Corporate Presentation

Immune Responses, On Cue™

Nasdaq: CUE

Oppenheimer 31st Annual Healthcare Conference, March 18, 2021

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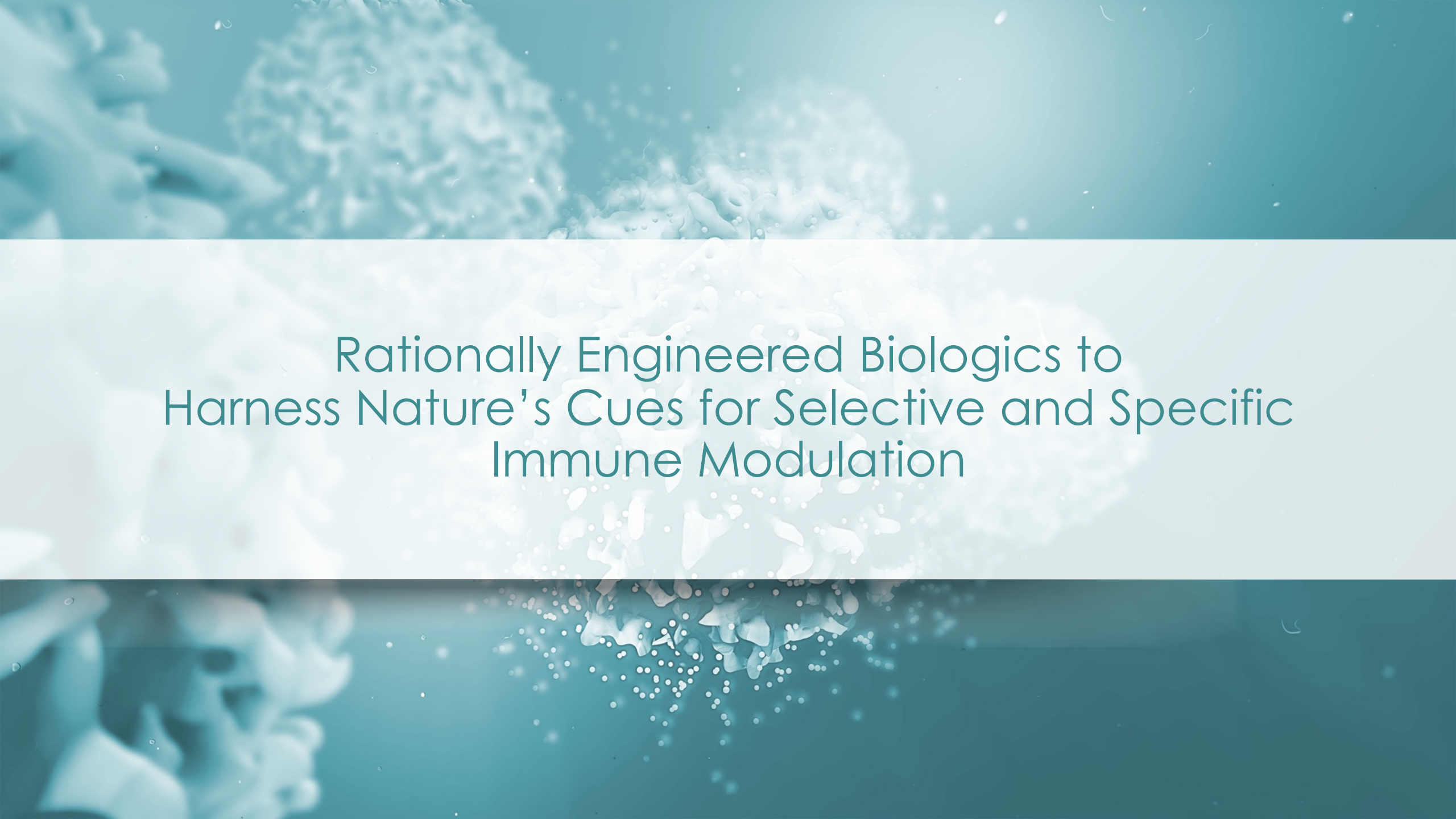
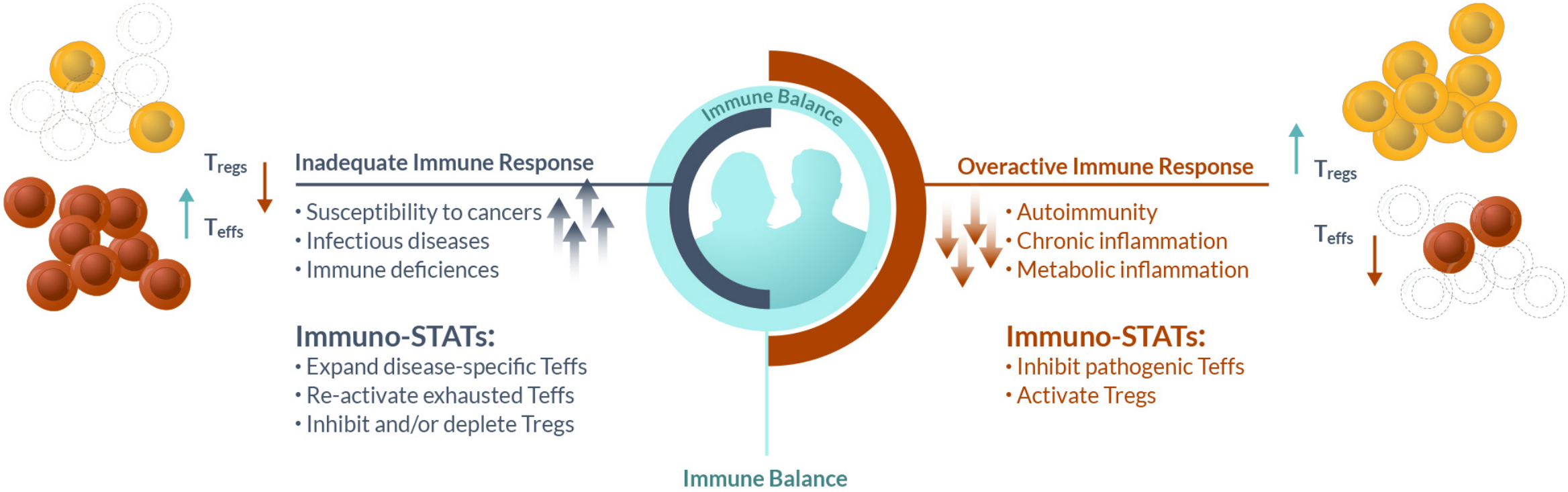


Rationally Engineered Biologics to Harness Nature's Cues for Selective and Specific Immune Modulation

Restoring Immune Balance

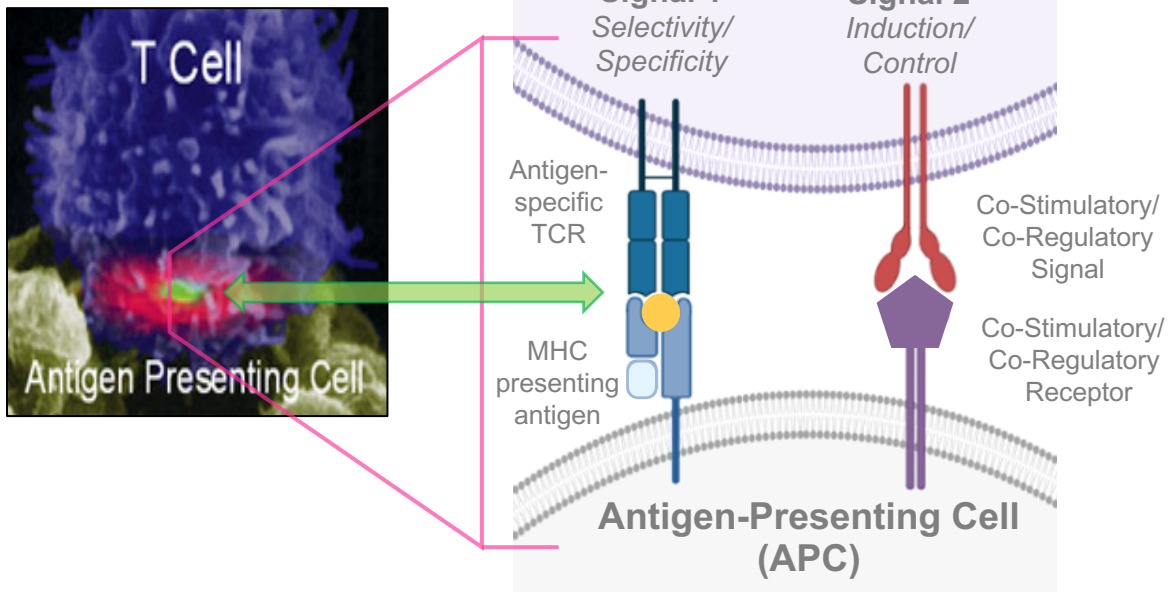


Restoration of immune balance is a key pillar of human health

KEY: T_{effs}, effector T cells; T_{regs}, regulatory T cells

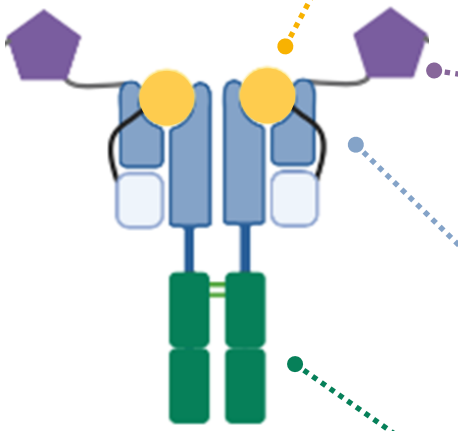
Immuno-STAT: Emulating Nature's Cues to Selectively Modulate T Cells

Immune Synapse



TCR = T Cell Receptor
MHC = Major Histocompatibility Complex

Immuno-STAT Framework



- Single molecule
- Stable, off-the-shelf
- IV or SQ administration
- No *ex vivo* manipulation

Platform Modularity

Peptide Antigen

Peptide epitopes to target different diseases

Co-Stim/Co-Reg

Distinct biological signals, including cytokines; cell-surface receptors; and/or other targeting modalities (e.g., scFv, etc.)

