

“Nanoparticle-Based Gene-Silencing Therapy of Hepatocellular Carcinoma”

This abstract should express the purpose and essence of the proposed activity in language understandable to nonspecialists. Classified information should not be included. These abstracts are relied upon heavily by those charged with explaining the University's research programs to the public and the state government. Therefore, the importance of preparing them carefully cannot be overemphasized.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related deaths worldwide, and its incidence in the United States is rising rapidly. The vast majority of HCC patients have limited treatment options with resultant dismal prognoses.

Several molecular targets for therapy within the Wnt/ β -Catenin pathway and the receptor tyrosine kinase-activated pathways (RAF/MEK/ERK, PI3K/AKT/mTOR) implicated in the initiation and progression of HCC are being studied for the treatment of HCC. The initial clinical trials utilizing mono-therapy targeting a single pathway have produced disappointing results with limited efficacy, in part due to the complex web of compensatory feedback and crosstalk that exists between these signaling cascades. Combinatorial inhibition of proximal and downstream targets that can negate feedback responses, and concurrent down-regulation of parallel pathways with established crosstalk have demonstrated improved therapeutic efficacy in preclinical studies. However, combining systemic targeted therapies has been limited by the inability to effectively deliver potent doses of these agents to the tumor cells without affecting the surrounding normal tissue, resulting in cumulative toxicity for the patient.

We propose a novel targeted approach to HCC treatment using a previously established nanoparticle system that can effectively deliver multiple pathway inhibitors via the hepatic artery, hence overcoming these limitations.

This is an imminently feasible project proposal, the results of which will lead to additional extramural funding and patents for the University of Washington. The preclinical results from this project can rapidly be translated to the clinical realm employing hepatic arterial catheter-based therapies already established in our Liver Tumor Clinic.

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