Establishment of an ex vivo tissue culture platform as a preclinical model to assess the mechanism of action of Bicycle® tumor-targeted immune cell agonists in NSCLC

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ABSTRACT

The translation of drug discovery to bedside for cancer therapy is beset with only 35% of anti-cancer compounds getting past phase III clinical trials. Since the tumor microenvironment is complex, there is a need for a relevant preclinical model to bridge the gap between tumor behavior and clinical therapeutic response for novel therapies.

We have developed a novel class of modular synthetic drugs, termed Bicycle® tumor-targeted immune cell agonists (BTICAs), which are multifunctional complexes comprised of constrained bicyclic peptides. 1

To investigate the mechanism of action of Bicycle® TICAs in a tumor model system, here we describe the development and optimization of an ex vivo organotypic histoculture model that uses freshly resected human non-small cell lung cancer (NSCLC) tumor tissue and preserves the tumor microenvironment and heterogeneity.

INTRODUCTION

CD137 and Nectin-4 proteins are highly co-expressed in human lung tumors. Nectin-4 and EphA2 protein detected at baseline in NSCLC tumors with variable expression profile. Some tumors show high expression of both Nectin-4 and EphA2, while others show low expression.

RESULTS

Tumor tissue stability and integrity was preserved up to 72 hours in culture. A heterogenous protein expression profile for Nectin-4 and EphA2 was observed in the tested samples. The tumor explants were infiltrated with viable immune cells. We were also able to elucidate a T cell-mediated cytokine response in the tumor area as shown with arrows (B). On average, about 14% CD3+ T cells were detected in the tumor area.

CONCLUSIONS

We demonstrate a rapid and reproducible ex vivo histoculture platform that is potentially valuable to evaluate functional proof-of-concept of Bicycle® TICAs molecules in a human model system. Our preliminary data shows NSCLC tumor explants can maintain tissue integrity and tumor cell viability up to 72 hours in culture. A heterogenous protein expression profile for Nectin-4 and EphA2 was observed in the tested samples. The tumor explants were infiltrated with viable immune cells. We were also able to elucidate a T cell-specific cytokine response within 48 hours that suggests our histoculture platform can inform and functional tumor infiltrating lymphocytes (TILs).

REFERENCES

1. Bicycle® (http://www.bicycletx.com)
3. Challita-Eid PM, et al., Cancer Res 2021;81:6059-6075
8. Images created with BioRender.com
9. Surface CD163 expression induced on CD8+ T cells post T cell stimulation

Figure 1: Establishment of an ex vivo tissue culture platform as a preclinical model to assess the mechanism of action of Bicycle® tumor-targeted immune cell agonists in NSCLC. A. Patient pathological information is shown in the table (N=6). B. Tumor tissue viability and integrity was measured using a single stain immunohistochemistry assay (IHC) demonstrating maintenance of tissue integrity up to 72 hours in culture. C. Nectin-4 and EphA2 protein detected at baseline in NSCLC tumors with variable expression profile. Some tumors show high expression of both Nectin-4 and EphA2, while others show low expression.