MHC

Different HLA alleles to address global patient populations

Fc Backbone

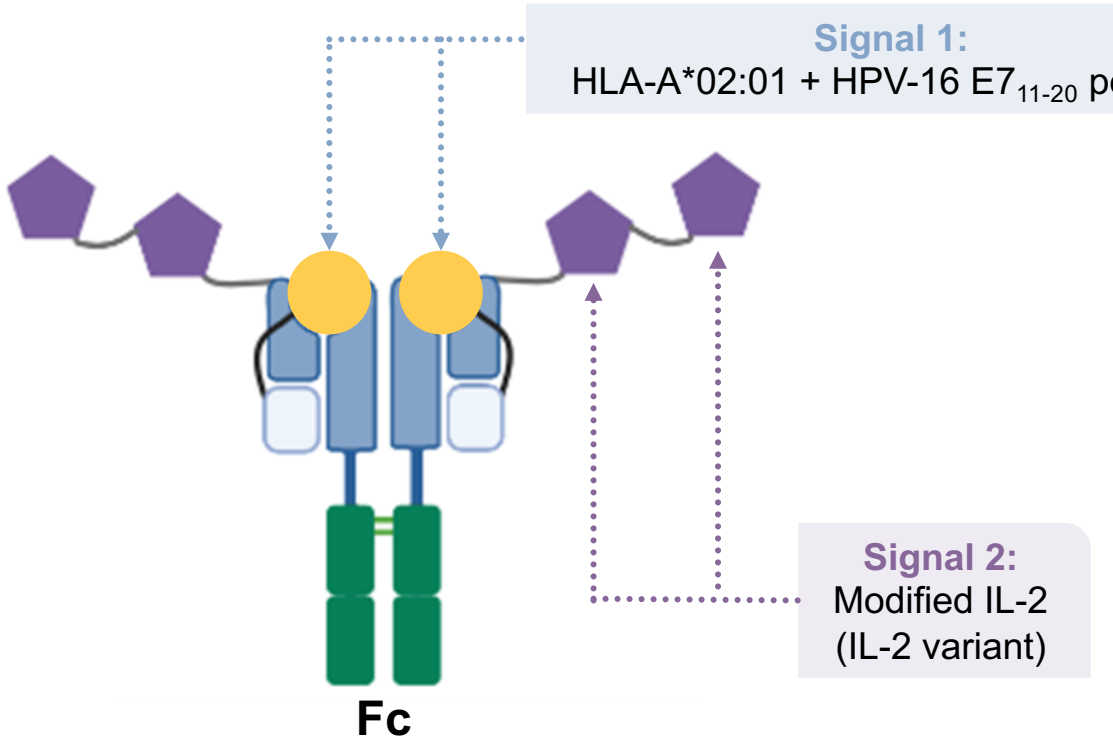
Fc engineering to dial in or out biological and effector functions

The Immuno-STAT platform has the potential to generate a diversity of therapeutic molecules to selectively target and modulate the activity of a broad range of disease-relevant T cells

Source: Dustin, Cancer Immunol Res 2014

CUE-101: Designed to Selectively Prime and Expand HPV-Specific T Cells

CUE-101 Immuno-STAT Design



Clinical Rationale

- 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[2]

1: Quayle et al., *Clin Cancer Res* Jan 2020 DOI: 10.1158/1078-0432.CCR-19-3354
2: Patients must be HLA:02:01 and HPV-16+

CUE-101: Phase 1 Clinical Development Network

Cue Biopharma has engaged a network of nationally recognized clinical investigators and 14 Phase 1 sites are now open

- **Emory Winship Cancer Institute** | Nabil Saba
- **Karmanos Cancer Institute** | Elizabeth Heath and Ammar Sukari
- **MD Anderson Cancer Center** | Bonnie Glisson
- **Memorial Sloan Kettering Cancer Center** | Lara Dunn
- **MGH/Harvard and Dana Farber Cancer Institute** | Sara Pai and Lori Wirth
- **Moffitt Cancer Center** | Christine Chung
- **Sidney Kimmel Comprehensive Cancer Center-Johns Hopkins** | Tanguy Seiwert
- **Stanford Cancer Center** | A. Dimitrios Colevas
- **University of Arizona Center** | Julie Bauman
- **University of Michigan Rogel Cancer Center** | Frank Worden
- **University of Washington Fred Hutch Cancer Center** | Cristina Rodriguez
- **Vanderbilt-Ingram Cancer Center** | Jill Gilbert and Mike Gibson
- **Washington University Siteman Cancer Center** | Doug Adkins
- **Yale Cancer Center** | Barbara Burtness

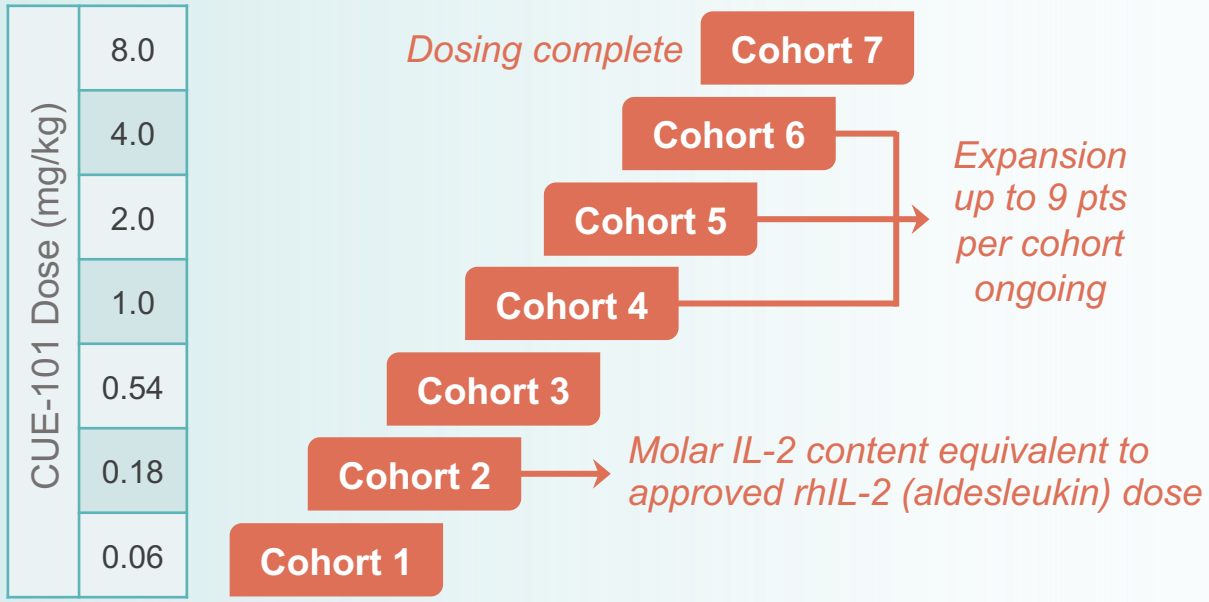
CUE BIOPHARMA

CUE-101: Ongoing Monotherapy First-In-Human Phase 1 Trial

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)

Parts A & B:

Primary endpoints:
- Safety and tolerability

Secondary endpoints:
- PK/PD
- Anti-tumor activity per RECIST 1.1

ClinicalTrials.gov: NCT03978689

CUE-101 has been well tolerated through 7 cohorts with evidence of clinical activity
Currently expanding Cohort 4, 5, and 6

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

CUE-101: Cohort 4 Case Study – 3rd line Systemic Treatment

	Treatment	Timeline	Outcome
1	Robotic transoral resection tongue base	First intervention	Curative intent
2	Adjuvant RT	1 mo	Curative intent
3	Carboplatin + fluorouracil + cetuximab for advanced, metastatic disease	1 yr, 1 mo	Duration: 6.0 weeks **Best Response = SD**
4	RT to metastatic mass	1 yr, 4 mos	Palliation
5	Pembrolizumab for advanced, metastatic disease	2 yrs	Duration: 9.4 weeks **Best Response = PD**
6	**CUE-101 (1 mg/kg, Q3W)**	2 yrs, 5 mos	Duration: 18.1 weeks

Tolerability

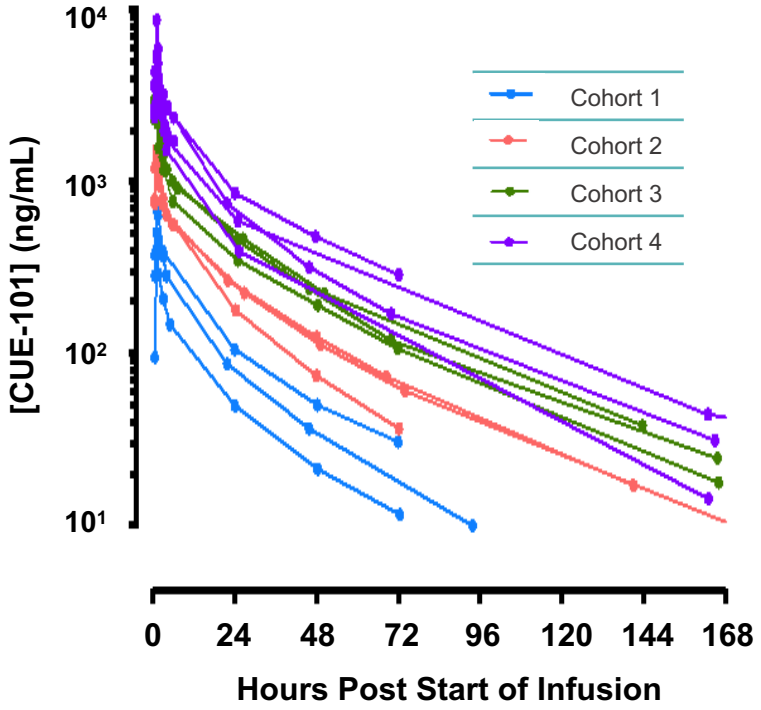
ECOG Status: 0 at screening; Unchanged while on CUE-101 therapy

