Introduction

Tarmogens [lipid-modified immunogens] are whole, heat-killed recombinant Saccharomyces cerevisiae strains engineered to express one or more major protein antigens, and activate both an immune response via Toll-Like Receptors (TLRs), as well as an adaptive, antigen-specific immune response. GI-5005 was engineered to express a hepatitis C virus (HCV) fusion protein comprised of large segments of NS3 protease and Core protein sequences. These proteins were chosen as targets for immunotherapy because they are essential for virus replication, contain multiple epitopes that are recognized by both CD4+ and CD8+ T cells in acute and chronic infections, and are highly conserved among the different HCV genotypes. GI-5005, by expressing multiple antigens, was designed to induce a broad cellular immune response, which is thought to be necessary to achieve a sustained viral response and HCV clearance in patients.

Preclinical Development of Yeast-Based Immunotherapy for Chronic Hepatitis C Virus Infection


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Tarmogen Technology

Heat inactivated, recombinant Saccharomyces cerevisiae engineered to express one or more major protein antigens, and activate both an innate immune response via TLRs, as well as an adaptive, antigen-specific immune response. GI-4014 (5 YU) was engineered to express a hepatitis C virus (HCV) fusion protein comprised of large segments of NS3 protease and Core protein sequences. These proteins were chosen as targets for immunotherapy because they are essential for virus replication, contain multiple epitopes that are recognized by both CD4+ and CD8+ T cells in acute and chronic infections, and are highly conserved among the different HCV genotypes. GI-5005, by expressing multiple antigens, was designed to induce a broad cellular immune response, which is thought to be necessary to achieve a sustained viral response and HCV clearance in patients.

Uptake of Transgenics by dendritic cells results in the activation of killer T cells against HCV-infected cells

Abstract

Background: Evidence suggests that control of hepatitis C infection in humans requires effective T-cell-mediated immunity. Previous studies have demonstrated that recombinant, heat inactivated, Saccharomyces cerevisiae yeast (xenomycins™) are phagocytosed by and directly activate dendritic cells that present disease-associated proteins contained within the Tarmogen to CD4+ and CD8+ T cells. Tarmogens are capable of mediating both therapeutic as well as prophylactic antigen-specific anti-tumor effects (Lu et al. 2004 Can Res 64, 5084). In this study, a Tarmogen that produces an HCV NS3-Core fusion protein (GI-5005) was evaluated for its ability to induce protective and therapeutic immunity in mice.

Methods: C57BL/6 and BALB/c mice were injected subcutaneously with GI-5005. Immunogenicity was determined using assays that measure antigen-specific lymphocyte proliferation, cytokine secretion, and cytotoxicity. A surrogate model for hepatitis C infection employing HCV antigen-expressing vaccine tumor cells implanted in mice was used to assess both preventive immunogenicity and therapeutic efficacy.

Results: Immunization with GI-5005 induced dose-dependent NS3 and Core antigen-specific cytotoxic T cell and helper T cell activity associated with secretion of IL-2, IFN-α, IL-12, IL-18, and TNF-α. Protective immunity was demonstrated in mice that were immunized prior to tumor challenge with NS3-expressing tumor cells. Therapeutic efficacy was demonstrated in mice that were immunized seven days after implantation of NS3-expressing tumor cells. No significant systemic adverse effects have been observed upon repeated administration of Tarmogen in mice, rats, rabbits, and macaques.

Conclusions: GI-5005 was found to elicit both protective and therapeutic cytotoxic T cell and helper T cell-mediated responses specific for HCV antigens. A Phase I study is being initiated to test GI-5005 in humans chronically infected with HCV.

Effect of Tarmogen dosage on specific lysis of EL4-rVV-NS3. The experiments were performed at an effector to target (E:T) ratio of 20:1.

Figure 1. T cells from GI-5005 immunized mice kill virus-infected cells expressing HCV NS3 or Core

Figure 2. Dose-dependent induction of CTLs with GI-5005

Table 1. Cytokine profiles from immunized mice

Table 2. Disease control in GI-5005 treated mice

Figure 4. Antigen-specific T cells in protected mice

Figure 5. GI-5005 overcomes antigen ignorance

Figure 6. GI-5005 eliminates established tumors

Figure 7. Dose-dependent cytokine production in response to GI-5005

Pre-clinical studies indicated that Tarmogens were well tolerated in animals given therapeutic doses ranging from 5-50 mg. The highest dose level tested (50 mg) was well tolerated and no reduction in body weight was observed.

Conclusions

- GI-5005 induces dose-dependent NS3 and Core-specific CTL and T+ helper immune responses in mice
- GI-5005 boosts pre-existing immune responses
- GI-5005 induces prophylactic immunity in mice
- GI-5005 induces therapeutic and protective immunity against HCV antigen-expressing tumors
- A Phase I study of GI-5005 in patients with chronic HCV infection is being initiated.