Immunotherapy of pemphigus

*From preclinical to clinical proof of concept*

Aimee S. Payne, MD, PhD

*Professor of Dermatology*

*University of Pennsylvania*

August 7, 2021
Disclosures

- Co-founder, Cabaletta Bio *(equity, grants, payments)*
- Novartis *(patent licensing)*
- Tmunity *(patent licensing)*
Pemphigus vulgaris (PV)  
a paradigm for human autoantibody-mediated disease

- Anti-desmoglein (DSG) antibodies are necessary and sufficient for blister formation
- Anti-DSG3 antibodies are 98-100% sensitive and specific for disease diagnosis
- Disease relapse is associated with recurrence of identical anti-DSG3 clones found in active disease
- No anti-DSG3 B cells are found in long-term remission
- Disease is caused by anti-DSG3 B cells and the antibodies they produce

http://www.vgird.org/archive/cases/2004/pv/pv.htm

First-line rituximab for pemphigus vulgaris

- Originally FDA-approved for the treatment of B cell lymphomas
- 90% rate of complete remission off steroids for at least 2 months at 24 months, compared to 28% with high-dose steroids alone
- After rituximab therapy, anti-DSG3 antibody titers drop to the normal range
  
  Repetitive treatments are required to restore or maintain disease remission
  8% of patients treated with rituximab and steroids experienced serious infections during the 2 year study, compared to 3% of patients treated with high dose prednisone alone

Joly et al, Lancet 2017; Rituxan™ package insert
Rituximab for relapsed-refractory pemphigus

- Maintenance dosing of rituximab with steroids leads to a **40.3% rate** of complete remission off steroids for at least 16 weeks at 12 months, compared to 9.5% treated with mycophenolate and steroids.
- 9% of patients experienced serious infections.
Chimeric antigen receptor (CAR) T cell therapy
*FDA-approved technology for lasting remission of B cell cancers*

**Antigen binding (anti-CD19)**

- **Tisagenlecleucel in B-cell acute lymphoblastic leukemia**
  - Maude et al, *NEJM* 2018
  - 81% complete remission
  - 50% long-term remission (12 mos)

- **Tisagenlecleucel in large B cell lymphoma**
  - Schuster et al, *NEJM* 2019
  - 40% complete remission
  - 65% relapse-free survival (12 mos)

**Costimulation (CD137 and/or CD28)**

**T cell activation (CD3ζ)**

- **Axicabtagene ciloleucel in large B cell lymphoma**
  - Neelapu et al, *NEJM* 2017
  - 54% complete remission
  - 40% long-term remission (median 15 mos)
Chimeric autoantibody receptor (CAAR) T cells

*Engineered for antigen-specific B cell depletion*

**Anti-DSG3 B cell receptor**: A membrane-bound autoantibody that defines autoimmune B cells in PV.
Chimeric autoantibody receptor (CAAR) T cells

*Engineered for antigen-specific B cell depletion*

**Chimeric antigen receptor (CAR)**

**DSG3 CAAR**: Directs T cell killing toward anti-DSG3 B cells and may generate memory CAART cells that persist long-term.

**Anti-DSG3 B cell receptor**: A membrane-bound autoantibody that defines autoimmune B cells in PV.

**Chimeric autoantibody receptor (CAAR)**
Advancing CAART technology to clinical trials

Investigational New Drug (IND) application

- Chemistry, Manufacturing, and Controls
- Pharmacology and Toxicology
- Clinical rationale and investigative plan

- Controls to ensure product quality (release criteria)
- Manufacturing consistency and stability (GMP engineering of DSG3 CAAR plasmid, DSG3 CAAR lentivirus, DSG3-CAART cells)
- Comprehensive toxicology at different timepoints and doses
- Efficacy against PV patient B cells and in an active immune mouse model of PV
- Screens against primary human cells and high-throughput proteome arrays to identify potential off-target toxicity
- Clinical trial protocol

➢ DSG3-CAART IND cleared in September 2019
Antigen-specific B cell depletion with DSG3-CAART

Histologic and serologic remission of PV without detectable off-target cytotoxicity

- Elimination of anti-DSG3 B cells and mucosal blistering
- Dose-dependent drop in anti-DSG3 antibody titers and increased DSG3-CAART engraftment
- No off-target toxicity identified in assays using human skin xenografts, primary human cells, and high-throughput membrane proteome arrays

Ellebrecht et al, Science 2016 and Lee et al, JCI 2020
DSG3-CAART is effective in an active immune model

*histologic remission of disease + specific reduction of pathogenic autoantibodies*

Adapted from Lee et al, JCI 2020
Investigating pharmacologic effects of serum autoantibodies

Inhibition due to antibody blocking?

