Immuno-STAT™ *(Selective Targeting and Alteration of T cells)* Platform: Targeting Tumor Heterogeneity and Tumor Escape Mechanisms

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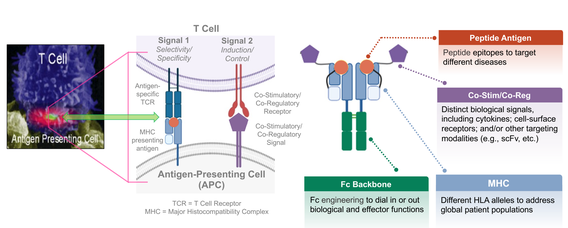
Introduction

Immuno-STATs™ (ISTs) are rationally engineered biologics comprised of a bivalent peptide-MHC complex and multivalent co-stimulatory molecules built on an Fc framework to enable stability, valency, favorable PK and manufacturability. Modularity of the IST framework enables targeting a variety of tumors by engineering different tumor-antigen epitopes in the pMHC complex. The CUE-100 series ISTs harness an affinity attenuated IL-2 variant (IL-2v) as a co-stimulatory signal. Our lead biologic, CUE-101, presents an HPV E7 T cell epitope and is now in a Phase 1 monotherapy trial in second-line or later recurrent or metastatic head and neck cancer, where early favorable signs of tolerability, pharmacodynamics, and anti-tumor activity have been observed. CUE-102, our second clinical candidate, presents a Wilms' tumor 1 (WT1) epitope and is expected to enter the clinic in 2022 to treat patients with WT1-positive malignances. Building on the CUE-100 series framework, our Neo-STAT™ platform contains an MHC with an "empty" peptide-binding pocket into which a TAA can be conjugated, thus efficiently and economically addressing tumor heterogeneity. Our RDI-STATs (Redirected Immuno-STATs) further expand the IST platform by redirecting the pre-existing protective viral-specific T cell repertoire to target tumor cells via scFv moieties. RDI-STATs circumvent tumor escape mechanisms linked to HLA loss or defects in antigen-presenting pathways. These IST platforms avoid systemic T cell activation and reduce the risk of cytokine release syndrome versus approaches that rely on global, unspecific T cell activation. We demonstrate here pre-clinical and clinical data supporting the mechanism of action of our three platforms to enhance anti-tumor immune responses.

Concept

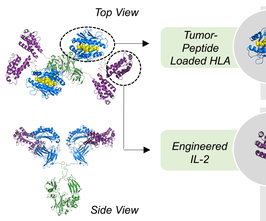
Selective and specific modulation of the anti-tumor immune response are of foremost importance for increasing therapeutic efficacy while not compromising patient safety. Many current therapeutic approaches deploy modalities that non-specifically enhance immune activation, which have not translated into meaningful benefit for the majority of patients suffering from cancer. To that end, we believe our therapeutic platform provides a unique opportunity to target tumor-specific cellular components of the immune system to selectively enhance anti-tumor immunity while avoiding toxicities associated with systemic immune activation. Importantly, drug candidates generated from our **Immuno-STAT** and derivative platforms are stable, off-the-shelf, engineered protein molecules that are suitable for IV or SQ administration. Importantly, these molecules are manufactured by well-established and efficient methods and do not require any *ex vivo* manipulation of immune cells.

Immuno-STAT design



The rationally engineered and modular biologics of the Immuno-STAT platform incorporate natural biological signals ("cues") for selective engagement and modulation of disease-relevant T cells.

IL-2v based CUE-100 Immuno-STAT series

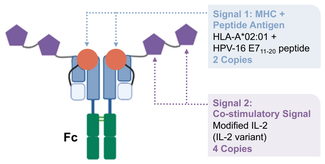


"Signal 1" engagement of T cells via their T cell receptor (TCR):
- **Selective delivery of an engineered IL-2 variant (IL-2v) to tumor-specific T cells**
- **Enables priming and expansion from naïve and pre-existing T cell repertoire**

"Signal 2" engagement with engineered IL-2v:
- **Abrogate binding to IL-2Rα to minimize regulatory T cell (Treg) activation**
- **Attenuate binding to IL-2Rβ to enable selective activation of tumor-specific T cells due to "Signal-1" guided IL-2 (which minimizes activation of irrelevant T cells)**
- **CUE-100 series is "not alpha *plus*" thus having a differentiated mechanism of action over other "not-alpha" IL-2 variants**

The CUE-100 series framework is designed to selectively deliver modified IL-2 to tumor-specific T cells.

