

**NON -TECHNICAL ABSTRACT:** (State in layman's terms the application's broad, long-term objectives and specific aims, making reference to the potential public benefits of the project for California.)

Transposons or transposable elements are discrete DNA sequences that are found in multiple copies in most, if not all organisms. They move (i.e. transpose) through a “cut-and-paste” mechanism in which the DNA transposon gets excised from one chromosomal site and is subsequently reinserted elsewhere in the genome by a transposase protein. This process appears to require only a single transposase protein that acts *in trans* on virtually any piece of DNA sequence containing the transposon. Thus, there is very little dependence on host factors. This feature allows the DNA transposon to be active in a broad host range and different cell types. While transposons have been developed into gene delivery tools and used for transformation of bacteria, fungi, plants, and insects for a very long time, they have only very recently been demonstrated to be capable of jumping at high frequencies in vertebrate, including human cell lines. This progress has led to the development of a new generation of “cut-and-paste” transposons for gene therapy applications. Currently, most gene therapy trials have used viral vectors for permanent or transient transfer of therapeutic genes. However, the use of viral vectors presents serious drawbacks. These range from failure to establish stable transgene expression or elimination of the gene-modified cells to triggering of acute systemic toxicity because of immune reactions, and even inadvertent risk of oncogenesis and cancer development. Transposable elements provide a potentially powerful alternative to viral vectors and several transposon systems are being developed to overcome some of these limitations. The long-term goal of this proposal is to develop *Hvmar1* transposon-derived vectors that are suitable for gene therapy and other transgenic applications. We have recently detected transposition activity of the *Hvmar1* transposon from the butterfly *Heliothis virescens* using genetic mobility assays performed in developing *Drosophila* embryos. We will explore *Hvmar1*'s potential for gene therapy by testing the transposition and gene transfer ability of *Hvmar1* into cultured human cells, which will include studies in adult stem cells. To date, transposon-based gene delivery in human adult stem cells has not been reported. The transposon created in this study could potentially be used as an improved non-viral integrating vector for use in gene therapy experiments and have an important impact in the area of stem cell therapy.