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Develop and launch the first curative targeted cellular therapies for patients with autoimmune diseases
Cabaletta overview

Developing highly specific CAAR T products to treat B cell-mediated autoimmune diseases
- Product design and manufacturing leverage Penn alliance and FDA-approved CAR T platform
- Pursuing diseases where there is a biologic opportunity for cure with the CABA platform

DSG3-CAART clinical program actively recruiting mucosal pemphigus vulgaris (mPV) patients
- Acute safety (8 day) data from initial cohort of the DesCAARTes™ trial expected by 1H21
- Multiple clinical sites engaged across the U.S. supported by validated manufacturing partnership with Penn
- Fast Track and Orphan Drug Designations granted

Preclinical pipeline led by MuSK-CAART for myasthenia gravis with IND filing anticipated in 2H21
- IND-enabling studies ongoing with in vivo preclinical data presented at American Academy of Neurology
- Manufacturing validation initiating with CMO partner in 2H20
- Three new discovery programs recently added through expanded SRA with Penn
- Gene editing collaboration established with Artisan Bio to develop potential next-generation CAAR T products

Issued U.S. patent on lead clinical program with emerging differentiated IP portfolio
- First issued CAAR T product patent covers all or any part of the relevant human antigens (DSG3 and DSG1)

Cash runway into at least 3Q22 with $123M in cash and investments at June 30, 2020
Our scientific platform leverages FDA-approved CAR T technology

CAAR T product candidates are designed for selective and specific elimination of the pathogenic B cells

Chimeric Antigen Receptor T cell

Kymriah

Chimeric AutoAntibody Receptor T cell

CABA CAAR T
CABA (Cabaletta Approach for Selective B cell Ablation) platform

Scientific, clinical and commercial assessment to inform product candidate development

Epitope mapping to determine regions targeted by autoantibodies

Optimize CAAR construct / design with the goal of selectively ablating reactive B cells

Preclinical in vitro and in vivo testing to evaluate efficacy and safety

Vector & Clinical Cell manufacturing

Clinical trials

MuSK-CAART

DSG3-CAART
Pipeline addressing disease targets where cure is possible

<table>
<thead>
<tr>
<th>Indication</th>
<th>Program</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Pemphigus Vulgaris</td>
<td>DSG3-CAART</td>
<td></td>
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<tr>
<td>Mucocutaneous Pemphigus Vulgaris</td>
<td>DSG3/1-CAART</td>
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<tr>
<td>MuSK Myasthenia Gravis</td>
<td>MuSK-CAART</td>
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<tr>
<td>Hemophilia A w/ FVIII Alloantibodies</td>
<td>FVIII-CAART</td>
<td></td>
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</table>

1 Three additional undisclosed discovery programs added to our pipeline portfolio through Sponsored Research Agreement expansion with the University of Pennsylvania not shown.
2 In our discovery stage, we perform epitope mapping and optimize CAAR construct and design.
3 May not be required if Phase 2 is a registrational clinical trial.
DSG3-CAART for patients with mucosal pemphigus vulgaris
PV is an optimal lead indication for CAAR T therapy

DSG3 antibodies are widely considered to be necessary and sufficient to cause PV. Serum anti-DSG3 antibodies are 98-100% sensitive and specific.


Depletion of B cells by rituximab or antibody by plasmapheresis transiently improves clinical disease.

Incomplete B cell depletion by rituximab leads to PV recurrences, with identical disease-causing B cell clones.

The B cell repertoire and antigenic epitopes on DSG1/3 are well understood, and formed the basis for DSG3 and DSG1 CAAR designs.

The DSG3 CAAR has published animal model proof-of-concept validation.
Overview of Pemphigus Vulgaris

Current treatments require broad immunosuppression associated with safety risks and transient efficacy.

