

**Human Gene Transfer Clinical Protocol entitled:
A PHASE II STUDY OF REPEAT INTRANODAL INJECTIONS OF ADENOVIRUS-CD154 (Ad-
ISF35) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL
LYMPHOCYTIC LYMPHOMA**

SCIENTIFIC ABSTRACT

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are diseases characterized by accumulation of slowly-dividing mature-appearing monoclonal B cells in the blood, marrow, and lymphoid tissues. There is no cure for CLL / SLL, which is the most common form of adult leukemia – lymphoma in Western societies. Therefore, it is extremely important to develop novel therapeutic treatment strategies.

Recognizing that CD40/CD40 ligand (CD154) interactions play a critical role in immune activation, we propose to treat patients by directly injecting into pathologically enlarged lymph nodes with a replication defective adenovirus that induces expression of a functional and stable chimeric ligand of CD40 (CD154) – Ad-ISF35. This clinical protocol is the continuation of a phase I single intranodal injection study in patients with CLL in which we observed safety and tolerability with doses $\leq 3.3 \times 10^{10}$ viral particles (vp) per injection. More importantly, we observed objective clinical benefit in some of the patients that received a single intranodal injection of Ad-ISF35 (Castro JE et al, American Society of Hematology, Abstract/ presentation, 2009). The proposed treatment schema will include repeat dose intranodal injection of Ad-ISF35 every 2-4 weeks up to six injections total using a fix dose of 3.3×10^{10} vp per injection.

We hypothesize that injection of Ad-ISF35 will lead to expression of CD154 in the injected lymph node tissue and promote immune activation against leukemia – lymphoma cells. This study will be conducted to assess the safety and potential clinical benefit of this novel immunostimulatory therapy at Moores Cancer Center-University of California San Diego Cancer Center, La Jolla, CA. To participate in this study, male or female patients with or without previous history of chemotherapy for CLL or SLL should be at least 18 years of age.

The study objectives are the following:

Primary Objectives

- 1) Determine and monitor clinical and biological responses in patients treated with repeat intranodal injections of Ad-ISF35.

Secondary Objectives

- 1) Determine the safety of repeat administration of Ad-ISF35 injected directly into lymph nodes of patients with CLL/SLL.
- 2) Determine pharmacodynamic (PD) parameters in patients treated with repeat intranodal injections of Ad-ISF35.