All TRAEs Grade ≤2

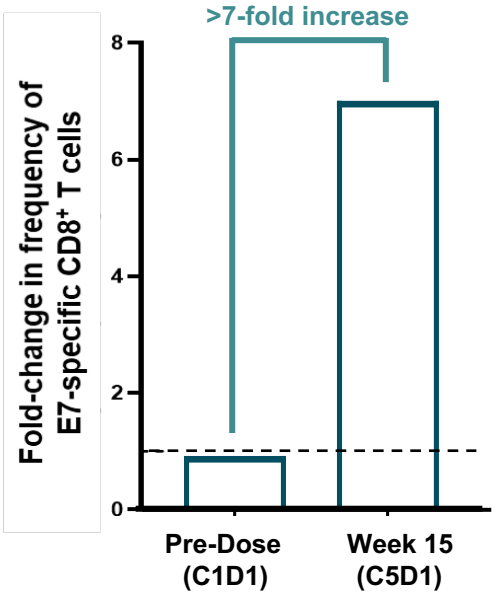
CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 18 weeks

CUE-101: Cohort 4 Case Study – PK, PD, Response

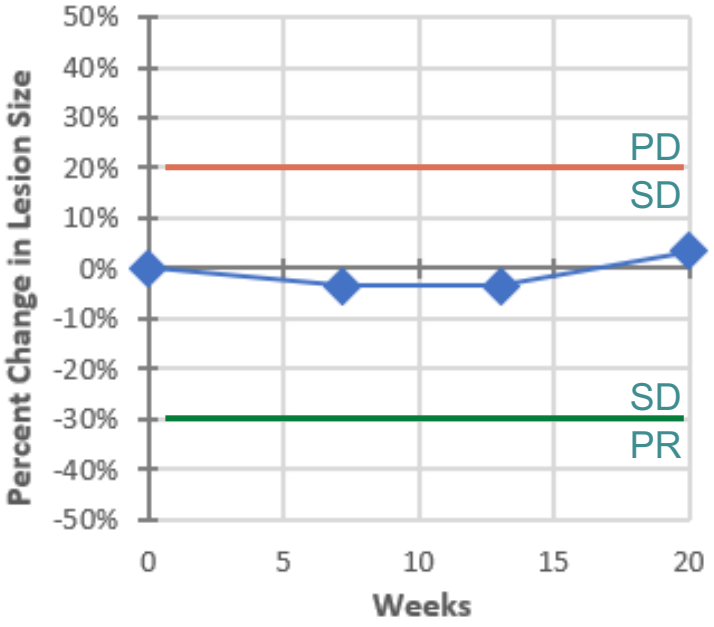
Pharmacokinetics:
Dose proportional



Pharmacodynamics:
Increase in peripheral blood E7-specific T cells



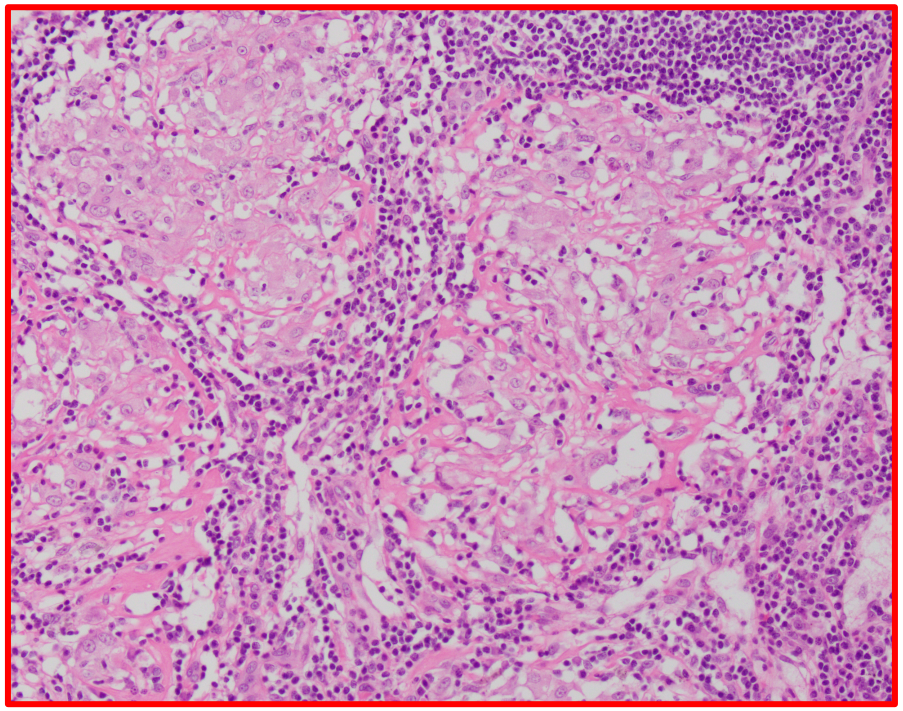
One target lesion at baseline:
Diameter: 58 mm
No change for 20 wks



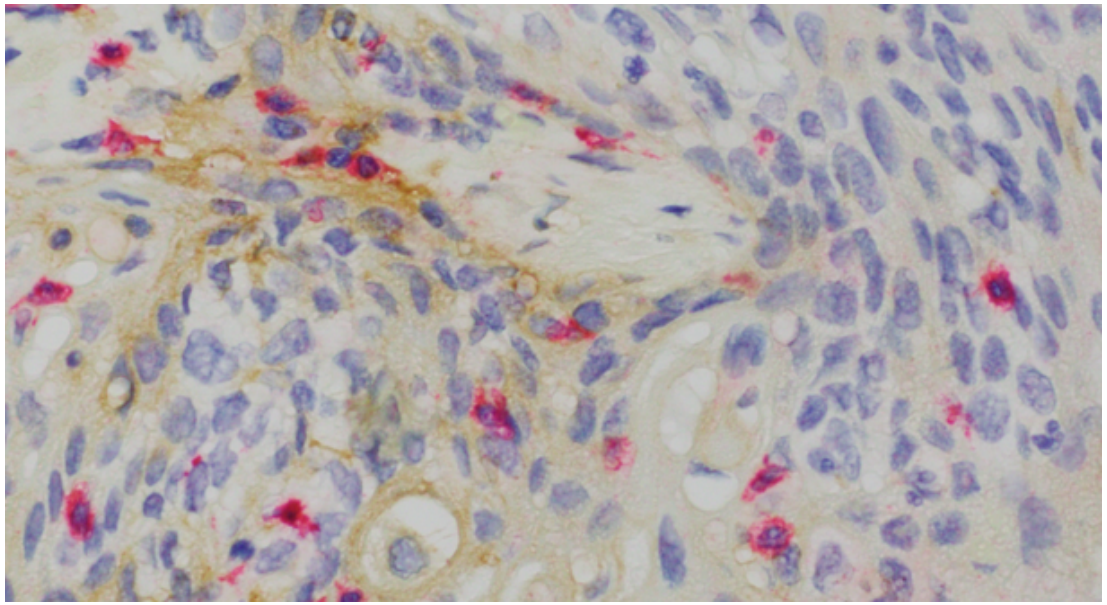
CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 18 weeks

CUE-101: Cohort 4 Case Study – Necrosis and a T Cell Infiltrate

Cohort 4 (1 mg/kg) patient was on therapy for over 18 weeks



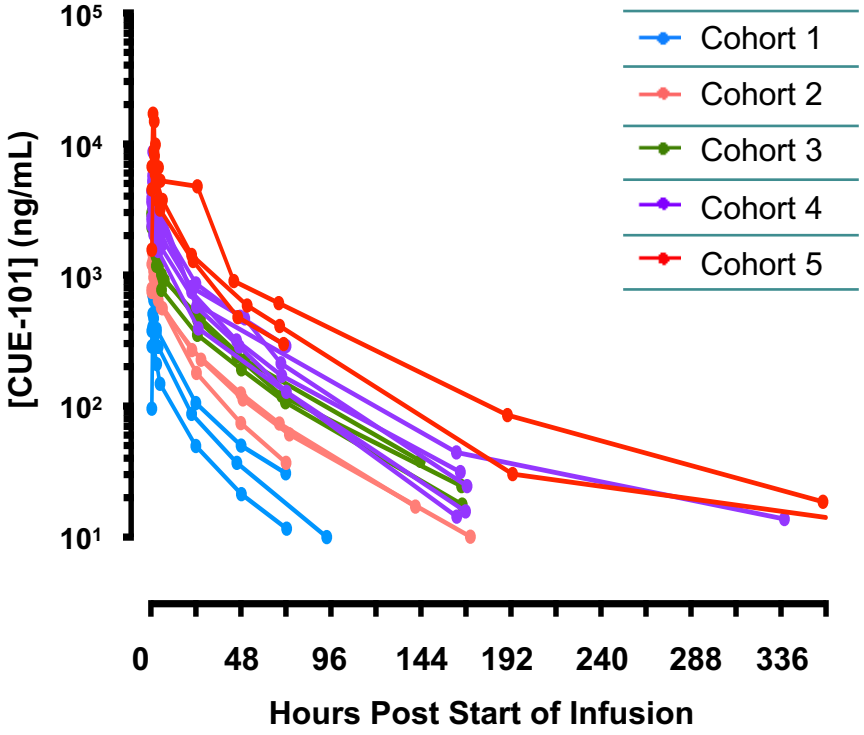
Hematoxylin and eosin stain
(cell nuclei = blue; extracellular matrix and cytoplasm = pink)



