

## Scientific Abstract

A number of human cancers have been shown to be associated with characteristic mutations in genes governing the production of proteins involved in cell division. The *ras* oncogene, and its Ras protein gene product, are mutated in many solid tumors including colorectal, pancreatic, ovarian and non-small cell lung cancers as well as malignant melanoma. The proto-oncogene *ras* is mutated in approximately 20% of lung cancers, shows a strong association with smoking history, and has been associated with poor prognosis in several studies. Anti-cancer drugs which target Ras function have been disappointing. As a result, there is increasing interest in targeting Ras via immunotherapy. Post-operative therapy is the perfect platform to study anti-Ras vaccines given the availability of tissue for molecular testing and design of mutation-specific vaccines, as well as the minimal-residual disease state of post-op patients.

GlobeImmune's GI-4000 product series represents the first in a novel class of yeast based immunotherapeutics designed to stimulate antigen specific T cell responses to target proteins, in this case, the mutated *ras* gene products seen in a number of solid tumors. Non-clinical efficacy studies have demonstrated antigen specific tumor regression in a number of models and non-clinical safety studies have not demonstrated any significant toxicity other than local reaction at the injection site that is consistent with the type of delayed-type hypersensitivity (DTH) that would be expected from a product with this mechanism of action.

GI-4000 is a recombinant, heat-inactivated yeast (*S. cerevisiae*) engineered to express one of three mutated Ras oncoproteins. The Ras proteins contain two mutations at codon 61 (glutamine to arginine [Q61R], and glutamine to leucine [Q61L]), plus one of three different mutations at codon 12 (either glycine to valine [G12V], glycine to cysteine [G12C], or glycine to aspartate [G12D]). Thus, GI-4000 is manufactured as three individual product configurations with the subnames GI-4014, GI-4015, and GI-4016 depending on the mutated Ras oncoprotein the product is engineered to express.

Two clinical studies have been initiated. The phase 1 dose escalation clinical study (GI-4000-01) has completed enrollment and has demonstrated good tolerability through the highest dose tested (40YU). The Phase 2 clinical protocol (GI-4000-02), a randomized, double blind, placebo controlled study in newly diagnosed, resected pancreas cancer is still enrolling patients.

This proposed clinical study (GlobeImmune identification number GI-4000-03; Memorial Sloan-Kettering Cancer Center (MSKCC) I.R.B. Protocol, identification number to be assigned in August, 2007) will be an open label, single-institution phase 2 trial evaluating GI-4000 in subjects with non-small cell lung cancer treated with curative intent who are disease free at their first post-treatment re-staging assessment (1-4 months after completion of therapy). This study will enroll approximately 24 patients. Following enrollment and obtaining baseline history, physical examination, laboratory and immunologic studies, patients will receive GI-4000 for 3 weekly doses, followed by 6 monthly doses, followed by vaccinations every 3 months for up to 3 years. Administration of study drug will continue according to this schedule until study withdrawal, disease recurrence, or death. In addition to safety and immunology assessments, subjects will be evaluated for clinical outcomes such as progression free survival and overall survival compared to matched case controls from the same institution.