A Genetic Approach to the Adoptive T Cell Therapy for CLL—Progress Report
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1. The initiation of a clinical trial utilizing genetically targeted patient T cells to treat patients with chemotherapy-refractory CLL.

The main focus of our research program is to develop novel approaches for the treatment of CLL. Specifically, using gene therapy techniques, we have developed a means of genetically altering a patient's own immune cells (called T cells) to recognize a protein (called CD19) which is present on the surface of CLL tumor cells. In the laboratory, these modified T cells can recognize and kill a patient's CLL tumor cells. More significantly, in mice, we have found that such T cells can cure mice from tumors which express the CD19 antigen.

Based on these promising studies, we have initiated a Phase I trial to study whether we can generate these tumor killing immune cells from patients with CLL, and test the efficacy and safety this treatment approach. While the process of obtaining FDA approval for this study was lengthy, we received the go-ahead to begin this trial roughly 6 months ago. To date, we have treated 2 patients with at the lowest dose of modified cells. Neither patient experienced significant side effects while both developed transient decreases in tumor size and decreases of tumor cells in the blood. Although promising at this early stage, we hope for even better results as we treat patients at higher more clinically relevant doses of modified cells. I look forward to keeping the CLL Foundation updated on this trial in the future.

2. Generation of a CLL patient data base of peripheral blood and serum samples.

The main focus of our proposal to the CLL foundation was to generate and test a robust data base of patient T cell and tumor cell samples. I'm pleased to report that the data base currently has 42 samples from different CLL patients at all stages of disease. Furthermore, based on serum samples analyzed from patients enrolled in the clinical trial, we have made interesting observations on distorted levels of immune signaling proteins (termed cytokines) in patients with CLL. To this end, we have modified our blood sample collection to include collection of serum samples and we are in the process of analyzing these samples to assess cytokine levels in blood samples from CLL patients in comparison with healthy donor samples. We hope that these studies may give critical insight into the mechanisms of immune dysfunction in patients with CLL. Furthermore, we have utilized CLL foundation funds to generate retroviral stock to study whether T cells from patients with CLL are equally susceptible to gene therapy when compared to T cells from normal donors. Significantly, data generated from these studies are being combined with those generated from the clinical trial. These studies are ongoing. Over the next year we hope to continue increasing our data base (long-term goal is >100 patient samples), conduct cytokine studies on patient serum samples, and continue our studies on CLL patient T cell function. As the patient data base expands, we anticipate

generating increasingly meaningful data which will give us greater insight into the biology of CLL.

3. Optimizing gene therapy of T cells in patient samples.

I am further pleased to report that funding from the CLL foundation has enabled us to conduct a series of studies designed to optimize our ability to genetically modify T cells. These studies have been critical to the clinical trial. The significance of these experiments is reflected in the fact that these studies were recently published in a leading gene therapy journal (Human Gene Therapy). In light of the foundation's support of these studies, the CLL foundation was cited in the acknowledgements. I have attached a copy of this manuscript for your and the foundation's review.