A novel fully synthetic dual targeted EphA2/CD137 Bicycle® peptide induces tumor localized CD137 agonism

ABSTRACT

• 4-188 (CD137) is a member of the TNFR superfamily involved in stimulation of several immune cell types, including T cells and NK cells. CD137 is well validated pre-clinically, as an agonist with anti-CD137 antibodies is effective in vivo, however, clinical utility to date has been limited by dose dependent hepatotoxicity.

• We hypothesized that the unique properties of Bicycle® are amenable to develop tumor targeted agonists that would offer significant advantages in terms of safety over other approaches. This lead to the development of tumor-targeted immune cell agonists (TICA®), that stimulate immune cells exclusively at the tumor site.

• EphA2 is highly expressed in several tumor types of high unmet medical need. EphA2/CD137 TICAs contain two Bicycle® arms, one targeting EphA2 (target arm target) and the other targeting CD137 (immune arm).

• Here, we present substantial preclinical data demonstrating the potent immunomodulatory activity of EphA2/CD137 TICAs.

• EphA2/CD137 TICA’s leads to an increase in CD8+ T-cells locally in tumor tissue in vivo.

• Intermittent dosing of the molecule leads to a robust anti-tumor activity in MC38 syngeneic mouse model, and more importantly leads to the development of immunogenic memory.

• These findings provide a strong rationale to further develop first-in-class Bicycle TICAs to potentially treat EphA2 expressing cancers.

INTRODUCTION

Figure 1A: Schematic of the process for generating CD137 TICA molecules using Bicycle®: Phage screening identified CD137 monoclonal antibodies (mAbs) and the lead monoclonal CD137 binder K5+M10 (SPE). CD137 and tumor targeting monomeric were synthesized with varying attachment points, affinities, physiochemical properties. TICAs of varying valency (1:1, 1:2 and 1:2) were constructed using different linkers. TICAs were optimized to obtain the desired PK and pharmacological properties.

Figure 1B: The concept of Bicycle tumor targeted immune cell agonist (TICA®):

RESULTS

Table 1: Tumoricidal activity in syngeneic MC38 mouse model.

Figure 2A: EphA2/CD137 TICA’s display >50% target coverage.

Figure 3: EphA/CD137 TICA’s promote cytokine secretion in PBMC / cancer cell co-culture experiments.

Figure 4: EphA2/CD137 TICA leads to tumor localized increase in CD8+ T cells in HT-29/BMPC engraftment model.

Figure 5: Intermittent dosing of BCY12491 leads to significant anti-tumor activity in syngeneic MC38 mouse model.

Figure 6: Complete responder animals to BCY12491 treatment were re-inoculated with MC38 tumor cells 61 days after the initial treatment initiation. In mice matched naive control mice (100% tumor growth), no tumor activity was observed in the complete responder mice implying a development of immunogenic memory (Tumor volumes are mean ± SD).

Figure 3B: EphA2/CD137 TICA’s display >50% target coverage.

Figure 4A: CD4+CD8+ T cells (Tumor) by flow cytometry.

Figure 4B: CD4+CD8+ T cells (Blood) by flow cytometry.

Table 1: Tumoricidal activity in syngeneic MC38 mouse model.

Table 2: EphA2/CD137 TICA’s exhibit highly potent, tumor localized ephA2 dependent stimulation of CD137 in precocellular models.

Table 3: Intermittent dosing of an EphA2/CD137 TICA leads to robust anti-tumor activity. IV/PD simulations indicate that sustained plasma exposure and continuous target coverage is not required for efficacy.

CONCLUSION

• EphA2/CD137 TICAs exhibit highly potent, tumor localized ephA2 dependent stimulation of CD137 in precocellular models.

• Intermittent dosing of an EphA2/CD137 TICA leads to robust anti-tumor activity. IV/PD simulations indicate that sustained plasma exposure and continuous target coverage is not required for efficacy.

• Based on these experiments, the pharmacokinetics and biological properties of TICAs are potentially suitable for once weekly dosing in the clinic.

• Bicycle Therapeutics are advancing an EphA2/CD137 TICA clinical candidate.

References