CUE-101: Leading drug candidate



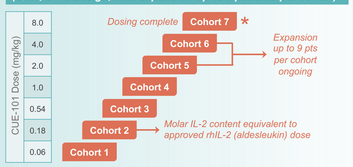
- HPV is recognized as a growing driver of head and neck cancer in the US; despite treatment with current standards of care, >50% of patients with advanced disease will experience recurrence
- The HPV-16 E7 protein is a primary driver of tumorigenesis and the E7 peptide presented by CUE-101 is a highly conserved T cell epitope and is immunogenic
- The CUE-101 clinical development strategy builds upon robust translational preclinical data[1] and patient stratification (i.e., CUE-101 is designed for patients that are HLA-A*02:01 and HPV-16 positive)

1. Quayle et al., CUE-101, a Novel E7-pHLA-IL2-Fc Fusion Protein, Enhances Tumor Antigen-Specific T-Cell Activation for the Treatment of HPV16-Driven Malignancies. *Clin Cancer Res 26:1953-1964,* 2020. DOI: 10.1158/1078-0432.CCR-19-3354.

Ongoing Phase 1 monotherapy clinical trial of CUE-101 in heavily pretreated patients with HPV+ head and neck squamous cell carcinoma

Indication: HPV+ Recurrent or metastatic head and neck cancer with confirmed progressive disease
Heavily pretreated: Refractory or resistant to 1st line platinum-based chemotherapy and/or CPIs

Part A: Monotherapy Dose Escalation
(Q3W, 3 + 3 design, with expansion up to 9 patients per cohort)



Part B: Monotherapy Expansion
(up to 20 total patients)

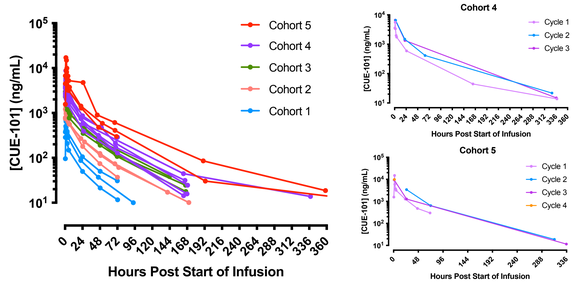
Expansion dose (RP2D) to be determined by mid-2021

- **Eligibility (Part A and B)**
  - HPV-16+ Head and Neck Cancer
  - Recurrent/Metastatic (R/M)
  - Second Line or Greater (2L+)
- **Design** (CUE-101 Q3W)
  - Part A: Dose Escalation (3+3 Pts)
  - Part A: PD & Activity Expansion (Up to 9 Pts)
  - Part B: Dose Expansion (10-20 Pts at RP2D)
- **Endpoints**
  - Primary: Safety and Tolerability
  - Secondary: PK/PD, Anti-Tumor Activity per RECIST 1.1
- **Biomarkers** (Pre/Post CUE-101 Dosing)
  - HPV E7-specific CD8+ T cell counts
  - HPV E7-specific CD8+ T cell functionality
  - Immunophenotyping, cytokine release, and TCR sequencing
- **NCT03978689**

* *Cohort 7 dose delivers 64 times the molar equivalent of rhIL-2 (e.g., aldesleukin)*

Abbreviations: CPI, checkpoint inhibitors; HPV, human papilloma virus; PK/PD, pharmacokinetics/pharmacodynamics; Pts, patients; Q3W, once every 3 weeks; rhIL-2, recombinant human interleukin-2; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, Recommended Phase 2 Dose; TCR, T cell receptor

CUE-101 pharmacokinetics

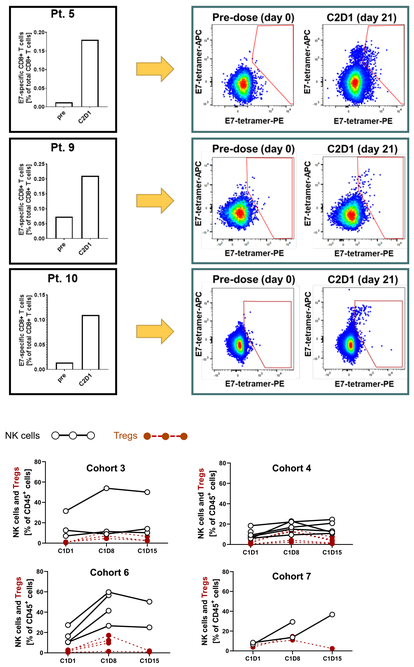


- Increase in dose-dependent exposure supports continued dose escalation
- Exposures are broadly in line with pre-clinical projections
- Repeated dosing in the same patient demonstrates comparable exposure

