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Correlative findings following DSG3-CAART infusion with & without combination preconditioning therapy in patients with Pemphigus Vulgaris (DesCAARTes study)

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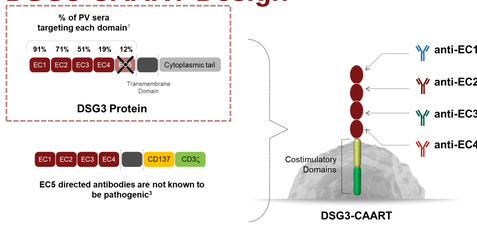
Background

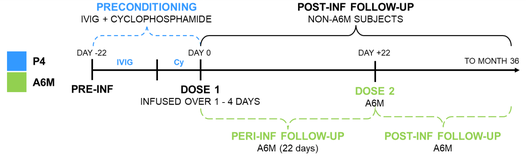
Mucosal-dominant pemphigus vulgaris (mPV) is a painful blistering mucosal disease mediated by anti-desmoglein 3 antibodies (anti-DSG3). The current standard of care for mPV includes broadly immunosuppressive therapies (corticosteroids, MMF, & rituximab) that are not curative, require chronic administration & have risks of serious or life-threatening infection. We are evaluating the safety & activity of a novel cellular therapy consisting of gene-modified autologous Chimeric Autoantigen Receptor T cells (CAART) engineered to selectively eliminate DSG3 reactive B cells while sparing non-autoreactive immune cells in subjects with mPV (NCT 04422912). We previously reported on translational & clinical data from mPV subjects receiving escalating doses of DSG3-CAART cells ranging from $2x10^5$ to $7.5x10^9$ transduced cells without preconditioning. DSG3-CAART cells were detected in the blood of all subjects within the first 29 days post-infusion; persistence via AUC for the first 29 days (AUC_{29d}) increased in a dose-dependent manner reaching a plateau at a dose of $2.5x10^9$ transduced cells. Here, we expand on those findings with data from two clinical strategies designed to increase DSG3-CAART cell exposure: 1) preconditioning with intravenous immune globulin (IVIG; to reduce anti-DSG3 concentrations) & cyclophosphamide (to reduce leukocytes) before CAART cell infusion (P4, n=2) & 2) multi-administration of two consecutive DSG3-CAART cell doses separated by 22 days (A6m, n=1). We report on peripheral blood cellular composition & serological factors before & after DSG3-CAART cell infusion utilizing these strategies.

DSG3-CAART Design



Overview of Dosing Cohorts

Cohort	Total Dose	Fold increase in dose	Patients per cohort
A1	2 x 10^7 DSG3-CAART	1x	3
A2	1 x 10^8 DSG3-CAART	5x	3
A3	5 x 10^8 DSG3-CAART	25x	3 [+1 A1-1 re-treated at the A3 dose]
A4	2.5 x 10^9 DSG3-CAART	125x	3
A5	5 - 7.5 x 10^9 DSG3-CAART	250 to 375x	4
P4	2.5 x 10^9 DSG3-CAART (with IVIG & cyclophosphamide)	125x	2 [+1 planned]
A6m	2 doses of 6.9 x 10^9 DSG3-CAART (13.8 x 10^9 total)	500x	1 [+2 planned]



