

Modulating oxidative stress as a strategy in the treatment hepatocellular carcinoma

Incidence of hepatocellular carcinoma (HCC), the most common form of liver cancer, has shown a dramatic progression. With a five-year survival rate of 15 %, HCC is also one of the deadliest form of cancer. Few therapeutic options exist for the advanced form of HCC including sorafenib and lenvatinib highlighting the need to develop additional therapeutic strategies.

Krebs cycle is a series of reactions responsible for the production of energy and for the generation of precursors that will be used for biomass generation such as lipid or nucleotide synthesis. Recent studies have demonstrated that blocking Krebs cycle at different levels generates anti-tumor activity in part by increasing the production of reactive oxygen species (ROS).

The aim of this project is to combine sorafenib or lenvatinib with molecules that target Krebs cycle to treat hepatocellular carcinoma by generating toxic levels of oxidative stress.

HCC cancer cells in 2D or 3D will be exposed to a panel of Krebs cycle inhibitory drugs in combination or not with sorafenib or lenvatinib. Cancer cell growth and death will be monitored by MTS proliferation assay and by flow cytometry. Levels of oxidative stress including reactive oxygen species, glutathione and NADPH levels will be monitored. Protective effects of anti-oxidant molecules such as vitamin C or N acetyl-cysteine will be tested. The most promising treatment combination will be tested in mice bearing tumor xenografts. Novel treatment strategies need to be developed for HCC. Results generated from this project could be easily translated in clinical trials as sorafenib, lenvatinib and Krebs cycle inhibitory drugs that will be used are already prescribed to cancer patients.