Quantitative analysis of CD137 and Nectin-4 expression across multiple tumor types to support indication selection for BT7480, a Bicycle tumor-targeted immune cell agonist™ (Bicycle TICA™)

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ABSTRACT

Bicycles are synthetic constrained peptides with antibody-like affinities that are selectively, readily penetrate tumor tissue, have relatively short half-lives, and can be chemically linked together to generate multifunctional molecules. BT7480 is a Bicycle TICA™ that binds both CD137 and Nectin-4 on cancer cells to deliver a potent anti-tumor immune signal in Nectin-4 expressing tumors. Nectin-4 has been reported to be highly expressed in a wide range of human solid tumors, however the expression of CD137, abundance and localization of CD137+ immune cells in Nectin-4+ tumors are unknowns. A translational and informatics pipeline was established to interrogate the human tumor microenvironment to identify patient populations most likely to benefit from BT7480, which is being developed as a potential first-in-class molecule for the treatment of high unmet need cancers associated with Nectin-4 expression.

INTRODUCTION

Nectin-4 is a cell adhesion molecule that is highly expressed in a wide range of solid tumor indications.1-3

RESULTS

CD137 and Nectin-4 transcripts are co-expressed across multiple solid tumor types

Figure 1: BT7480 is a fully synthetic bicyclic TICA™ that delivers CD137 immune agonist activity to Nectin-4-expressing tumors. CD121 is a co-receptor that drives T cell function and survival and is also expressed on NK and myeloid cells. Nectin-4 is a cell adhesion molecule that is highly expressed in a wide range of solid tumor indications.1-3

Figure 2: A) Transcription co-expression analysis across TCGA. B) Frequency of samples within the top 10 indications expressing high levels of CD137 and Nectin-4 transcripts across TCGA are shown.

Spatial proteomic profiling of Nectin-4+ and CD137+ cells using Multiom™ technology

Figure 3: A) 43 FFPE tumor samples were profiled for target expression, immune cell infiltrate and spatial proteomic analysis using proprietary BicycleMulti™ panel. B) 20 ROIs were selected from whole tissue slides (example H&E sample is shown) or 1 ROI from each TMA core was selected for image analysis. C) A single ROI from each H&E sample was selected for manual cell counting. D) Nectin-4+ and Nectin-4- tumors were stained with a 1:10 dilution of Nectin-4 antibody and detected with a Nikon microscope with a 40x objective and 10x Plan-Apochromat objective. E) Nectin-4 FISH expression in a prostate cancer tumor sample is shown. Nectin-4 is highly expressed in the tumor stroma but not within the tumor. F) A) Nectin-4+ and Nectin-4- tumors were stained with a 1:10 dilution of Nectin-4 antibody and detected with a Nikon microscope with a 40x objective and 10x Plan-Apochromat objective. E) Nectin-4 FISH expression in a prostate cancer tumor sample is shown. Nectin-4 is highly expressed in the tumor stroma but not within the tumor.

Figure 4: A) CD137 and Nectin-4 proteins detected in >50% cancer samples tested

Spatial profiling of immune infiltration and tumor immunity

Figure 5: A) Ploietic analysis of Nectin-4 and CD137+ expression across H&E tumor samples. Nectin-4+ and CD137+ tumor cells are identified by Nectin-4+ and CD137+ immunofluorescence detection in H&E slides. B) Frequency of samples co-expressing Nectin-4 and CD137+ in the protein level (>1% positive cells) is shown.

Spatial proteomic profiling of Nectin-4+ and CD137+ cells using Multiom™ technology

RESULTS

Majority of CD137+ immune cells in Nectin-4 expressing tumors are T cells and macrophages

Figure 6: A) Subsets of CD137+ immune infiltrates detected across samples are included and include T cells (CD3+CD4+ and CD3+CD8+), macrophages (CD16+CD14+), NK cells (CD56+), and B cells (CD19+). B) Data are total cells per tissue sample normalized to total CD137+ cells detected across samples within each indication. C) Average frequency of CD137+ immune cell subsets across each indication is shown.

CONCLUSION

Results from this study support prioritization of indications for BT7480 clinical development and the utility of the Multiom™ assay to monitor Nectin-4 and CD137 expression and to demonstrate proof-of-mechanism in the BT7480 FIH clinical trial expected to start in 2H-2021.

REFERENCES

4. Data generated by the TCGA Research Network.

Bicycle Therapeutics Limited
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