Non-Technical Abstract

The long-term objectives of this research program are to develop a novel form of cancer therapy specifically for patients with tumors that have started in the liver or spread to the liver. Only a small minority of such cancers can be removed surgically, and current treatment options are inadequate. Patients with these tumors have a poor prognosis. Thus, there is strong rationale for development of new and effective therapies. Replication of viruses in tumor cells leads to their destruction, with liberation of daughter viruses that infect and destroy adjacent cancer cells in a process referred to as viral oncolysis. Research in animal models demonstrates that a common cold sore virus, Herpes simplex virus 1 (HSV-1), can be engineered (mutated) such that they destroy cancer cells preferentially relative to non-cancer cells. One specific mutant, rRp450, replicates preferentially in liver tumors rather than normal liver following administration into the blood supply of the liver. This selective viral replication dramatically reduces liver tumor burden and enhances animal survival. On the basis of these and several other preclinical studies, the National Cancer Institute Rapid Access to Intervention Development (RAID) program has taken responsibility of translating this lead discovery into an initial clinical trial. Specifically, RAID is responsible for production of rRp450 in a formulation suitable for administration to human subjects, formal studies of rRp450-induced toxicity in animals, and release of cGMP rRp450 to the Principal Investigator via the National Cancer Institute's Cancer Therapy Evaluation Program.

The proposed clinical trial studies the safety of 4 weekly administrations of rRp450 into the liver arterial blood supply in study subjects with unresectable liver tumors. While all eligible study subjects will have a diagnosis of a terminal cancer, disease must be limited to less than 50% of the liver; life expectancy must be at least 12 weeks; and no treatments may have been administered within 4 weeks of enrollment into this study. Important exclusion criteria include absence of underlying liver disease such as cirrhosis, seizure disorder, or spread of cancer to the brain. Study objectives are to [i] determine maximum tolerated dose and dose-limiting toxicity; [ii] study the biodistribution rRp450 in the body of study subjects after its administration; [iii] assess the study subjects' immune responses to rRp450; and [iv] correlate radiographic studies of the subjects (e.g. CAT scan) with pathologic studies (e.g. liver biopsies examined under the microscope). This clinical trial is designed primarily to study the relationship between dose-schedule and toxicity, and uses a standard algorithm for dose escalation between successive cohorts of study subjects. Data from this trial are a necessary first step to determine whether further clinical study of this novel and promising therapy is warranted. These data will also provide insight into rRp450 mechanism of action.