Results

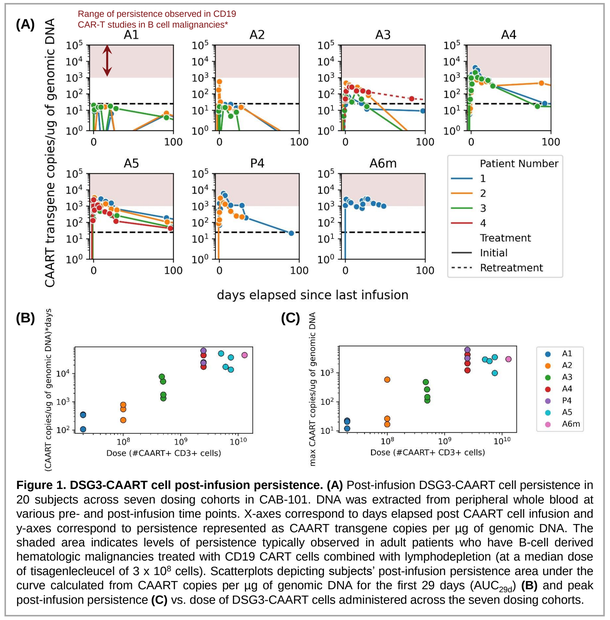


Figure 1. DSG3-CAART cell post-infusion persistence. (A) Post-infusion DSG3-CAART cell persistence in 20 subjects across seven dosing cohorts in CAB-101. DNA was extracted from peripheral whole blood at various pre- and post-infusion time points. X-axes correspond to days elapsed post CAART cell infusion and y-axes correspond to persistence represented as CAART transgene copies per µg of genomic DNA. The shaded area indicates levels of persistence typically observed in adult patients who have B-cell derived hematologic malignancies treated with CD19 CART cells combined with lymphodepletion (at a median dose of tisagenlecleucel of 3 x 10^8 cells). Scatterplots depicting subjects' post-infusion persistence area under the curve calculated from CAART copies per µg of genomic DNA for the first 29 days (AUC_{29d}) **(B)** and peak post-infusion persistence **(C)** vs. dose of DSG3-CAART cells administered across the seven dosing cohorts.

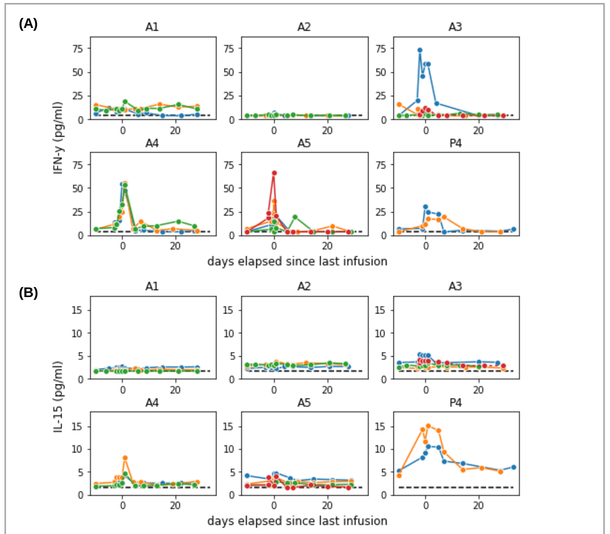


Figure 3. Pre- & post-infusion serum cytokine levels. Cytokine concentrations of **(A)** IFN-γ and **(B)** IL-15 were quantified via MSD in serum samples collected pre- & post-DSG3-CAART cell infusion from 20 subjects dosed in CAB-101. Serum concentrations represented as pg per mL (y-axes) and the x-axes correspond to days elapsed since last infusion. A6m data was not available due to data cutoff. Subject A3-1 tested positive for COVID-19 on Day +1 post-infusion.

