Identification and Characterization of a Potent Anti-Human TIM-3 Antagonist

Jean da Silva Correia, Patty McNeely, Minjee Do, Larry Altbelt, Mark Chhoa, Geoff Tomlinson, Joe Sheller, Marilyn Kehry, Margaret Malone, Haley Laken*, David J. King

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Abstract

The activation of anti-tumor immunity through the blockade of immune checkpoints has become one of the more promising approaches to tumor therapy. Significant clinical activity in a number of settings has been shown through the blockade of PD-1 or CTLA-4, although there remains room for improving the efficacy of these agents. TIM-3 [T-cell immunoglobulin and mucin-domain containing]-B has been reported to play a role as an additional immune checkpoint which may limit anti-tumor T-cell responses. To identify potential therapeutic molecules that could enhance the activity of anti-PD-1 therapy in patients, we have generated a panel of human tumors of both origins using SHM-REX®, which combines mammalian cell display of human IgG with somatic hypermutation in vitro to select and mature antibodies with desired biological activities. Potent anti-TIM-3 antagonistic antibodies, with pAb affinities for human TIM-3 were identified. These antibodies enhanced T cell function at low nanomolar concentrations as measured by direct cytotoxic proliferation in vitro, representing the most potent anti-TIM-3 antibodies known. In addition, anti-TIM-3 antibodies augmented T cell activation in a dendritic cell/T cell mixed lymphocyte reaction. Assays were developed to evaluate the activation of endogenous inhibition of multiple checkpoint molecules, which demonstrated that combination of anti-TIM-3 therapy with a novel anti-PD-1 antibody increased specific human T cell activation over that seen with blockade of single antibodies. We have shown that the activity of anti-TIM-3 antibodies was tested in several syngenic tumor models, including MC38. Anti-TIM-3 alone showed some inhibition of established MC38 tumor growth but was less potent than anti-PD-1 alone, while the combination of both antibodies using SHM-REX® resulted in sustained tumor regressions. These data suggest that therapy with anti-TIM-3 and combination immunotherapy with anti-TIM-3 and anti-PD-1 is worthy of clinical evaluation.

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