivatives and the structure-activity and structure-solubility relationships derived therefrom. We show that a subset of these derivatives are equipotent to DNQ and are up to 4-fold more soluble in water, 250-fold more soluble in organic solvents, and 9-fold more soluble in an aqueous solution of HPβCD. Furthermore, we show that the most promising of these derivatives are tolerated by mice at doses up to 4-fold higher than DNQ. We predict that derivatives of DNQ will exhibit a broad therapeutic window in murine tumor models of cancer and will progress rapidly toward human clinical trials.