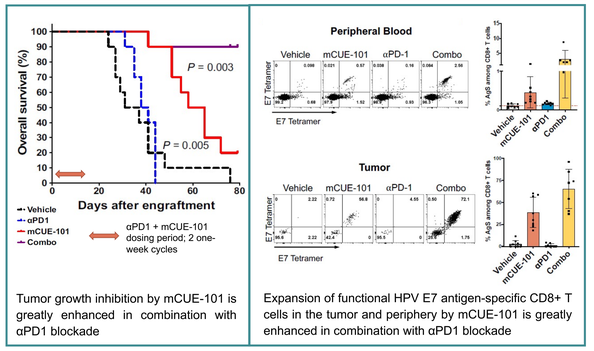
CUE-101 pharmacodynamics

Right panels:
- Blood samples are collected prior to dosing (pre) and at several different time points following CUE-101 administration. C2D1 refers to Cycle 2, Day 1 where dosing cycles are every 3 weeks.
- Preliminary data from peripheral blood mononuclear cell (PBMC) immunophenotyping and tetramer staining show early signals of expansion of HPV-16 E7$_{11-20}$-specific CD8+ T cells.

Panels below:
- Blood samples were obtained from patients at the indicated times and analyzed by flow cytometry for the presence of natural killer (NK) cells and Tregs
- A dose-dependent, sustained increase in NK cells and a transient increase in Tregs, consistent with IL-2 pharmacology, is observed.



CUE-101 preclinical studies support ongoing Phase 1 pembrolizumab combination trial



Tumor growth inhibition by mCUE-101 is greatly enhanced in combination with αPD1 blockade

Expansion of functional HPV E7 antigen-specific CD8+ T cells in the tumor and periphery by mCUE-101 is greatly enhanced in combination with αPD1 blockade

Abbreviations: AgS, antigen-specific; mCUE-101, mouse surrogate of human CUE-101; αPD1, anti-PD1 surrogate

Source: Quayle SN, Girgis N, et al., CUE-101, a Novel E7-pHLA-IL2-Fc Fusion Protein, Enhances Tumor Antigen-Specific T-Cell Activation for the Treatment of HPV16-Driven Malignancies. *Clin Cancer Res 26:1953-1964,* 2020.

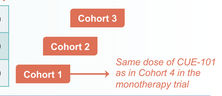
ClinicalTrials.gov:
NCT03978689

Eligibility:
- HPV-16+ Head and neck cancer
- Recurrent/Metastatic (R/M)
- 1st Line
- HLA-A*0201 genotype
- Life expectancy ≥ 12 weeks
- Eligible for pembrolizumab in the first-line setting

Design:
- Dosing Q3W
- Part C: 3 + 3 Dose escalation
- Part C: PD and activity expansion up to 9 patients
- Part D: Expansion to total of 10-20 patients at RP2D

Part C: Pembrolizumab Combination Dose Escalation

Initiated February 2021



Part D: Combination Expansion at RP2D Dose

Objectives:
- *Primary:* Safety and tolerability
- *Secondary:* PK/PD, Anti-tumor activity

Biomarkers: (Pre/Post CUE-101 dose)
- HPV E7-specific CD8+ T cell counts and functionality
- Immunophenotyping, cytokine release, TCR sequencing

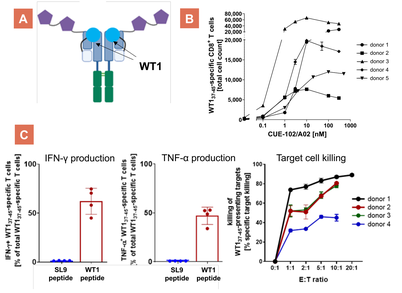
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; RP2D, Recommended Phase 2 Dose; TCR, T cell receptor

CUE-102: Exploiting Signal 1 modularity

Panel A: WT1$_{37-45}$-HLA-A*02 peptide-MHC complex targets T cells specific to Wilms' Tumor-1 (WT1) expressing tumors (e.g., lung, brain, acute myeloid leukemia, and others).

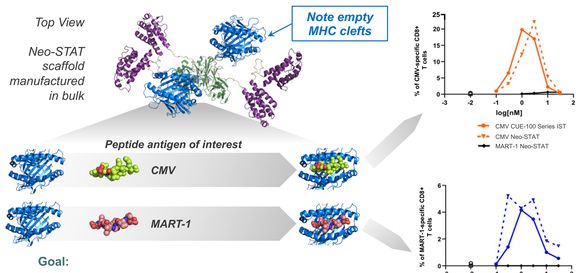
Panel B: CUE-102 expands WT1$_{37-45}$-specific CD8+ T cells in vitro from human PBMCs.

Panel C: Polyfunctionality and cytolytic activity of the CUE-102-induced T cell repertoire in vitro.



