A Phase 1 trial of desmoglein 3 chimeric autoantibody receptor T cells (DSG3-CAART) for targeted B cell depletion in patients with mucosal-dominant pemphigus vulgaris: The DesCAARTes™ Trial

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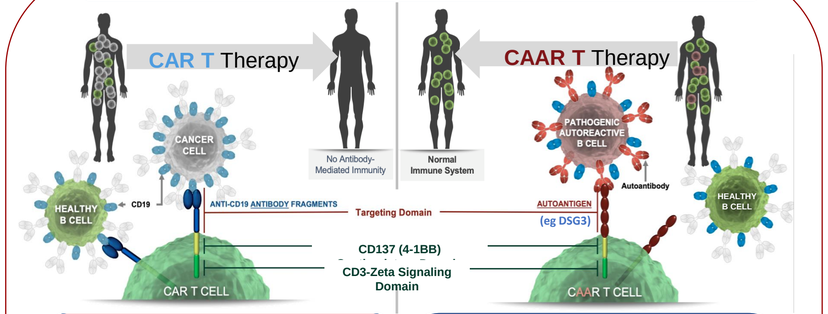
Introduction



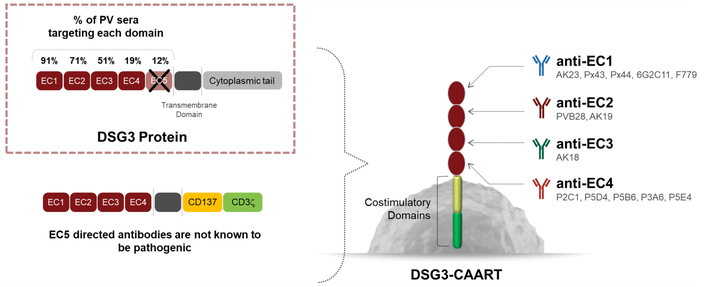
Chimeric Antigen Receptor T cell

- Type of immunotherapy of genetically engineered autologous T cells to target and eliminate specific cells
- CD19 CAR T: anti-CD19 antibody fragment targeting domain against CD19+ cells, including healthy B cells
  - 1st CAR T approved 2017 for relapsed or refractory B cell leukemia or lymphomas
  - Potential remission for at least 5 years
- 5 CAR T therapies approved for oncology indications in the US

Chimeric AutoAntibody Receptor T cell

- Based on CAR T platform used in oncology but replaces targeting domain with an autoantigen
- Intended to direct CAART cells to selectively and specifically eliminate pathogenic B cells in autoimmune diseases while preserving the healthy B cells
- In mPV, the autoantigen is DSG3, and the pathogenic B cells, representing ≤1% of the total B cell population, express anti-DSG3 autoantibodies

Background



DSG3-CAART Cells

- DSG3-CAART cells express all the relevant DSG3 domains
- Since all pathogenic autoantibodies in mPV are directed against EC1, EC2, EC3, or EC4 of the DSG3 protein, the same manufacturing approach can be used for all patients.

Study Design

Major Inclusion Criteria

- Age: ≥18
- Inadequately managed by ≥1 immunosuppressive therapy
- Biopsy-confirmed diagnosis
- Active disease on PDAI
- Anti-DSG3 antibody positive

Major Exclusion Criteria

- Rituximab recently administered
- Prednisone > 0.25mg/kg/day
- Other autoimmune disorder requiring immunosuppressive therapies
- Recent investigational treatment
- ALC < 1,000 at screening

SCREENING → LEUKAPHERESIS & MANUFACTURING → TREATMENT (~1 WEEK) → MONITORING (1-4 WEEKS) → Next Patient

Part	# Cohorts	# Subjects
A – Dose Escalation 4 fractionated infusion at increasing dose levels	4	3 (+3) per cohort
B – Dose Consolidation Consolidating selected dose fractions into a single infusion	2	3 (+3) per cohort
C – Expansion Expanded subject enrollment at final selected dose	1	~12
	Total	~30 (+18)

Study Endpoint & Objectives

Primary Endpoint: Adverse Events, including Dose Limiting Toxicity (DLT)