**Current Treatment Landscape**

**Broad immunosuppression**
- Modestly effective
- Poorly tolerated

**B cell depletion with rituximab**
- Transient remission ~ 70% CROT*
  - ~30% relapse in 1 year
  - >50% relapse within 2 years
- ~30% never achieve CROT
- 5.4% annual risk of severe infection
- Up to 1.9% lifetime risk of fatal infection

*CROT = complete remission off therapy

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1. Image credit: D@nderm
DSG3-CAART encompasses all known pathogenic epitopes


2. Antibodies that target the specific extracellular domain are shown below each extracellular domain.
### DSG3-CAART preclinical data

No evidence of toxicity at clinically relevant doses with selective and specific target engagement

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tolerability</strong></td>
<td></td>
</tr>
<tr>
<td>In vitro off-target toxicity</td>
<td>No specific cytotoxicity at clinically relevant cell numbers vs FcγR-expressing cells</td>
</tr>
<tr>
<td></td>
<td>No interactions confirmed with human membrane proteins</td>
</tr>
<tr>
<td>In vivo off-target toxicity</td>
<td>No off-target effects detected at clinically relevant doses</td>
</tr>
<tr>
<td><strong>Target Engagement</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-DSG3 autoantibody titer</td>
<td>Serologic ‘remission’ - dose-dependent elimination of anti-DSG3 B cells and antibodies</td>
</tr>
<tr>
<td>CAAR T cell engraftment</td>
<td>Dose-dependent increase in CAAR-positive cells observed via flow cytometry</td>
</tr>
<tr>
<td>Tissue blistering</td>
<td>Histologic ‘remission’ - no blistering of oral mucosa</td>
</tr>
<tr>
<td>Anti-DSG3 hybridoma outgrowth</td>
<td>Significantly delayed outgrowth despite soluble anti-DSG antibodies</td>
</tr>
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</table>
DesCAARTes™:
Phase 1 clinical trial in mucosal-dominant PV (mPV) patients

Open-label study to determine the maximum tolerated dose & fractionation of DSG3-CAART

**Major Inclusion Criteria**
- Age: ≥18
- Inadequately managed by standard immunosuppressive therapies
- Confirmed diagnosis
- Active disease
- Anti-DSG3 antibody positive

**Major Exclusion Criteria**
- Rituximab in last 6 months
- Prednisone > 0.25mg/kg/day
- Other autoimmune disorder requiring immunosuppressive therapies
- Recent investigational treatment
- ALC < 1,000 at screening

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<table>
<thead>
<tr>
<th>Part</th>
<th>Cohort</th>
<th># Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – Dose Escalation</td>
<td>A1-A4</td>
<td>3 (+3) per cohort</td>
</tr>
<tr>
<td>Fractionated infusion at increasing dose levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B – Dose Consolidation</td>
<td>B1-B2</td>
<td>3 (+3) per cohort</td>
</tr>
<tr>
<td>Consolidating selected dose fractions into a single infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C – Expansion¹</td>
<td>C</td>
<td>~12</td>
</tr>
<tr>
<td>Expanded subject enrollment at final selected dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>~30 (+18)</td>
</tr>
</tbody>
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**Study Endpoint & Objectives**

**Primary Endpoint:** Adverse Events, including Dose Limiting Toxicity

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

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¹ FDA has requested, and the Company has agreed, that we will share data from part A to inform a discussion on the optimal design of part C. According to FDA guidance, the submission of part A data is not gating to planned enrollment in part B.
DesCAARTes™ clinical trial assessments and timeframes

Safety assessed acutely and at 3 months, with ability to measure CAAR T engagement by 6 months

2. To be potentially incorporated in future protocol amendments or trials after discussion with FDA.

### Key Risks

<table>
<thead>
<tr>
<th>Risk Type</th>
<th>To reduce risk of occurrence</th>
<th>If risk encountered</th>
</tr>
</thead>
</table>
| CRS / Neurotoxicity               | • Product designed to kill <1% of B cells  
• Low initial dose with fractionation  
• No lymphodepletion               | • Manage with standard protocols |
| Soluble antibody                  | • Fractionated dosing designed to mitigate against potential toxicity | • Pretreat w/ plasmapheresis or IVIG  
• Limit soluble anti-DSG3 antibody inclusion criteria |
| Insufficient efficacy / CAAR T engraftment | • Wide cell dose range planned | • Consider increased dose and/or preconditioning / lymphodepletion |
| Disease flare with medication taper | • Limit dose of corticosteroid use to enroll | • Local / oral steroids; plasmapheresis |
| Skin toxicity from cross-reactivity | • No preclinical signals | • Local / oral steroids; plasmapheresis |
| New autoimmune disorder or worsening | • Patients with active autoimmune disorders requiring immunosuppressants excluded | • Autoimmune therapies as needed |

