Phase I Trial of Systemic Administration of Edmonston Strain of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide, in Patients with Recurrent or Refractory Multiple Myeloma

Multiple myeloma is a disseminated malignancy of antibody-secreting plasma cells. The cells reside predominantly in bone and bone marrow where they secrete monoclonal immunoglobulin and proliferate to form discrete, well-vascularized tumors (myelomas) that often induce strong osteoclast activation with bone resorption. The monoclonal immunoglobulin provides a convenient and reliable marker of the disease burden and response to therapy. This year, myeloma will be diagnosed in almost 15,000 patients and will be responsible for 11,000 deaths in the United States. The disease is not curable with current therapy despite the use of high-dose chemotherapy and stem cell transplantation. Relapse after stem cell transplantation is the rule and survival is not significantly prolonged. New therapies such as thalidomide and bortezomib have significant activity against the disease but so far, have not been shown to improve survival. Indeed, the median survival of patients with this disease is 4 years.

Over the last few years, our laboratories have pioneered the use of recombinant measles viruses derived from the Edmonston vaccine strain to treat a variety of tumors in animal models. The rationale behind the use of these viruses is their potent and selective oncolytic effect on tumor cells while leaving normal cells relatively unharmed. The basis for this tissue selectivity is the over-expression of CD46 by myeloma cells, the receptor that is preferentially utilized by these viruses for cell entry. In addition, measles virus vaccines have an exceptional safety record since they have been given to millions of people worldwide with minimal toxicity and very rare mortality. Recently we engineered a recombinant measles virus that induces NIS expression in infected cells (MV-NIS). NIS is a plasma membrane protein that is physiologically expressed in a variety of tissues but mainly in the thyroid gland. NIS concentrates iodide ions in cells against an electrochemical gradient and provides the basis for radioiodide therapy of well-differentiated thyroid malignancies. MV-NIS retains the potent and selective oncolytic activity of the parent virus but in addition induces NIS expression. This allows the repeated and non-invasive monitoring of viral gene expression using ^{123}I followed by gamma camera imaging. In addition, in vivo studies show that MV-NIS has potent oncolytic activity against a variety of myeloma tumor cell lines.

In this protocol, we propose to explore the use of escalating doses of MV-NIS in a Phase 1 trial for patients with relapsed or refractory multiple myeloma. The study objectives are (1) to determine the safety and toxicity of the intravenous administration of MV-NIS without or with cyclophosphamide in patients with relapsed or refractory multiple myeloma, (2) to determine the maximum tolerated dose of MV-NIS administered intravenously, (3) to determine the time course of viral gene expression and elimination and the biodistribution of virally infected cells at various times points after virus administration using ^{123}I gamma camera imaging, (4) assess viremia, viral shedding and viral persistence after intravenous administration, (5) monitor the humoral immune response to the virus and (6) explore the anti-myeloma efficacy of the virus using

standard myeloma response criteria. The protocol is divided in two stages. During Stage 1, MV-NIS will be administered alone in escalating doses starting from $1x10^6$ $TCID_{50}$ up to $1x10^9$ $TCID_{50}$. The presence of pre-existing anti-measles immune responses might interfere with delivery of MV-NIS to myeloma cells. Thus in Stage 2 of the protocol we propose to pre-treat patients with intravenous cyclophosphamide that can suppress the immune response to the virus and allow more efficient infection and propagation of the virus in myeloma cells. In patients who are pre-treated with cyclophosphamide, the starting dose of virus will be 100-fold less than the MTD and slowly escalated in 3-fold increments with subsequent cohorts. Patients will be followed by radioiodine imaging and regular estimation of monoclonal protein levels to assess any anti-myeloma activity.

We also propose to perform comprehensive correlative studies aimed to understand the kinetics of viral gene expression, elimination kinetics, viremia and viral shedding. The study will require a maximum of 54 patients. The studies aimed to determine the MTD may require up to 24 patients and the study where patients are pretreated with cyclophosphamide prior to MV-NIS may require up to 30 patients. It is estimated that complete accrual for the study will take up to 4 years.