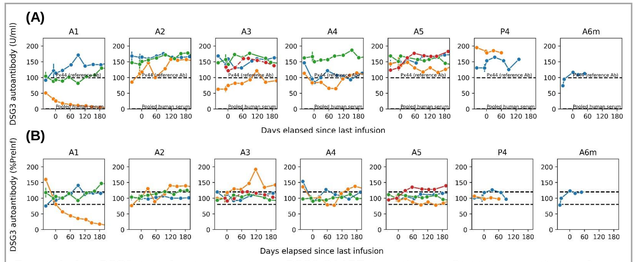


Figure 4. Anti-DSG3 auto-Ab levels following DSG3-CAART cell infusion. Screening, pre-infusion, & post-infusion anti-DSG3 Ab levels were measured by ELISA (MBL International) as U/mL in serum isolated from 20 subjects from the first seven dosing cohorts of CAB-101. (**A**) Line graphs depicting absolute values of anti-DSG3 auto-Ab levels in U/mL over time. X-axis refers to time pre-infusion & up to 180 days post-infusion (to date, subjects from P4 & A6m have not reached 180 days post-infusion clinically). Dashed line depicts DSG3 antibody control for assay. (**B**) Line graphs depicting relative anti-DSG3 auto-Ab levels over time normalized to the pre-infusion timepoint for each subject. Dashed lines represent changes from the baseline, ± 20%, which are considered significant in this assay. *Subject A1-2 was treated with rituximab within 12 months prior to DSG3-CAART cell infusion (enrollment criteria modified since to exclude subjects dosed with Rituximab within 12 months of infusion).

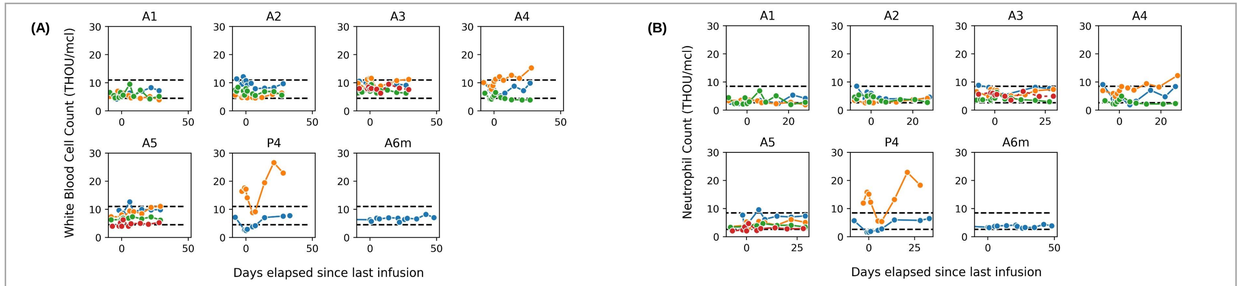


Figure 2. Leukocyte & neutrophil counts pre- and post-DSG3-CAART cell infusion. Leukocyte **(A)** and neutrophil **(B)** concentrations were measured using a Complete Blood Count (CBC) test in 20 subjects dosed with DSG3-CAART cells in CAB-101. X-axis of all plots corresponds to days elapsed since last infusion. Dashed lines indicate the lower and upper bounds of what are considered normal values.

Conclusions

- No DLTs were observed for any of the A6m or combination cohort patients reported
- DSG3-CAART persistence peak and AUC in mPV subjects is modestly impacted by cyclophosphamide only combination therapy and multi-dosing strategies
  - The data to date is insufficient to establish if pretreatment with cyclophosphamide alone enhances persistence
  - The multi-dose strategy employed in one A6m subject extends DSG3-CAART persistence; however, this does not increase the early persistence AUC over the first 29 days after dosing
  - Peak persistence of DSG3-CAART cells reaches levels observed in hematologic CD19 CAR-T trials with cyclophosphamide and fludarabine lymphodepletion (>1000 copies / ug DNA)
- Preconditioning with IVIG and cyclophosphamide reduced leukocyte counts, driven by neutrophils, and increased serum IL-15
- A more aggressive preconditioning regimen consisting of cyclophosphamide plus fludarabine may further enhance both lymphocyte depletion and CAART cell persistence and is planned following the completion of the DLT-window for the P4 cohort
- To date, there is no clear pattern of changes in anti-DSG3 autoantibody levels across dosing cohorts despite increased DSG3-CAART cell persistence
  - Subject A4-2 demonstrated a transient decrease (>20% of pre-infusion values) in anti-DSG3 levels at Months 2 & 3, coinciding with substantially higher DSG3-CAART persistence at Month 3