### Declining anti-DSG3 titers

Assuming selective B cell ablation in 2-4 weeks, serum IgG (half-life ~3 weeks) should fall within 6 months

### Key efficacy measures

- DSG3 antibody titer (ELISA)
- Disease activity (clinical)
- Steroid / immunosuppressive use
Soluble antibodies may alter the dynamics of DSG3-CAART proliferation

Preclinical data suggests soluble antibodies can partially activate or inhibit DSG3 CAAR T cells

Inhibitory antibodies may reduce, but do not prevent, DSG3-CAART target engagement

![Graph showing specific lysis vs. soluble IgG concentration](image)

- Increased target engagement
- Decreased target engagement

EC1-4 vs. PV Ab #1
EC1-4 vs. PV Ab #2
NTD vs. PV Ab #1
NTD vs. PV Ab #2

Soluble anti-DSG3 induces CAAR T cell proliferation

![Graph showing T cell division](image)

- Increased T cell division compared to response to normal human IgG

Cell division

2. Antibodies derived from a hybridoma model.
3. Non-transduced T cell.
4. CFSE (carboxyfluorescein diacetate succinimidyl ester) is a dye used in flow cytometric monitoring that reduces in intensity as it is distributed in actively dividing cells. Non-dividing cells will retain more CFSE dye.
Active Immune Model: Target engagement despite soluble antibody

DSG3-CAART demonstrates target engagement in presence of physiologic DSG3 antibody titer

1. The DSG3 protein is made of up of 5 extracellular (EC) domains, EC1-5. Antibodies against EC1-4 can be pathogenic, but antibodies against EC5 are not. Therefore, antibodies against EC5 are not targeted by the CAAR by design.

2. In this model, the human DSG3-CAART product is rapidly rejected. In these two animals, an incomplete response against EC1 was observed, which correlated with loss of persistence.
**Preconditioning regimens in CAAR T cell therapy may not be required**

Past successes in HIV and multiple myeloma without preconditioning plus differences in patient populations are relevant\(^1,2\)

- Data suggest preconditioning may not be necessary to drive responses beyond leukemia / lymphoma

- Potential activating effect of soluble antibody on engraftment and function is a key consideration in autoimmune patients

- Multiple infusions, higher dose, and cytokine use may offer more tolerable approach for autoimmune patients

<table>
<thead>
<tr>
<th>Lymphodepletion Mechanism</th>
<th>Oncology</th>
<th>Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of T cell growth cytokine sinks(^3)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Depletion of suppressor cells(^4)</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^{+}\) Lymphodepletion mechanism likely to apply

\(^{-}\) Lymphodepletion mechanism unlikely to apply

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DSG3/1 CAART for mucocutaneous PV (mcPV)

Plan to potentially submit an IND after review of safety and target engagement data from DSG3-CAART

**DSG3/1 CAARs designed for mcPV**

- DSG3 and DSG1 autoantibodies
- Most severe and common form of PV (~75%)
- Mucosal blistering, plus skin erosion and blistering
- Managed with immune suppression, similar to mPV
  - High risk of relapse
  - Potential for hospitalizations and fatal infections

% of PV sera targeting each domain

<table>
<thead>
<tr>
<th>Domain</th>
<th>EC1</th>
<th>EC2</th>
<th>EC3</th>
<th>EC4</th>
<th>EC5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSG1</td>
<td>98%</td>
<td>26%</td>
<td>9%</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Transmembrane Domain

Cytoplasmic tail

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**DSG1-CAART and DSG3-CAART both demonstrated specific cytotoxicity in vitro**