Immunostaining
(cell nuclei = blue; CD8+ T cells = rose; PD-LI = brown)

CUE-101: Cohort 5 Case Study – PK, Response

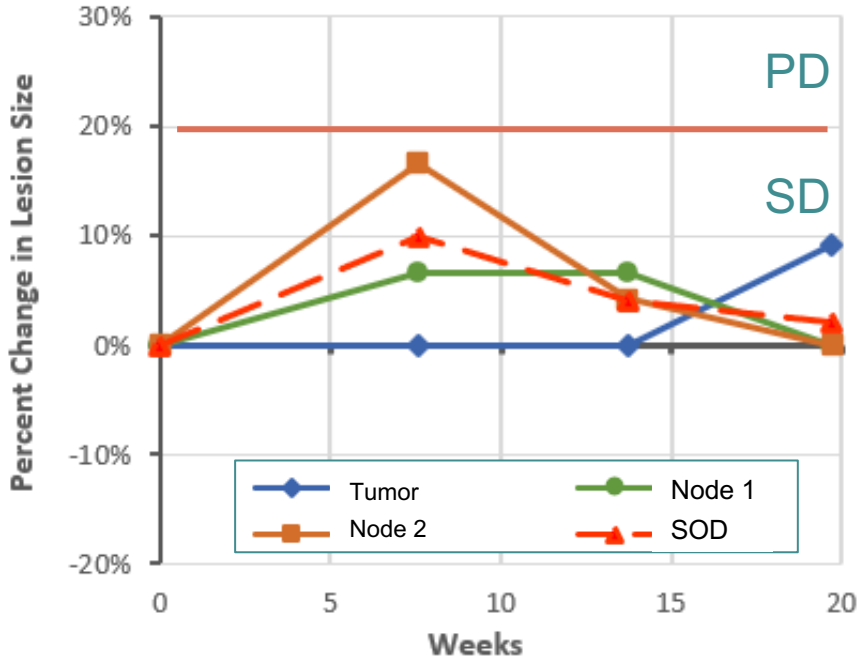
Pharmacokinetics:
Dose proportional



Three target lesions at baseline:

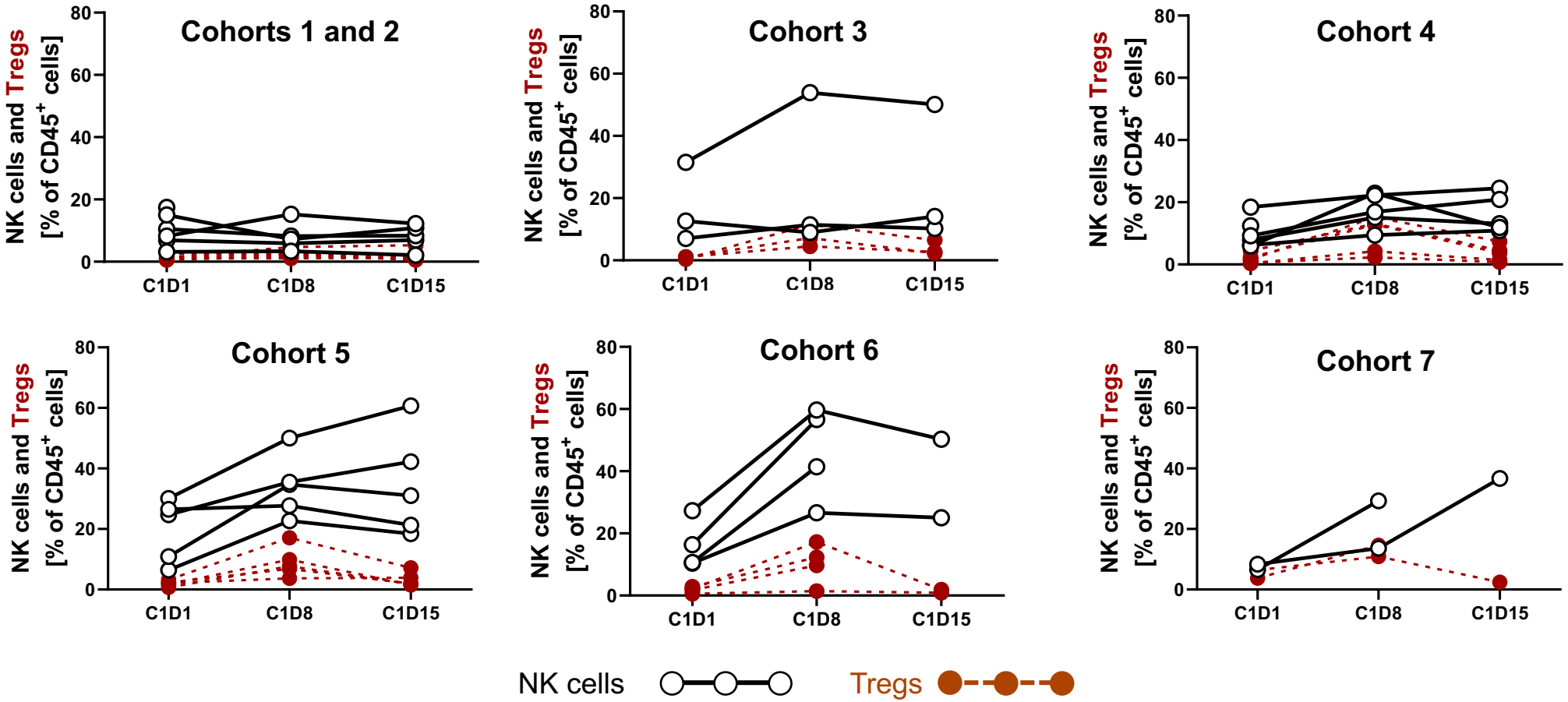
1) Tumor mass: 11 mm
2) Lymph node No.1: 15 mm
3) Lymph node No. 2: 24 mm

Sum of Diameters (SOD) = 50 mm



CUE-101 Best Response: Confirmed SD by RECIST 1.1 for 28 weeks; acquired COVID-19 and came off study

CUE-101: Induced Changes in NK Cells and Tregs in Cohorts 1 - 7



Dose-dependent, sustained increase in NKs with transient increase in Tregs, consistent with IL-2 pharmacology observed in the clinic

CUE-101: Ongoing Pembrolizumab Combination Study

ClinicalTrials.gov:
NCT03978689

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

Part C: Pembrolizumab Combination Dose Escalation

Initiated February 2021

Pembrolizumab 200 mg, Q3W	CUE-101 Dose (mg/kg)
	4.0
	2.0
	1.0

Cohort 3

Cohort 2

Cohort 1 → *Same dose of CUE-101 as in Cohort 4 in the monotherapy trial*

Part D: Combination Expansion at RP2D Dose

Design:
- Dosing Q3W
- Part C: 3 + 3 Dose escalation with 1-week safety follow up of 1st patient required at each dose prior to dosing patients 2 and 3
- Part C: PD and activity expansion up to 9 patients
- Part D: Expansion to total of 10-20 patients at RP2D

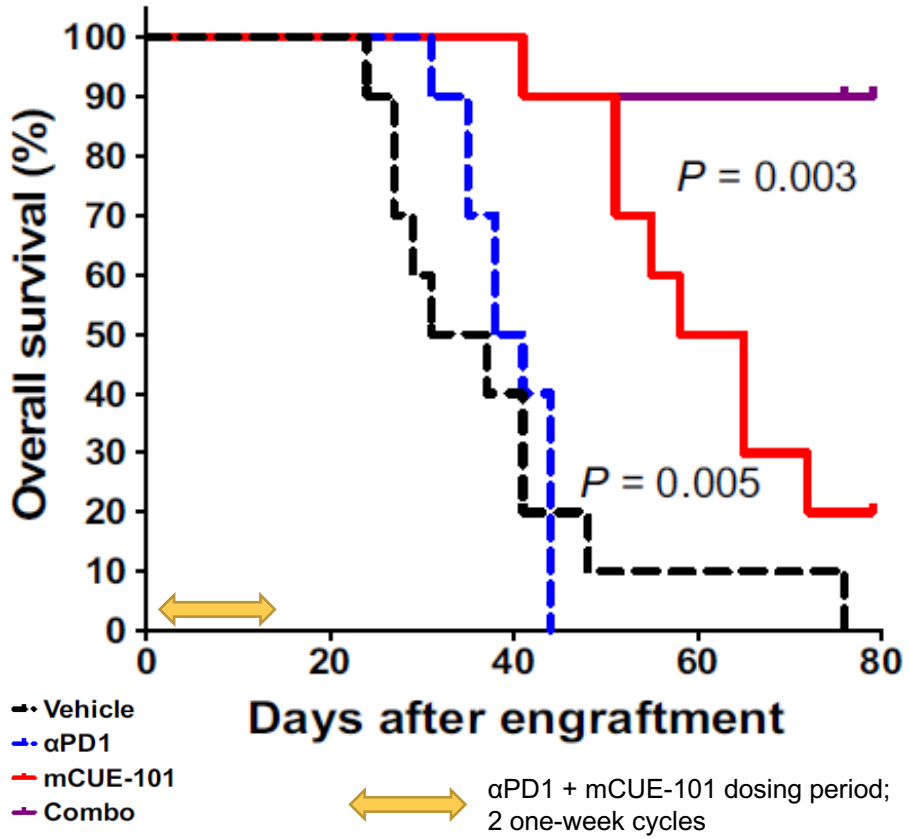
Objectives:
- *Primary:* Safety and tolerability
- *Secondary:* PK/PD, Anti-tumor activity

