

THE SCIENTIFIC ABSTRACT

Numerous studies in both human and animal systems have provided compelling evidence to indicate that the immune system can be directed to specifically recognize and destroy human tumor cells. The effector cell of antigen-specific anti-tumor immunity is the CD8+ cytotoxic T lymphocyte (CTL) specific for tumor-associated antigens (TAA). Clinical efforts to stimulate effective immunity have been limited, in part because most tumor antigens are restricted in expression to one or a few tumor types and further restricted to a fraction of patients with these types of tumors.

Recently, data have been published to suggest that cytochrome P450 isoenzyme 1B1 (CYP1B1), which is widely expressed in human cancer, may be a useful tumor antigen. In contrast to other cytochromes, CYP1B1 is not expressed in human adult liver and does not have a major role in hepatic metabolism. Detailed analysis of cancer and normal tissues by immunohistochemistry and western blotting has suggested that high level and constitutive expression of CYP1B1 is primarily limited to cancer tissues. In fact, CYP1 B1 protein is expressed in >95% of human tumors, irrespective of tissue origin. Additionally, CYP1B1 tumor expression results in processing and presentation of CYP1B1 peptides by human histocompatibility surface antigen-A2 (HLA-A2) molecules. Human T cells stimulated in the presence of at least one of these naturally processed peptides lyse tumor cells but not normal cells which do not express CYP1B1. Immunization of HLA-A2 transgenic mice with the relevant CYP1B1 peptides, or plasmid DNA encoding CYP1B1, elicits a specific T cell response. These and other data provide a rationale for the development of a cancer vaccine candidate to target CYP1B1.

ZYC300 (supplied by ZYCOS Inc) is a plasmid DNA, encoding CYP1B1, formulated within biodegradable Poly(DL-lactide-coglycolide) (PLG) microparticles. The plasmid contains a cytomegalovirus promoter to drive CYP1 B1 expression and the resulting protein contains point mutations that remove enzymatic activity. Animal data demonstrate that the protein is processed and the peptide epitopes are presented on the cell surface in the context of MHC class I molecules. A biocompatible microparticle system has been developed to facilitate the immunogenicity of the plasmid vaccine. The particles protect the encapsulated DNA from nucleases, and target it to phagocytic cells. Previous clinical experience with this type of DNA construct and microparticle formulation has demonstrated it's safety, biological activity and clinical efficacy in human papillomavirus infected patients with dysplasia of the uterine cervix. Previous clinical experience with ZYC300 demonstrated that immunization with the formulation elicited immune responses in a number of patients and that this response was likely to be dose dependent. In this submission, a Phase 1 clinical trial in advanced cancer patients is proposed to test the feasibility, safety, and potential immunogenicity of ZYC300 in combination with adjuvants including GM-CSF and Imiquimod. Because of the increasing evidence that regulatory T cells (T regs) inhibit the development of tumor immunity, half of the patients will be randomized to receive 14 days prior to immunization pre-dosing 2gm/m² of cyclophosphamide in an attempt to deplete T regulatory cells.