Taking aim at autoimmunity with CAAR T cells

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Disclosures

• Co-founder with equity, consulting, grant funding, Cabaletta Bio
• Inventor on patents licensed by Novartis, Cabaletta Bio
• Off label use of treatments for pemphigus will be discussed
Autoimmunity in the United States

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Cancer</th>
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<td>Prevalence</td>
<td>24 million</td>
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<tr>
<td>Annual direct healthcare costs</td>
<td>$100 billion+</td>
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<td>NIH research funding (2020)</td>
<td>$1 billion</td>
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“In general, two approaches to treatment are currently available. The first involves replacing or repairing impaired function...The second treatment approach centers on suppressing the destructive immune response.”

*Progress in Autoimmune Diseases Research, NIH ADCC report, 2005*
We declared war on cancer

Are we waging an effective war on autoimmunity?
Pemphigus vulgaris (PV): A paradigm for human autoantibody-mediated disease

- Anti-desmoglein (DSG) 3 antibodies are 98-100% sensitive and specific for disease diagnosis
  
  *Ishii JI 1997; Schmidt Exp Derm 2010*

- Anti-DSG3 antibodies are necessary and sufficient for blister formation, even as monovalent antibody fragments
  
  *Amagai JCI 1992; Amagai JCI 1994; Yeh Clin Immunol 2006; Payne JCI 2005*
Pemphigus treatment paradigm, circa 2000:
Global immune suppression with corticosteroids and adjunctive immunosuppressants

- **Corticosteroids**
  - Relatively rapid disease control with prednisone and slow taper
  - Increases expression of DSG3 and other adhesion molecules by inhibiting STAT3

- **Off-label treatment with adjunctive immunosuppressants** for steroid-sparing effect
  - mycophenolate, azathioprine, methotrexate

- **IVIG** infusions as an alternative or adjunctive therapy for disease control

- Severe hospitalized cases often treated with **plasmapheresis and cyclophosphamide**

➤ **Managing risk of disease versus risk of therapy:** GI bleed, avascular necrosis, agranulocytosis, Pneumocystis pneumonia, sepsis, secondary cancers, blood clots, aseptic meningitis

Nguyen JBC 2004, Mao JCI Insight 2017
Wide variation exists in diagnostic techniques and treatment of PV, even among the world’s experts... There is clearly a need for consensus standard with regard to patient stratification and randomized controlled trials.
Consensus definitions and disease activity instruments

Paving the way for clinical trials

Complete remission on minimal therapy: blister-free on prednisone ≤10 mg daily and/or half-maximal dose of adjunctive immunosuppressants

Complete remission off therapy: blister-free for at least 2 months off systemic and topical therapy
Randomized clinical trials in pemphigus
The start of the evidence-based era

- Azathioprine, mycophenolate and cyclophosphamide are effective steroid-sparing agents in pemphigus
  Beissert Arch. Dermatol. 2006; Chams-Davatchi JAAD 2007
- Infliximab and etanercept did not demonstrate significant therapeutic effect in placebo-controlled RCTs
  Hall, BJD 2015; Fiorentino JAMA Derm 2010

Journal of Investigative Dermatology
Volume 130, Issue 8, August 2010, Pages 2041-2048

Original Article
Treating Pemphigus Vulgaris with Prednisone and Mycophenolate Mofetil: A Multicenter, Randomized, Placebo-Controlled Trial
Stefan Beissert 1, Daniel Mimouni 2, 3, Amrinder J. Kanwar 4, Neil Solomons 2, Veena Kalia 2, Grant J. Anhalt 5

Prednisone 1-2 mg/kg/day until disease control

placebo  MMF 2 g/day  MMF 3 g/day

Proportion in CR on prednisone ≤10 mg daily at 48-52 weeks

MMF failed to reach the primary endpoint
- Faster and more durable CRs with MMF
- Lower total prednisone dose with MMF
Moving toward more effective pemphigus therapies

Anti-CD20 B cell depletion with rituximab

Early RTX therapy = better clinical response
Lunardon, JAMA Dermatol 2012

- Retrospective cohort (n=34)
• FDA-approval of rituximab in June 2018 for PV
  - Increased efficacy and safety of first-line RTX plus short-term prednisone vs high-dose prednisone alone
  - Anti-DSG3 titers drop to negative range with repeated rituximab infusions

• Up to 90% of responders relapse without maintenance therapy

• 2nd line RTX + maintenance is superior to MMF
  - 40.3% vs 9.5% remission at 52 weeks

• Chronic B cell depletion with rituximab:
  - 4-9% annual rate of serious infections
  - Up to 1.9% lifetime risk of fatal infection

Prospective randomized clinical trials of rituximab
Maintenance RTX and prednisone versus high-dose prednisone or MMF

Joly Lancet 2017; Colliou STM 2013; Tony Arthr Res Ther 2011; Werth et al, NEJM 2021
Mechanisms of relapsed and refractory disease after RTX

Incomplete B cell depletion by rituximab

Hammers, JID 2015; Ellebrecht, JCI Insight 2017; Colliou, Science Transl Med 2013
What can the war on cancer teach us?