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

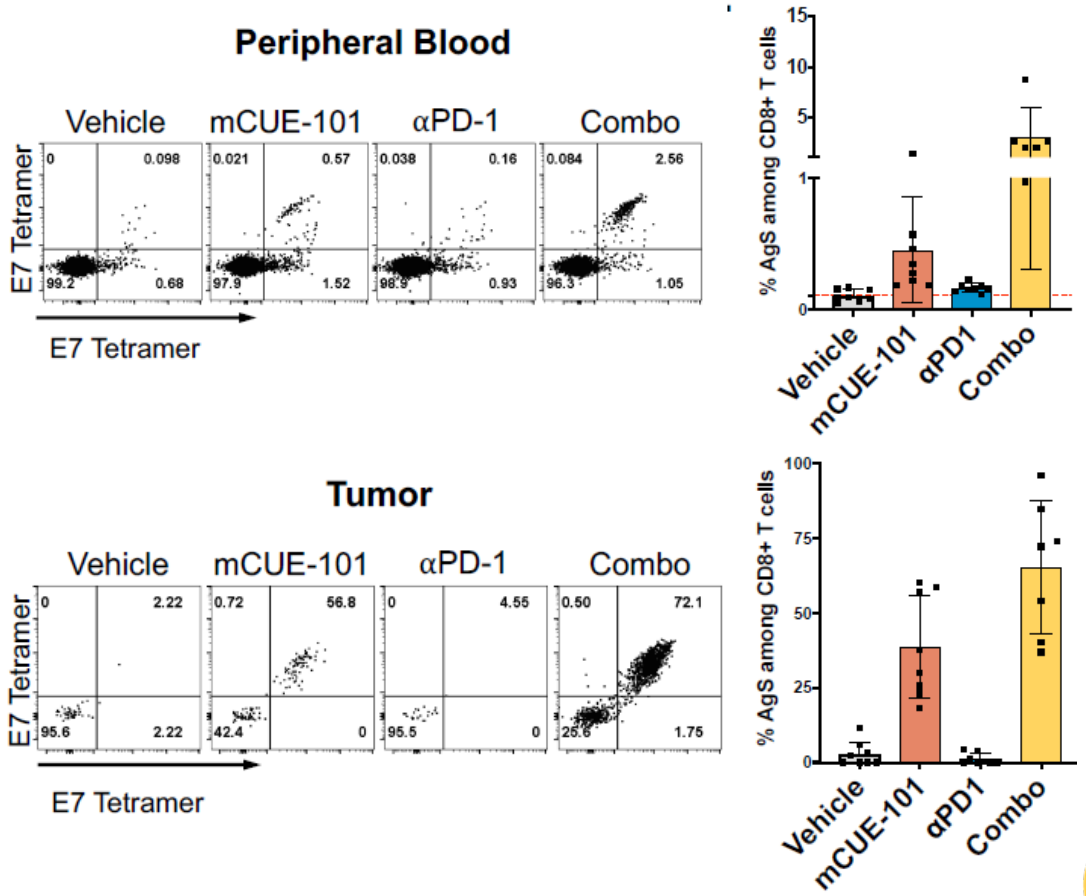
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; RP2D, Recommended Phase 2 Dose

CUE-101: Preclinical Studies Support Pembrolizumab Combination

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



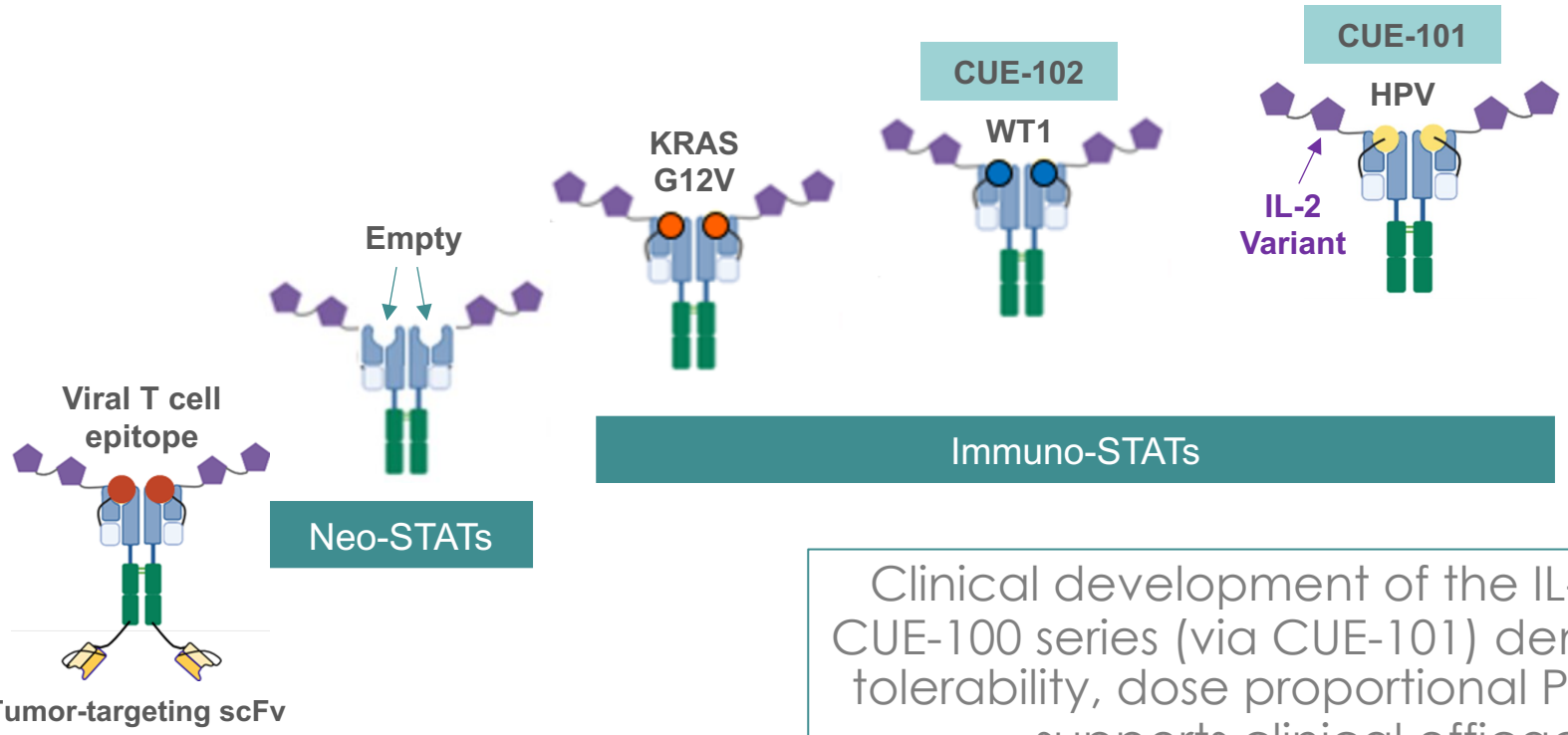
Source: *Quayle SN, Girgis N, et al. Clin Canc Res 26:1953-64, 2020.*

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

CUE-101, CUE-100 Series and Derivatives

PROTEIN DESIGN	TARGET SELECTION	PRE-CLINICAL IND-ENABLING	PHASE 1 (A)/(B)	PHASE 2

Immuno-oncology Pipeline



LG Chem

Asia Rights:
CUE-101
CUE-102
CUE-103 (TBD)

Clinical development of the IL-2-based CUE-100 series (via CUE-101) demonstrates tolerability, dose proportional PK/PD and supports clinical efficacy

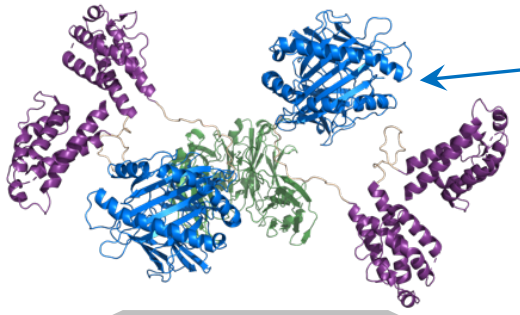
IL-2-based CUE-100 Series

CUE BIOPHARMA

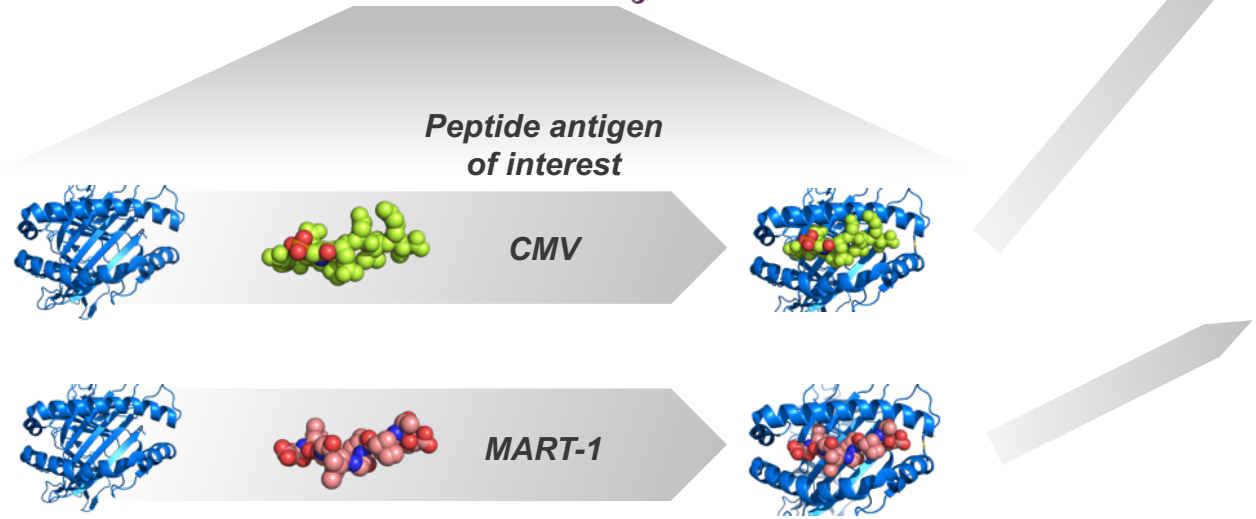
CUE-100 Neo-STAT: Addresses Tumor Heterogeneity