Potentiation due to activation and proliferation?
Investigating effects of serum autoantibodies

CAART proliferation/CAAR renewal counters potential inhibition by anti-DSG3 IgG

Cytolytic inhibition or potentiation

Interferon gamma production

DSG3-CAART proliferation

Renewal of free cell-surface DSG3 CAAR

Pulse-chase labelling with anti-DSG3 IgG

Titer-dependent IFNγ production

PV IgG-induced proliferation

Potentiation

Inhibition

Anti-DSG3 IgG (µg/mL)

Specific lysis (%)

Ellebrecht et al, Science, 2016; Lee et al, JCI 2020
Activity against the intended human target cells

*Anti-DSG3 and total B cell ELISpot killing assay*

Harvest and purification of PV or healthy donor (HD) patient B cells

- PV B cells + NTD
- PV B cells + DSG3-CAART
- PV B cells + CART19
- HD B cells + NTD
- HD B cells + DSG3-CAART
- HD B cells + CART19

DSG3 antihIgG BSA Coating
Activity against the intended human target cells

*Anti-DSG3 and total B cell ELISpot killing assay*

Anti-DSG3 B cells comprise 0.5-1% of total IgG B cells in PV patients

No anti-DSG3 B cells detected in HD patients

Plated cells

100K 1K 1K
Activity against the intended human target cells

*Anti-DSG3 and total B cell ELISpot killing assay*

DSG3-CAART and CART19 reduce anti-DSG3 B cells

Only CART 19 reduces total IgG B cells
Unbiased screen for potential off-target toxicity

Membrane proteome array screening with DSG3 CAAR ectodomain

5,300 membrane proteins

Measure binding

Membrane proteome binding profile
Unbiased screen for potential off-target toxicity

Membrane proteome array screening with DSG3 CAAR ectodomain

Lee et al, JCI 2020
Off-target cytotoxic interactions were not observed

No DSG3-CAART activation by CLEC4M-overexpressing cells

- CLEC4M interaction may be an artifact of additional/aberrant glycosylation in the Fc-tag, which is not present in DSG3-CAART
- The affinity or intermembrane distance of the interaction may be suboptimal for an effective immunological synapse to form

Lee et al, JCI 2020
**DesCAARTes™ Study: Phase 1 trial in mucosal PV Patients**
Open-label study to evaluate the safety and efficacy of DSG3-CAART (NCT04422912)

**Key Inclusion Criteria**
- Age 18 or over
- Inadequately managed by 2+ standard immunosuppressive therapies
- Confirmed diagnosis
- Active disease
- Anti-DSG3 antibody positive

**Key Exclusion Criteria**
- Recent rituximab use
- Prednisone > 0.25 mg/kg/d
- Other autoimmune disorder requiring immunosuppressive therapy
- Recent investigational treatment

**Study Endpoint & Objectives**

**Primary Endpoint:** Adverse Events, including Dose Limiting Toxicity (DLT)
- DLTs include any grade 3 or 4 CRS or neurotoxicity, or any grade 2 CRS or neurotoxicity that failed to improve to ≤ Grade 1 or baseline within 7 days

**Secondary Objectives:** DSG3 ELISA titer changes, rate of/time to/duration of remission, manufacturing success rate, CAAR T expansion/persistence

**Sponsor:** Cabaletta Bio
Cell therapy for pemphigus
Entering the precision medicine era

• DSG3-CAART is a precision cellular immunotherapy for autoimmunity that aims to durably eliminate DSG3-specific B cells while sparing normal B cells
• A phase 1 multisite trial of DSG3-CAART for mucosal PV is currently enrolling
• No dose-limiting toxicities or clinically relevant adverse events have been observed in the first 28 days after infusion for the first cohort (DSG3-CAART cells detectable at low levels in all 3 pts)
• Once proven successful in mucosal pemphigus vulgaris, precision therapies for other antibody-mediated diseases could follow