Bicycles are small (~1.5 kDa), chemically synthetic, structurally inherent disadvantages in this application. Thus, alternative approaches are warranted.

We have developed a novel modular compound with high affinity and selectivity to NK cell receptors with specific tumor binding arms: EphA2 (BCY17226), MT-1 (BCY18046), or PD-L1 (BCY18053). ADCC-capable anti-EGFR antibody was used as positive control. Luminescence values for no NK-TICA™ addition is arbitrarily shown as 5 x 10⁻¹⁵ M.

**RESULTS**

We have developed a novel modular compound with high affinity and selectivity to NK cell receptors with specific tumor targeting potential. In vitro, selective binding of our Bicycles to receptor-expressing cells and the capability of the bifunctional molecule to induce primary human NK cell function in vitro.

**CONCLUSIONS**

- Building on success with CD137 Bicycle® TICAs, the Bicycle® platform has now been successfully applied to build prototype NK cell engagers.
- NK-TICAs drive NK cell-mediated tumor cell killing and cytokine production in vitro and as such have the potential to catalyze the development of durable anti-tumor immunity in tumor types not well served by current therapies.

**REFERENCES**

- Lari et al. PEG-Boston (2017)
- Images created with BioRender.com (2022)
- PDB4942, 3eap, 1hzh, Gauthier et al. (2021)
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**INTRODUCTION**

Natural killer (NK) cells are immune cells that can detect and eliminate tumor cells and bridge innate to adaptive immune responses. Tumor Natural killer (NK) cells are immune cells that can detect and eliminate tumor cells and bridge innate to adaptive immune responses. Tumor Natural killer (NK) cells are immune cells that can detect and eliminate tumor cells and bridge innate to adaptive immune responses. Tumor Natural killer (NK) cells are immune cells that can detect and eliminate tumor cells and bridge innate to adaptive immune responses. Tumor Natural killer (NK) cells are immune cells that can detect and eliminate tumor cells and bridge innate to adaptive immune responses. Tumor

**GENERATION OF COMPONENT PARTS TO CONSTRUCT NK-TICAs**

Using our unique phage display screening platform, we identified high affinity, selective binders to NKp46. For proof-of-concept, NKp46 binding Bicycles were conjugated with an EphA2 binding Bicycle. The EphA2 and PD-L1 binding Bicycle® is specific and potent with ~1.7 nM and ~5 nM, respectively, evaluated by SPR (Upadhyaya et al., 2021). The MT-1 Bicycle® is specific and potent with ~15 nM evaluated by SPR (Lari et al., 2017). The resulting bifunctional NK-TICAs were then tested in primary human cell-based functional models.

We have developed a novel, fully synthetic tumor binding and NKp46 binding Bicycle™ that is capable of inducing NK cell activation in the presence of tumor. As an immunotherapeutic agent, Bicycle’s NK-TICA™ molecules are positioned to engage NK cells in a tumor antigen dependent manner to kill and drive adaptive immunity in solid tumors.