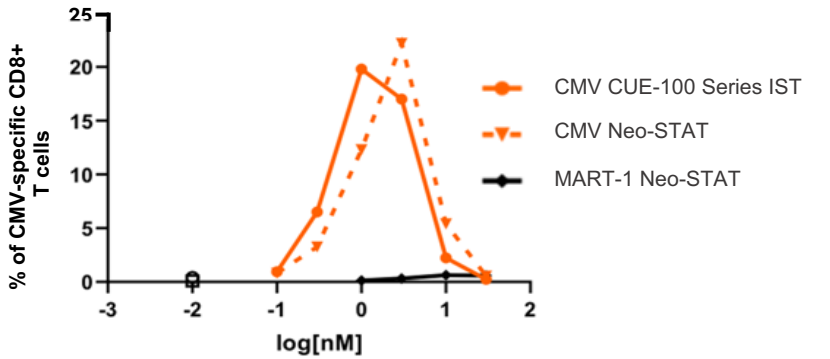
Top View

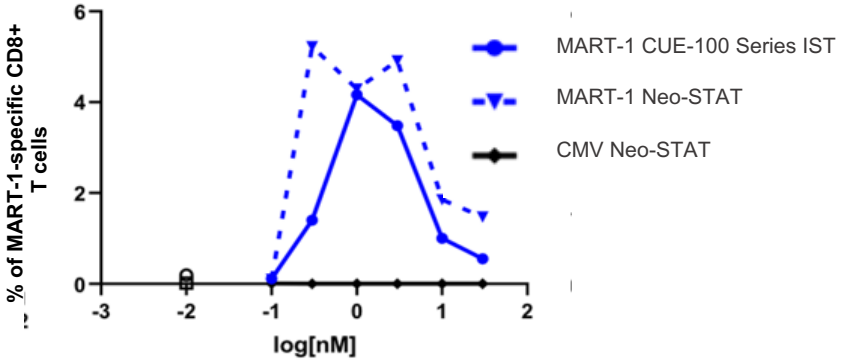
Neo-STAT scaffold manufactured in bulk



Note empty MHC clefts



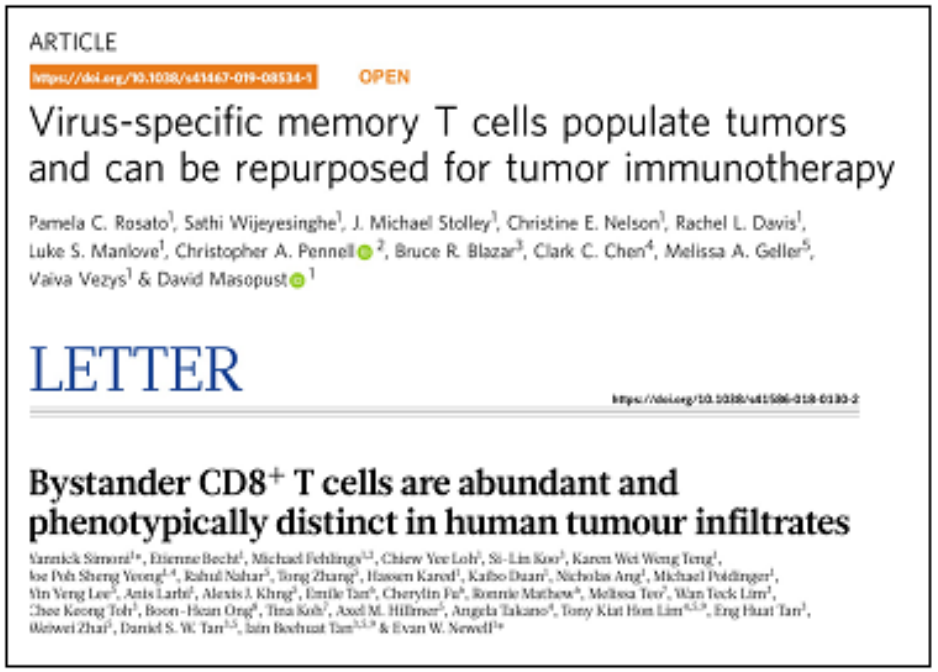




Potential Therapeutic Applications to include:

- 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

RDI-STATs: Novel Bi-specifics Re-directing Viral-Specific T Cells to Tumor Cells



ARTICLE

https://doi.org/10.1038/s41467-019-08534-1 OPEN

Virus-specific memory T cells populate tumors and can be repurposed for tumor immunotherapy

Pamela C. Rosato[1], Sathi Wijeyesinghe[1], J. Michael Stolley[1], Christine E. Nelson[1], Rachel L. Davis[1], Luke S. Manlove[1], Christopher A. Pennell[2], Bruce R. Blazar[3], Clark C. Chen[4], Melissa A. Geller[5], Vaiva Vezys[1] & David Masopust[1]

LETTER

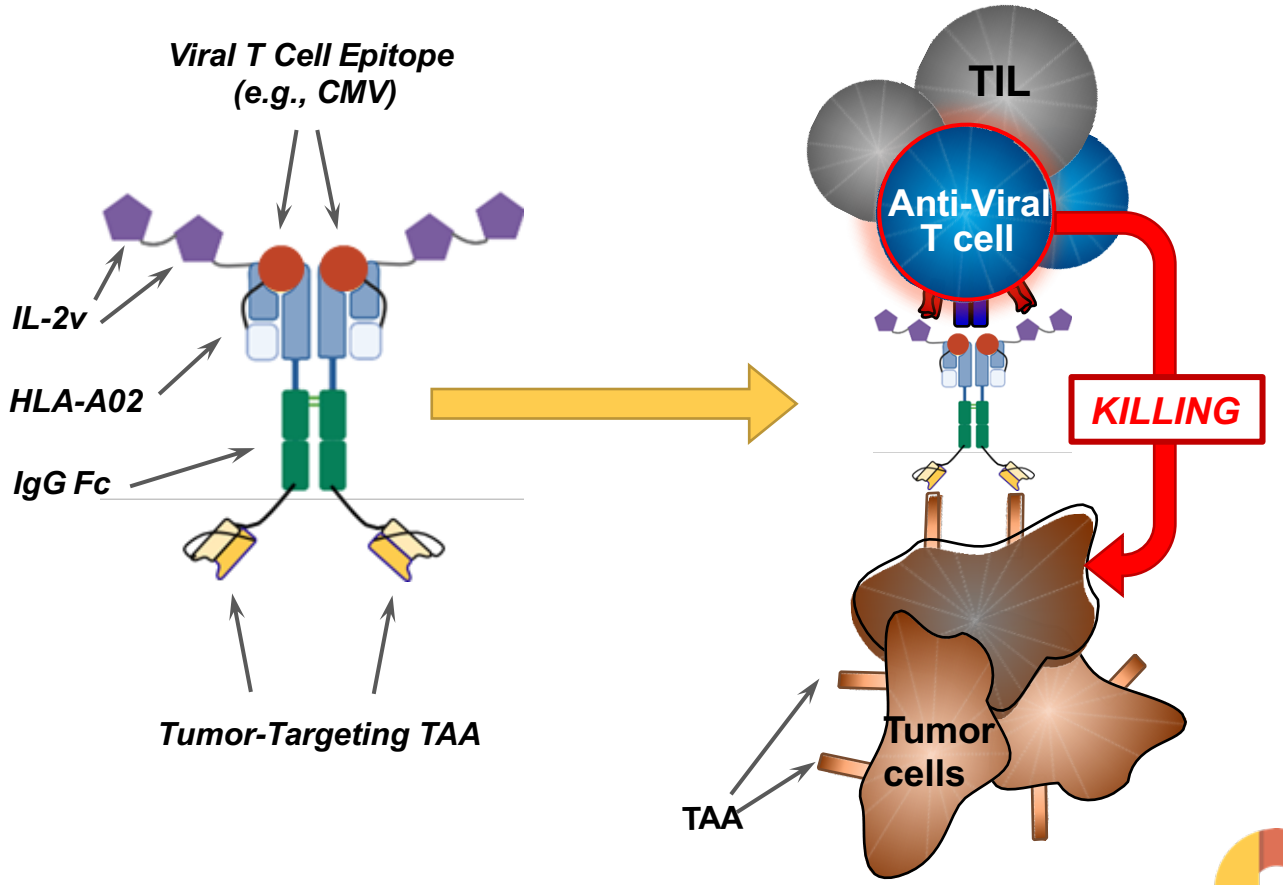
https://doi.org/10.1038/s41586-018-0130-2

