ASGR1-TLR8, an ASGR1-Directed TLR8 ImmunoTAC Therapeutic, is a Potent Myeloid Cell Agonist with Liver-Localized Activity for the Treatment of Chronic HBV

Peter Baum, Ty Brendler, Jeff Adamo, Li-Qun Fan, Jenny R. Chang, Hengyu Xu, Ben Setter, Brenda Stevens, Mike Comeau, Monica Childs, Ray Carrillo, David Purdy, Yvette Latchman, Robert Dubose, Graham Jang, Phil Tan, Sean Smith, Valerie Odegaard
Silverback Therapeutics, Seattle, WA | Contact information: info@silverbackx.com

Introduction

ASGR1-TLR8 ImmunoTACTherapeutic comprises a TLR8 agonist conjugated to an antibody directed to the liver-restricted ASGR1. ASGR1 is designed to promote functional cure of chronic HBV (cHBV). cHBV infection remains a global unmet medical need contributing to an estimated 887,000 deaths per year. Clinical and preclinical evidence demonstrates that effective IFN-$\gamma$, T cell and IgG anti-viral immune responses can lead to functional cure, and a major goal for therapy is increasing these immune-mediated responses. Prior studies have shown that TLR8 is particularly effective in generating IFN-$\gamma$-biased adaptive immunity through myeloid cell activation. Consistent with this, oral administration of a TLR8 agonist small molecule, CG-486, attained systemic activation in animal models of chronic HBV and has shown signs of clinical activity. However, toxicities due to systemic activation of TLR8 may limit dose and liver exposure in patients. We believe that a systemically delivered TLR8 agonist with liver-localized activity could better realize the potential for effective therapy and functional cure. There is significant unmet need for clinical therapies that can elicit a functional cure, which is defined as sustained loss of hepatitis B surface antigen (HBsAg) from the liver. Many of the approved therapies for cHBV have low functional cure rates or lack durability over time. Here we describe the activities of our ASGR1-TLR8 conjugate and an ASGR1 mouse surrogate (ASGR1-S) that demonstrate the potential of liver localized myeloid cell activation for promoting functional cure in cHBV. The presented data show:

- ASGR1 conjugate potently activates human myeloid cells in an ASGR1-dependent manner
- ASGR1-TLR8 myeloid activating activity is a strong $\gamma$-secretase-dependent determinant
- ASGR1-S lowers viral DNA titers 2.5 logs in mice

Conclusions

- ASGR1-TLR8 ImmunoTAC therapeutic, designed to activate an anti-HBV response by liver-localized activation, potently activates myeloid cells in an ASGR1-positive cell dependent manner
- ASGR1-TLR8 myeloid activation promotes a strong IFN-$\gamma$ response and cell activation in co-culture assays
- ASGR1-S drives HBsAg seroconversion with lowering of HBsAg and viral DNA titers, without evidence of liver damage in an AAV-HBV mouse model
- ASGR1-S significantly induces IFN-$\gamma$-anti-HBV and HBsAg T cell responses as well as an anti-HBsAg B cell response

Together, these data support the continued preclinical development of ASGR1-TLR8 as a potential future treatment for patients with CHBV.