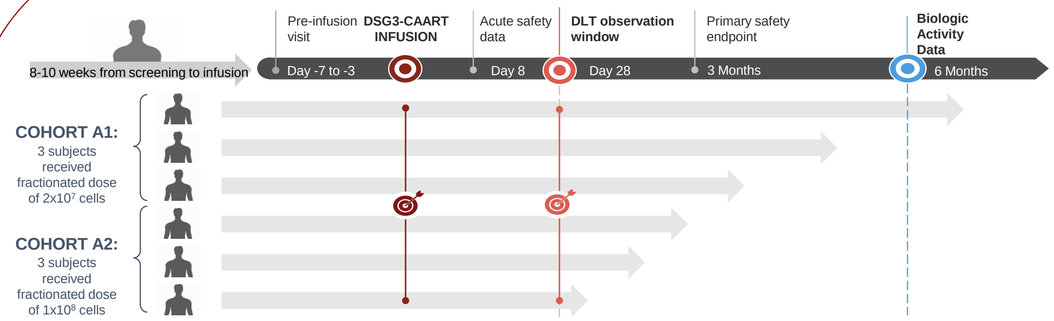
- DLTs include any moderate to severe cytokine release syndrome or neurotoxicity

Secondary Objectives: DSG3-CAART persistence, change in anti-DSG3 antibody levels, use of mPV medications and rescue therapies, change in disease activity, manufacturing success rate

The DesCAARTes™ Trial

- A phase 1 open-label 36-month clinical trial in mPV patients
- The objective is to determine the maximum tolerated dose of DSG3-CAART cells

Results*



No DLTs or clinically relevant adverse events in the 1st 6 patients

- 6 patients have been treated in the 1st two cohorts and monitored for at least 28 days
- Baseline characteristics of patients included a broad range of ages, disease duration, autoantibody levels, and number of prior PV therapies
- No DLTs or any clinically relevant toxicities have been observed in any patients in the setting of no pretreatment lymphodepletion, but in presence of anti-DSG3 antibodies*
- DSG3-CAART cell persistence via qPCR was observed in all patients during the 28 days post infusion

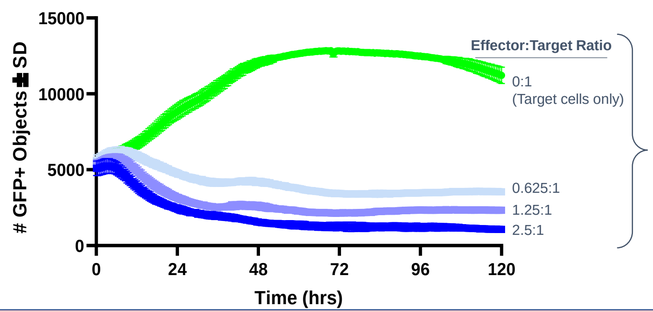
Manufacturing

- Strong operating partnership with Penn manufacturing organization
- Use of validated process from CAR T experience at Penn
- 100% success rate for DesCAARTes™ trial manufacturing*

Biologic Activity Indicators

- Ongoing and planned evaluations:
  - Persistence of DSG3-CAART detected via qPCR
  - Change in level of anti-DSG3 antibodies (targeting persistent reduction)
  - Reduced mPV therapy and absence of new systemic rescue therapy
  - Change in disease activity based on clinically validated scales (e.g. PDAI)

* As of 2021.09.08



Samples run in triplicate

1 × 10^5 target cells per well

Manufactured DSG3-CAART cells have exhibited target elimination *in vitro*

- An image-based *in vitro* cytotoxicity assay incubated manufactured DSG3-CAART cells from the 1st subject with anti-DSG3-expressing target cells labelled with GFP at various DSG3-CAART effector cell to target cell ratios
- The manufactured DSG3-CAART cells exhibited elimination of target cells in a dose dependent manner.

Conclusions

- Administration of 2x10^7 and 1x10^8 DSG3-CAART cells in the 1st two cohorts of mPV subjects has been well-tolerated through Day 28 in the Phase 1 DesCAARTes™ trial
- Manufactured DSG3-CAART cells from the 1st subject have exhibited selective *in vitro* cytotoxicity
- Based on the safety data, the next cohort of subjects will be administered a dose of 5x10^8 DSG3-CAART cells
- Ongoing and planned evaluations will assess for biologic activity indicators of DSG3-CAART

References::
Ellebrecht, Christoph T., et al. "Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease." Science 353.6295 (2016): 179-184.
Lee, Jinmin, et al. "Antigen-specific B-cell depletion for precision therapy of mucosal pemphigus vulgaris." The Journal of Clinical Investigation (2020).

Disclosures:

- Hoffman, Nunez, Volkov, Basu, Chang: Full-time employees of Cabaletta Bio:
- Payne: Co-founder with equity, consulting, grant funding, Cabaletta Bio; Inventor on patents licensed by Novartis, Cabaletta Bio

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