Bystander CD8+ T cells are abundant and phenotypically distinct in human tumour infiltrates

Yannick Simoni[1,*], Etienne Becht[1], Michael Fehlings[1,2], Chiew Yee Loh[3], Si-Lin Koo[3], Karen Wei Weng Teng[3], Ioe Poh Sheng Yeong[1,4], Rahul Nahar[3], Tong Zhang[3], Hassen Kared[1], Kaibo Duan[3], Nicholas Ang[1], Michael Poidinger[1], Yin Yeng Lee[3], Anis Larbi[3], Alexis J. Khng[5], Emile Tan[5], Cherylin Fu[5], Ronnie Mathew[5], Melissa Teo[5], Wan Teck Lim[5], Chee Keong Toh[5], Boon-Hean Ong[6], Tina Koh[7], Axel M. Hillmer[7], Angela Takano[8], Tony Kiat Hon Lim[8,9], Eng Huat Tan[5], Weiwei Zhai[1], Daniel S. W. Tan[3,5], Iain Beehuat Tan[3,5,9] & Evan W. Newell[1,*]

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

Bi-specific RDI-STAT



CMV, cytomegalovirus; TAA, tumor-associated antigen; TIL, tumor-infiltrating lymphocyte

Approaches to Modulate Autoreactive T Cell Responses

T Cell Mediated Autoimmune Diseases

MERCK

Antigen-Specific Approach

AIM: Deploy class I/II Immuno-STATs to modulate autoreactive T cells and/or generate antigen-specific inhibitory Tregs

- Focus on diseases with restricted autoreactive antigens
- Focus on earlier stages of breakdown of tolerance prior to antigen/epitope spreading

CUE-300 Series

Pathway-Specific Approach

AIM: Engineered key signals to restore immune balance through generation of polyclonal induced Tregs (iTregs)

- Focus on IL-2 and TGF-β for iTreg induction and expansion
- Focus on indications and chronic disease stages with diverse self-antigens

CUE-400 Series

Cue Biopharma is applying **protein engineering** and **mechanistic biology** to develop drug candidates applicable to both approaches

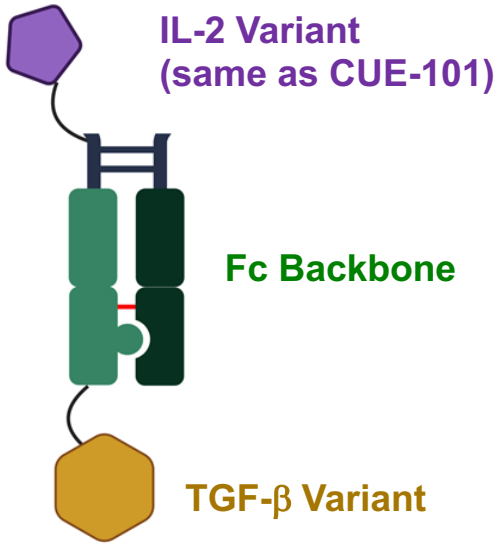
CUE BIOPHARMA

CUE-401: Immune Balance Restoration via Induced Tregs (iTregs)

Advantages for iTregs vs. nTregs

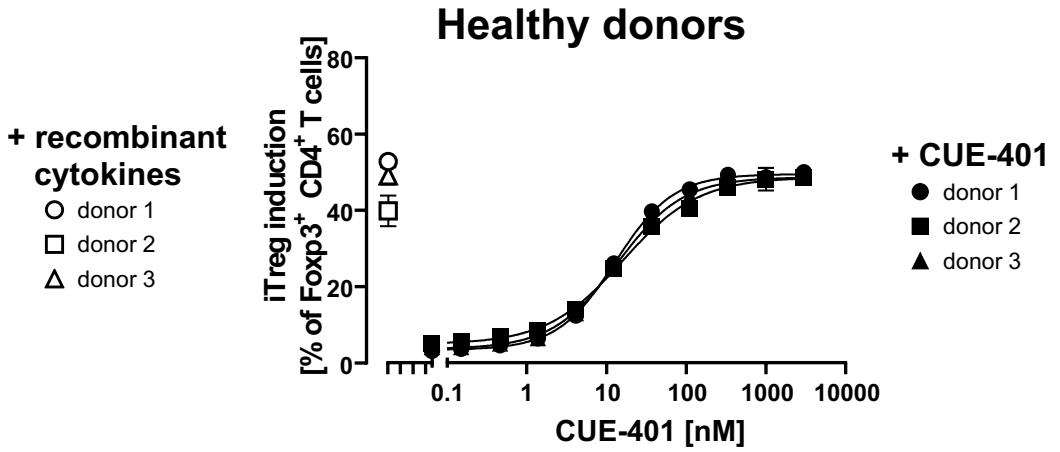
- **Numbers**: nTregs are limited in numbers vs iTregs, which can be generated from the broader CD4+ T cell repertoire
- **Diversity**: TCR specificity of nTregs is pre-determined and fixed, while iTregs can be generated from vastly diverse polyclonal CD4+ T cells
- **Phenotype**: regulatory phenotype of iTregs can be achieved and sustained via IL-2 and TGF-beta signals
- **Disease impact**: Conversion of pathogenic T cells into regulatory phenotype is an attractive therapeutic strategy for immune re-set
- **Application**: Broad applications for iTregs in numerous autoimmune diseases, GVHD and transplantation