- Together, DSG1-CAART and DSG3-CAART demonstrated cytotoxicity towards anti-DSG3 and anti-DSG1 B cells

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MuSK-CAART for patients with MuSK myasthenia gravis
High unmet need in MuSK myasthenia gravis; a valuable CAAR target

All known extracellular domains can be included in the CAAR design

Similarities to pemphigus support clinical potential of CAAR T in MuSK MG

1. Autoantibody titers drop after rituximab\(^1,2\)
2. Pathogenic B cells are incompletely eliminated by rituximab and persist during relapse\(^3\)

MuSK has similar modular structure and size as DSG3

Seronegative MG
- Low affinity AChR, LRP4
- 9%

AChR MG Early Onset
- Age <50; F>M
- 65%

AChR MG Late Onset
- Age >50; M>F
- 20%

Prevalence: ~65,000 patients in the US

Typically more severe
- Limited treatment options
- Early onset – 7:1 females

MuSK-CAART in vitro selective & specific target engagement

MuSK-CAART showed similar potency against target cells that bind to different epitopes

MuSK-CAART demonstrated specific *in vivo* target engagement¹

MuSK-CAART eliminated anti-MuSK target cells² in an animal model where CART19 cells were a positive control.

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2. Target cells represent a B cell tumor line (CD19 positive) that has been modified to express the anti-MuSK antibody.
Manufacturing
Manufacturing strategy
Three-stage approach allows for efficient allocation of capital while leveraging experienced partners

<table>
<thead>
<tr>
<th>Stage 1: Penn DSG3-CAART Phase 1¹</th>
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<tbody>
<tr>
<td>2019 –</td>
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<tr>
<td>• Cell processing capacity secured through Penn partnership</td>
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<tr>
<td>• SOPs previously used to develop an FDA approved product</td>
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<tr>
<td>• Clinical vector validated</td>
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<table>
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<tr>
<th>Stage 2: CDMOs &amp; CABA Process MuSK-CAART Phase 1</th>
</tr>
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<tbody>
<tr>
<td>2021 –</td>
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<tr>
<td>• CDMOs for vector and cell processing with commercial support capabilities</td>
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</table>

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<tr>
<th>Stage 3: Cabaletta Facility Commercialization &amp; Scale-Up</th>
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<tbody>
<tr>
<td>Data-gated investment</td>
</tr>
<tr>
<td>• Build out Cabaletta-owned manufacturing facility</td>
</tr>
</tbody>
</table>

¹ Penn-sponsored CD19 CAR IND CMC data has been cross-referenced in DSG3-CAART IND to provide additional data reflecting alignment.
Parallel steps in manufacturing process\(^1\) for CAR T vs CAAR T

Vector production and cell processing are key risks mitigated by strategy, partnership, process and people

Conserving the clinically validated CART19 cell manufacturing process mitigates risks

- Cross referenced Penn CART19 IND including CMC process\(^1\)
- Penn process, not Novartis process, avoiding Kymriah release challenges\(^2\)
- Engineering runs have demonstrated efficient manufacture of DSG3-CAART cells from PV patients\(^3\)

Multiple runs contractually secured each month at Penn

- Subject to future COVID-19 impact

DSG3 vector supply secured for next 2-3 years

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1. Penn-sponsored CD19 CAR IND CMC data has been cross-referenced in DSG3-CAART IND to provide additional data.
3. T cells isolated from patients with a range of treatment regimens of low to high intensity were tested; the highest intensity regimen and patients with ALC<1000 cells/uL expanded less well and will be excluded from the trial design.
Corporate Summary
Recent highlights and anticipated upcoming milestones

- **DSG3-CAART**
  - IND cleared within routine 30-day window
  - Fast Track and Orphan Drug Designation
  - Multiple sites across the U.S. engaged
  - *In vivo* target engagement data presented at AAN

- **MuSK-CAART**
  - Validate MuSK-CAART manufacturing process with CMO partner
  - Acute safety data from first cohort by 1H21
  - IND filing 2H21
  - IND enabling studies initiated

**Cabaletta Bio**