Abbreviations: E:T, effector:target; IFN-γ, interferon-gamma; PBMC, peripheral blood mononuclear cells; SL9, irrelevant peptide; TNF-α, tumor necrosis factor-alpha

Neo-STAT platform: Addressing tumor heterogeneity

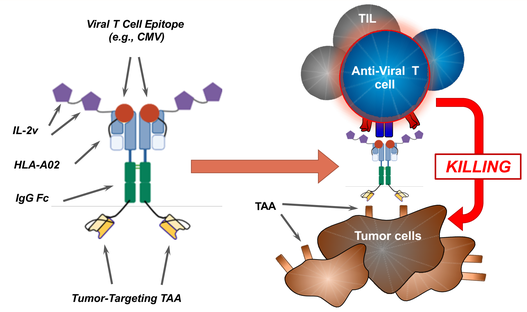


Goal:
- To generate a universal Immuno-STAT (IST) scaffold via a singular CMC cell line (e.g., MCB) enabling more competitive development metrics (time and cost savings).

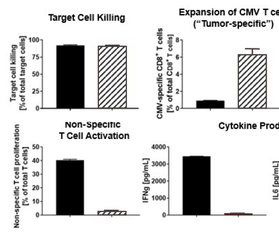
Therapeutic opportunities may include:
- Peptide mixes / Multi-antigen based cocktail therapy
- Integration of post-translationally modified peptides
- Difficult to manufacture peptides / Altered peptide ligands
- Extension to cancer neoantigens → Personalized medicine

Abbreviations: CMC, chemistry, manufacturing and controls; CMV, cytomegalovirus; MART-1, Melanoma Antigen Recognized by T cells-1; MCB, master cell bank; MHC, major histocompatibility complex

Bi-specific Redirected Immuno-STAT (RDI-STAT) platform: Addressing tumor escape mechanisms



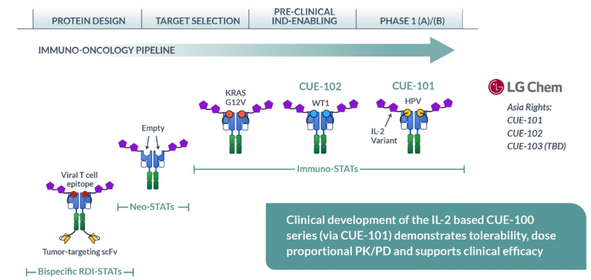
- **Harnesses** the pre-existing and robust viral T cell repertoire present in high frequency in tumors
- **Superior specificity:** avoids systemic activation of all T cells
- **Superior safety:** minimizes potential for cytokine release
- **De-risked** by CUE-101 clinical experience



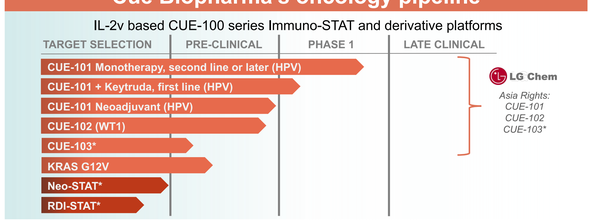
- Both RDI-STAT and a CD3-CD19 BiTE molecule promote redirected killing of tumor cells
- At the concentration for maximal killing, RDI-STAT stimulated the selective expansion of CMV-specific T cells while the BiTE expanded T cells without specificity
- Exposure to BiTE, but not RDI-STAT, at these target concentrations stimulated significant cytokine production

Abbreviations: BiTE, bi-specific T cell engager; CMV, cytomegalovirus; IFNg, interferon-gamma; IL6, interleukin-6; TAA, tumor-associated antigen; TIL, tumor-infiltrating lymphocyte

CUE-101, CUE-100 series and derivatives



Cue Biopharma's oncology pipeline



CUE-101: Human papilloma virus (HPV)-positive head and neck squamous cell carcinoma (HNSCC)
CUE-102: Wilms' tumor 1 (WT1)-positive cancers (e.g., multiple solid cancers and leukemia)
KRAS G12V is a KRAS mutation associated with many cancer types
* Indication(s) undisclosed or to be determined

Note: The modular Immuno-STAT platform has also been applied to generate drug candidates for treating infectious diseases (CUE-200 series) and autoimmune diseases (CUE-300 and CUE-400 series).

Conclusions

- Immuno-STAT and its derivative platforms offer distinct and differentiated mechanisms of action for selective modulation of disease-relevant CD8+ T cells directly in a patient's body for the treatment of cancer by mimicking nature's own cue's for mounting an effective anti-tumor immune response
- As monotherapy, our CUE-101 lead drug candidate has been dose escalated up to 8 mg/kg without establishing a maximally tolerated dose (MTD)
- Emerging clinical data with CUE-101 potentially de-risks the CUE-100 series-based Immuno-STAT platform, including demonstration of safety/tolerability, dose-dependent PK and PD metrics, and early evidence of anti-tumor activity
- Early preclinical study results with Neo-STAT and RDI-STAT suggest that these derivative platforms may effectively address tumor heterogeneity and escape mechanisms

Presented at The Frontiers in Cancer Immunotherapy Symposium at the New York Academy of Sciences, May 12-14, 2021