Precision Oncology

Immunotherapy

President Richard Nixon signing the National Cancer Act of 1971. Credit: National Cancer Institute

CANCER MOONSHOT

INITIATIVES 2017–2020

OVER 70
CONSORTIUMS OR PROGRAMS

OVER 240
RESEARCH PROJECTS
Chimeric antigen receptor (CAR) T cells:
Precision cures of B cell cancers

58 - 81% complete remission
40 - 57% long-term remission

Maude et al, NEJM 2018
Locke et al, Lancet Oncol 2018
Wang et al, NEJM 2020
Pathogenic B cells in PV are uniquely defined by a surface anti-DSG3 B cell receptor.

Replacing the anti-CD19 domain with the DSG3 autoantigen directs antigen-specific rather than total B cell depletion.

Targeted B cell depletion with CAAR T cells could lead to durable remission of PV without global immune suppression.

From CARs to CAARs
Adapting precision cures of B cell cancers for B cell-mediated autoimmune diseases
Antigen-specific B cell depletion with DSG3-CAART

Histologic and serologic remission of experimental 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
Moving CAART technology forward to clinical trials

**Basic research**
- Discovery
- Proof of concept

**Investigational New Drug application**
- Chemistry, Manufacturing, and Controls
- Pharmacology and Toxicology
- Clinical Trial Protocol

**Clinical research**
- First-in-human clinical trial

- GMP manufacturing
- Clinical operations
- Regulatory teams
- Financial support

- IND cleared by FDA in September of 2019
- FDA Orphan Drug Designation
- FDA Fast Track Designation
Considerations on clinical application
CARTs for cancer versus CAART for pemphigus

- Mechanisms of anti-CD19 CART resistance
  - Shedding of CD19
    - Unlikely - BCR negative cells may be functionally anergic
  - Mutation of CD19
    - If BCR no longer binds DSG3 it will be irrelevant to disease

- Cytokine release syndrome (CRS)
  - Unlikely from target cell burden (anti-DSG3 B cells are <1% of total B cells)
  - May occur from serum anti-DSG3 antibody if it activates DSG3-CAART (start with low fractionated dose)

- Lymphodepletion may not be required in non-oncologic indications
  - Reduces regulatory T cells that suppress CART function – but in autoimmunity Tregs are typically dysfunctional
  - CD4 CAR T cell trials for HIV indicate 11+ year engraftment after infusion of 1-2e9 CART cells without lymphodepletion
  - Higher CAART dose (+/- in vivo expansion from soluble anti-DSG3 antibody) may be sufficient for engraftment

The DesCAARTes™ Phase 1 Trial (NCT04422912)
Open label study of DSG3-CAART in mucosal PV patients

Major Inclusion Criteria
- Age ≥ 18, confirmed diagnosis
- Inadequately managed by std immunosuppressive therapies
- Active disease
- Anti-DSG3 antibody positive
- Recent rituximab
- Prednisone > 0.25mg/kg/day
- Other autoimmune disorder requiring immunosuppressive therapies
- Recent investigational treatment
- ALC < 1,000 at screening

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Part | Cohorts | # Subjects
--- | --- | ---
A – Dose Escalation
Fractionated infusions 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 | Approx 12

Currently enrolling at 3 sites:
- Penn (Porter/Micheletti/Werth)
- UC-Davis (Abedi/Maverakis)
- Stanford (Marinkovich/Weng)
The DesCAARTes™ Phase 1 Trial (NCT04422912)
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<th>Screening</th>
<th>Apheresis</th>
<th>DSG3-CAART INFUSION</th>
<th>Acute safety data</th>
<th>Primary safety endpoint</th>
<th>Evidence of target engagement</th>
<th>Efficacy</th>
<th>Long-term follow-up</th>
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<td>Week -10 to -8</td>
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### Primary Study Endpoint

#### Adverse Events
Dose Limiting Toxicities include:
- Grade 3+ cytokine release syndrome or neurotoxicity
- Grade 2 cytokine release syndrome or neurotoxicity that fails to improve to Grade 1 or baseline within 7 days

### Other measures
- Manufacturing success rate
- CAART expansion / persistence
- Maximum tolerated dose and optimal fractionation regimen

- No DLTs or clinically relevant toxicities observed in the first 28 days following infusion for all 3 patients in the first cohort
  - DSG3-CAART cells were detected at low levels by qPCR in all 3 patients

- Declining anti-DSG3 titers
  Assuming selective B cell ablation in 2-4 wks and IgG half-life of 3-4 wks, anti-DSG3 antibody titers should fall within 6 months

- Key efficacy measures
  - Anti-DSG3 antibody titer
  - Disease activity (clinical)
  - Steroid / immunosuppressive use
  - Rate of / time to / duration of remission

**Adjunctive immunosuppressants are stopped; prednisone tapered to low dose prior to infusion**
Precision medicine for pemphigus

- Collaboration between cancer and autoimmune disease researchers has enabled the discovery and advancement of CAART technology from the laboratory to the clinic
- DSG3-CAART represents the first precision cellular immunotherapy to enter clinical trials for an autoimmune disease indication
- DSG3-CAART aims to durably eliminate antigen-specific B cells while sparing normal B cells, potentially leading to safe and lasting remission of mucosal PV with a one-time treatment
- Once proven successful in mucosal PV, precision therapies for other antibody-mediated diseases could follow, including mucocutaneous (DSG3+DSG1) PV, MuSK myasthenia gravis, PLA2R membranous nephropathy, and hemophilia A with Factor VIII inhibitors
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