A novel fully synthetic dual targeted Nectin-4/4-1BB Bicycle® peptide induces tumor localized 4-1BB agonism

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ABSTRACT

- 4-1BB (CD137/TNFRSF9) is a costimulatory receptor belonging to the TLR receptor superfamily.
- Despite compelling preclinical data, 4-1BB agonistic antibodies have been hampered by failure to deliver pharmacokinetics and efficacy in class I (1, 2). Next-generation strategies are focused on bispecifics.
- Bicycle® platforms allow us to rapidly generate fully synthetic molecules linking the CD137 ligand (CD137L) to a target receptor of choice.
- Nectin-4/4-1BB TICAs represent a new class of drugs that have antibody-like affinity and selectivity to their targets, unlike traditional antibody bispecifics. Applications of Nectin-4/4-1BB TICAs are in bladder, pancreatic, and lung cancers.

INTRODUCTION

Image screening, affinity maturation, and chemical optimization resulted in the lead CD137-binding Bicycle®. This novel class of drugs allows for rapid generation of fully synthetic bispecifics. "Bicycling the Bicycle®" is a broad range of tumor antigen-binding Bicycle® at different dilutions.

RESULTS

Bicycle® platforms display superior pharmacodynamic efficacy to single-dosing regimens across strategy and cell line.
- Nectin-4/4-1BB TICAs are cytotoxic in primary immune cells and reporter assays to induce systemic and intratumoral T-cell expansion.
- Nectin-4/4-1BB TICAs induce complete regressions and resistance to re-challenge in immune competent models with interspecies dosing.

CONCLUSIONS/SUMMARY

- Bicycle Therapeutics is building a new generation of chemically synthetic (CBE) tumor antigen targeted CD137 agonists.
- Next-generation strategies are focused on bispecifics.
- Nectin-4/4-1BB TICAs are highly expressed on numerous tumors, including bladder, pancreatic, and lung cancers.

REFERENCES


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