CUE-101, a novel Fc fusion protein for selective targeting and expansion of anti-tumor T cells for treatment of HPV-driven malignancies

Steven N. Quayle1, Dharma Raj Thapa1, Sandrine Hulot1, Alyssa Nelson2, Lauren Kraemer1, Zohra Merazga1, Robert Ruidera1, Dominic Beal1, Gurpenna Saggio1, Maria Hackett1, Mark Haydock2, Jonathan Soriano2, Luke Witt1, Simon Low1, Saso Cemerski2, Natasha Girgis1, Emily Spaulding1, John F. Ross1, Anish Suri1, Rodolfo Chaparro3, Ronald Seidel1, Kenneth J. Pienta2, Mary C. Simcox1

1Cue Biopharma, Cambridge, Massachusetts; 2The James Buchanan Brady Urological Institute and the Department of Urology, Johns Hopkins School of Medicine, Baltimore, Maryland

**Background**

- Human papilloma virus (HPV) is responsible for 72% of oropharyngeal, 70% of cervical, 90% of anal, and 71% of vulvar, vaginal, or penile cancers, causing significant morbidity and mortality worldwide. Innovative therapies are urgently needed for these malignancies, particularly in the largely incurable metastatic setting.
- The E7 oncoprotein is constitutively expressed in HPV-associated cancers, is necessary for initiation and maintenance of malignant transformation, and is genetically conserved in cancer (Minarelli 2017).
- Clinical trials of agents for HPV-targeted T cell therapy include demonstration of complete regression of metastatic cervical cancer upon adoptive transfer of tumor-infiltrating T cells (Stevanovic 2015; Stevanovic 2017).
- The E7 sequence, including that encoding the E7-8-10 peptide in CUE-101, is maintained in cancer and this epitope is immunodominant in humans (Ressing 1995).
- Immuno-STAT (R) molecules are engineered to selectively modulate the activity of antigen-specific T cells in situ.

**Methods**

- CUE-101 cellular binding, specificity, TCR- and IL-2 receptor (IL-2R)-induced signaling, and induction of activation and cytotoxic T lymphocyte markers, were measured using flow cytometry with human E7-specific CD8+ T cells (Astarte Biologics, Bothell, WA).
- Enzyme-Linked Immunosorbent (ELISpot) assays were performed to measure peptide-specific secretion of interferon (IFNγ).
- Selective expansion of HLA E7-specific CD8+ T cells by CUE-101 was performed from primary human PBMCs in vitro, and in HLA-A2 transgenic mice in vivo.
- Anti-tumor efficacy with a murine surrogate molecule (mCUE-101) was assessed in the TC-1 syngeneic tumor model, and antigen-specific T cell expansion in vivo was measured via tetramer staining.

**CUE-101 selectively binds antigen-specific T cells**

**CUE-101 selectively elicits effector cytokine production**

**CUE-101 selectively expands HPV E711,26-specific CD8+ T cells from healthy human PBMCs**

**CUE-101 selectively expands HPV E711,26-specific CD8+ T cells in naive HLA-A2 transgenic mice**

**Conclusions**

- CUE-101 demonstrates selective binding, receptor signaling, effector T cell cytokine secretion, and expansion of HPV E711,26-specific human primary CD8 T cells.
- A murine surrogate of CUE-101 inhibits the growth of E7-expressing TC-1 syngeneic tumors, selectively expands antigen-specific CD8+ T cells in the tumor and periphery, and generates immunologic memory against TC-1 tumor cells.
- Increased expression of PD-1 was observed in tumor-infiltrating antigen-specific T cells after Immuno-STAT treatment, and combination therapy with PD-1 blockade further enhanced anti-tumor activity in the TC-1 model.
- The novel mechanism of action of CUE-101, namely targeted activation of tumor-antigen-specific CD8+ T cells via delivery of reduced affinity mutant IL-2, supports its increased potential for anti-cancer efficacy and reduced toxicity relative to non-targeted forms of immunotherapy.