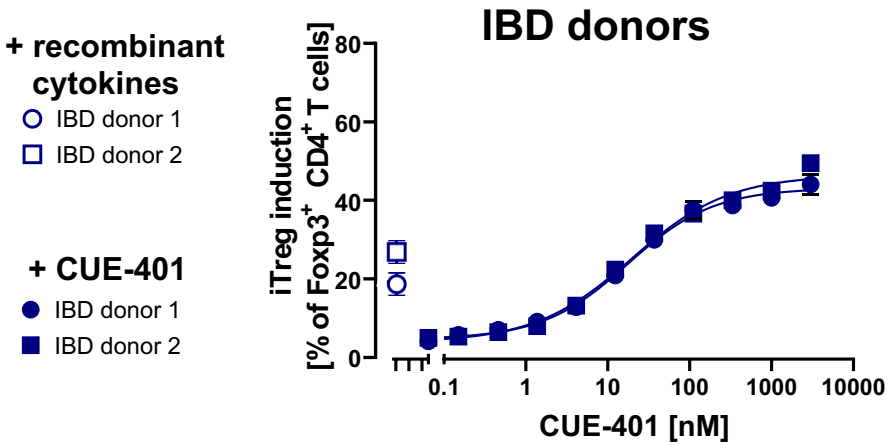
CUE-401

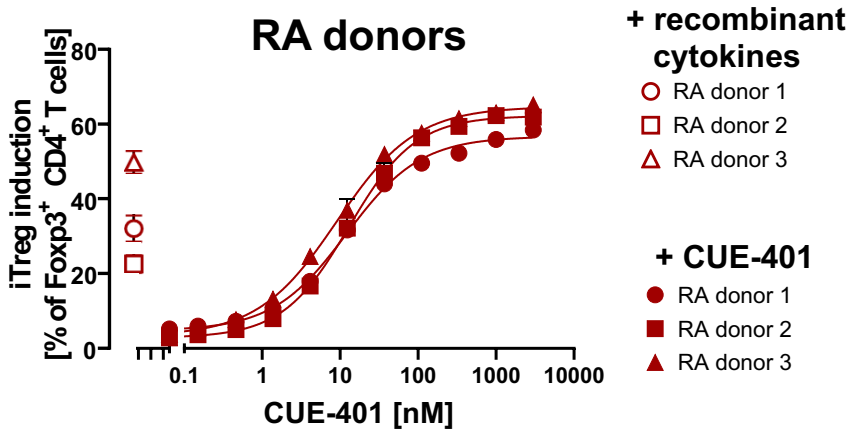


CUE-401: Induction of FoxP3+ iTregs

All assays performed in presence of TCR activation via CD3/CD28 stimulation



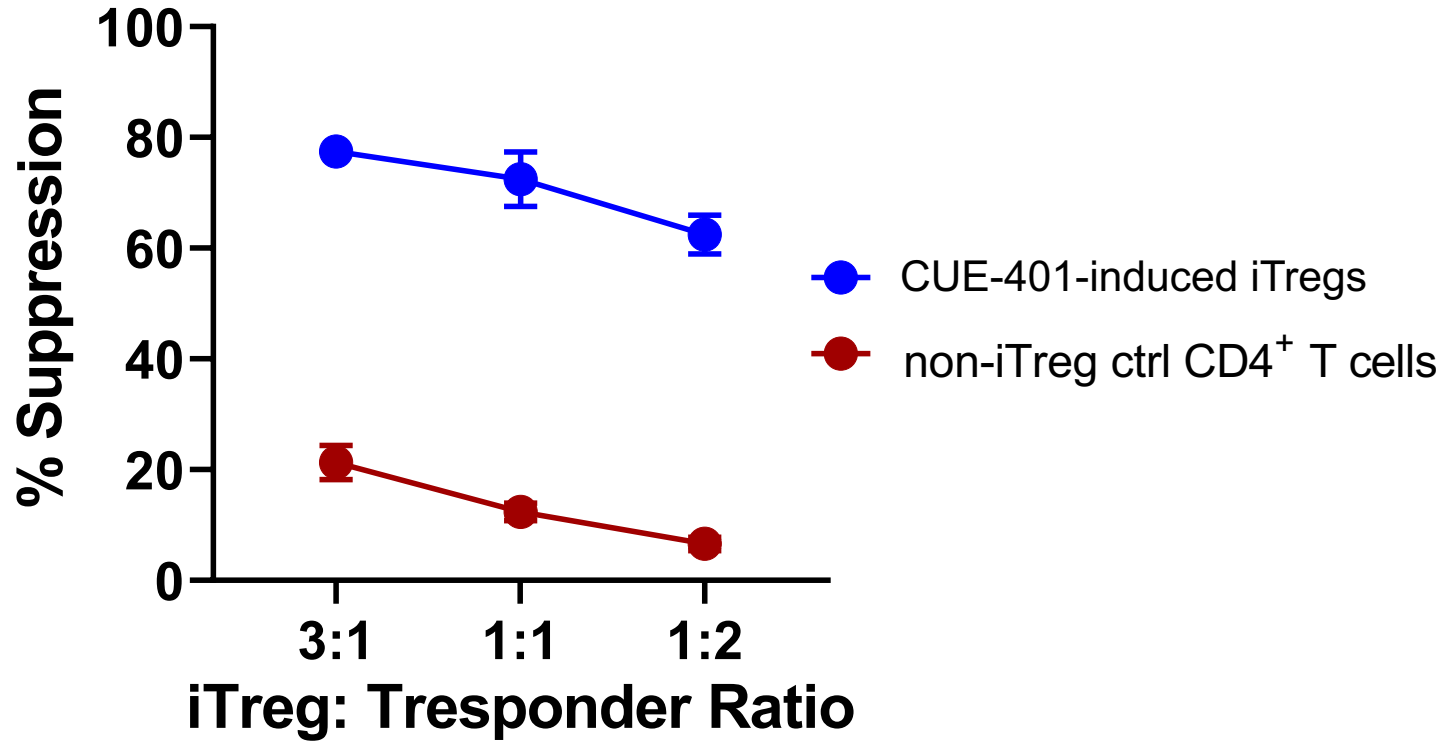




CUE-401 enhances iTregs as measured by induction of expression of the master Treg transcription factor FoxP3

CUE-401: Suppression of T Cell Responses by iTregs Induced by CUE-401

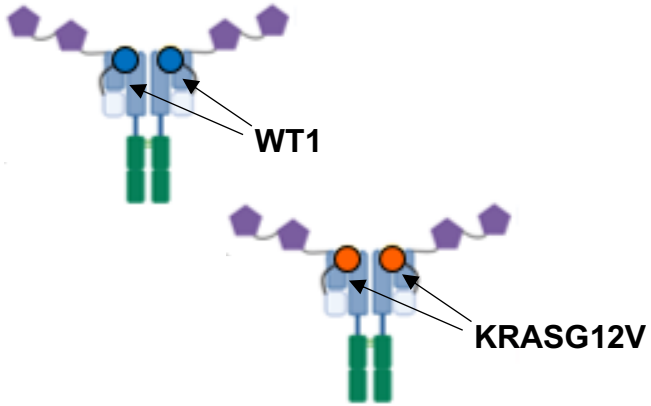
iTreg suppression of polyclonal T cell proliferation



Average of 3 donors
% suppression compared to T responder alone

CUE-101 Experience: Potential for Broad Opportunities in IO and AI

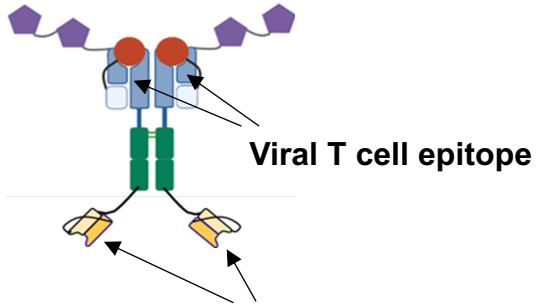
Immuno-STAT Pipeline

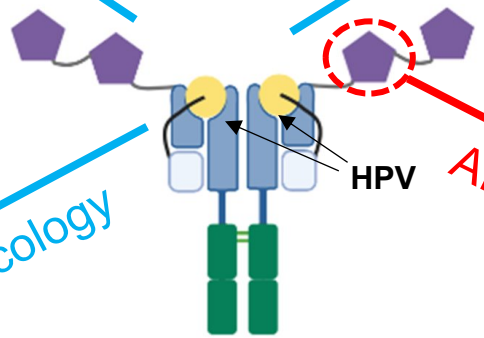


Immuno-oncology

Immuno-oncology

Bi-specific RDI-STATs Pipeline
(addresses tumor-escape mechanisms)



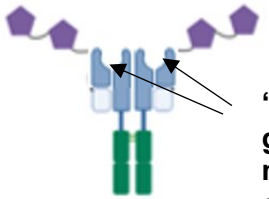


CUE-101

Immuno-oncology

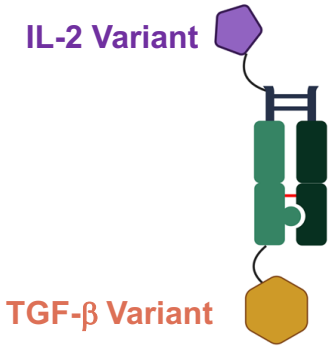
AI & Inflammation

Neo-STAT Pipeline
(addresses tumor heterogeneity)

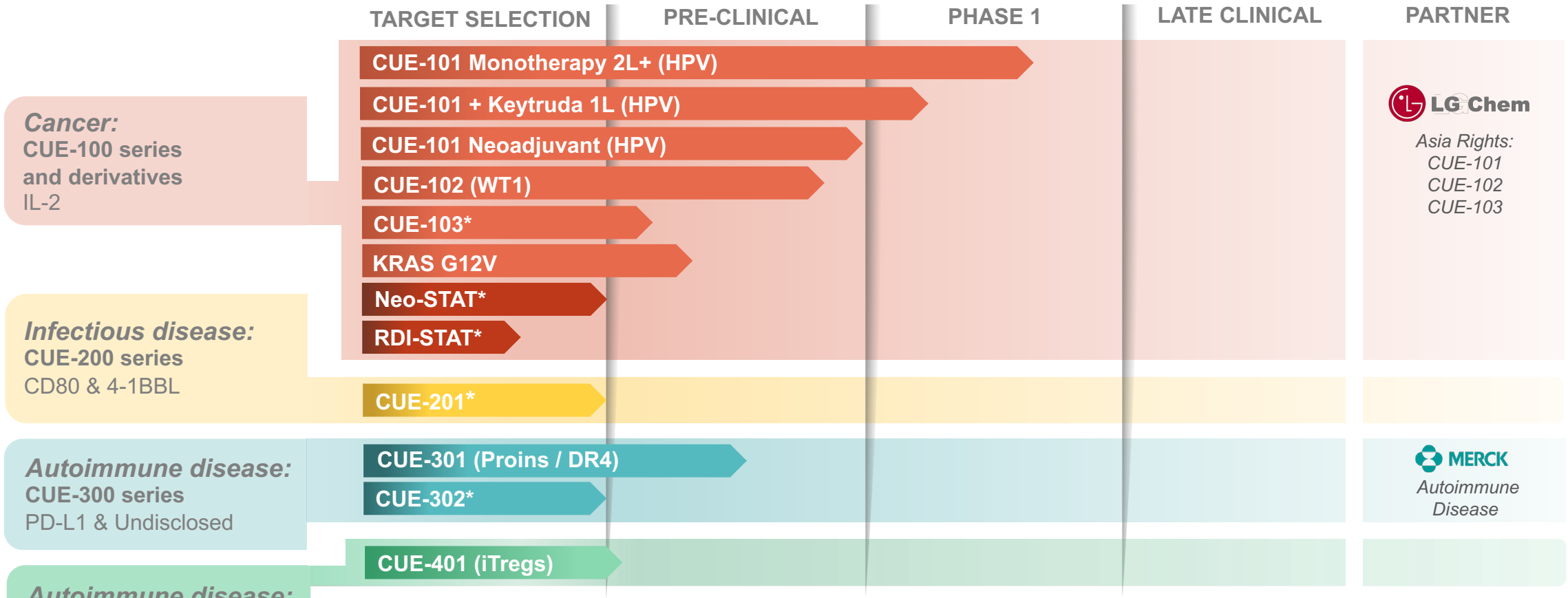


"Empty" HLA for rapid generation of therapeutic molecules that can accommodate multiple tumor epitopes

CUE-401: iTreg Inducer



Cue Biopharma Drug Product Candidate 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., leukemia and multiple solid cancers)
CUE-301: Type 1 diabetes with autoreactive T cells targeting pancreatic beta cells producing proinsulin (Proins)
KRAS G12V is a KRAS mutation associated with many cancer types
CUE-401: Rheumatologic and gastrointestinal autoimmune/ inflammatory disorders, GvHD
* Undisclosed

CUE BIOPHARMA

Key 2021 Anticipated Milestones: Risk Reduction and Value Creation

1
Select CUE-101 monotherapy recommended Phase 2 dose in **mid-2021**

2
Report initial results of CUE-101 + pembrolizumab Phase 1 combination trial in **2H21**

3
Initiate CUE-101 neoadjuvant study to enable intratumor PD **in 2H21**

4
Continue CUE-102 IND-enabling studies with IND filing in **1H22**

5
Initiate & expand KRAS G12V, & Neo-STAT CMC activities in **2H21**

6
Achieve optimization of lead candidate for CUE-301 in **2H21**

7
CUE-401 Preclinical validation of iTreg function in **2H21**

We believe our cash, cash equivalents and marketable securities at December 31, 2020 are sufficient to support CUE-101 clinical proof of concept and pipeline advancement into the third quarter of 2022

Thank you

Immune Responses, On Cue™

Nasdaq: CUE | March 18, 2021