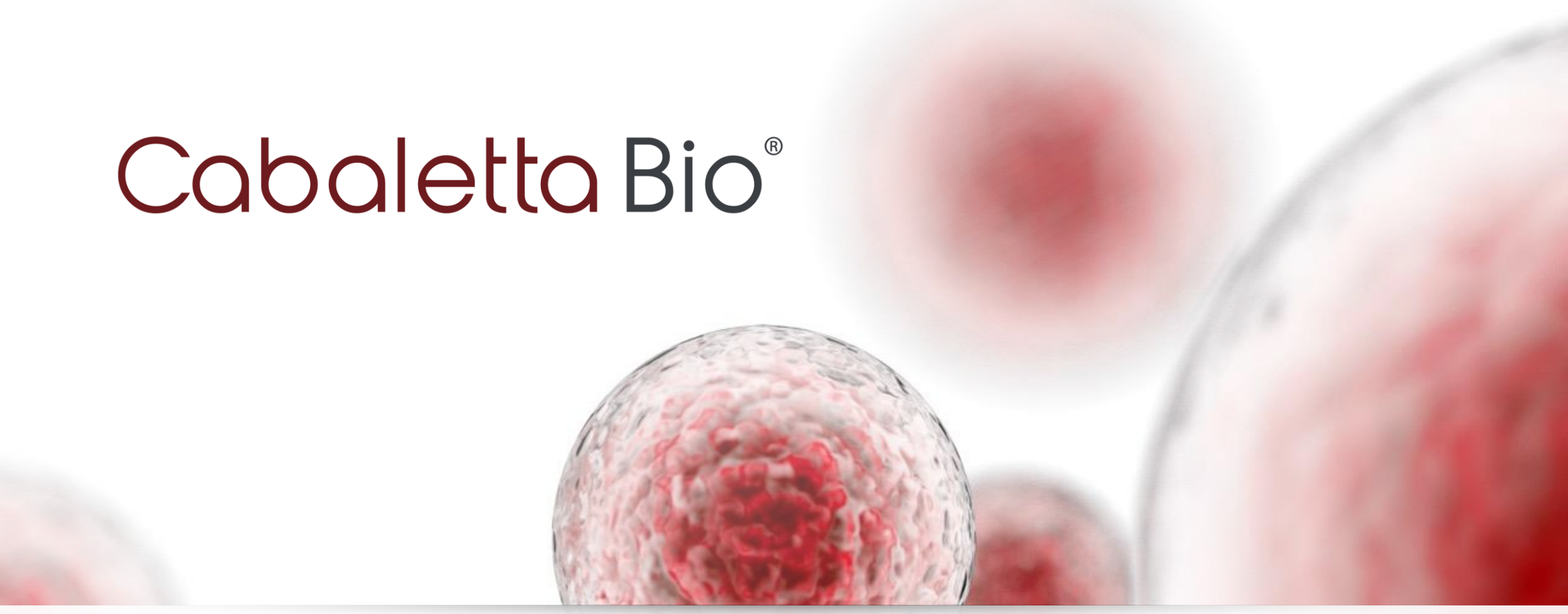
Cabaletta Bio®



DesCAARTes™ Trial Update & PLA2R-CAART Introduction

MAY 3, 2021

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Today’s agenda

AGENDA TOPIC		SPEAKER
Platform Overview		Steven Nichtberger, M.D. President & Chief Executive Officer
DSG3-CAART Update	Pemphigus Overview	Russ Hall, M.D. *J. Lamar Callaway Professor of Dermatology, Duke University School of Medicine*
	DesCAARTes™ Trial	David Chang, M.D., M.P.H. Chief Medical Officer
PLA2R-CAART Introduction		Gwendolyn Binder, Ph.D. Executive Vice President, Science and Technology
Conclusions		Steven Nichtberger, M.D. President & Chief Executive Officer
Q&A		

Cabaletta Today

Leveraging a clinically validated CAR T platform as a novel approach to treating autoimmune diseases aiming to provide:

- **Deep and durable responses**, potentially cures, for autoimmune patients
- **Highly specific, targeted therapy** designed to eliminate only pathogenic B cells
- **Target engagement** based on strength of biological rationale, deep understanding of translational data and many ways to deliver on the promise for patients

Multiple potential near-term clinical data catalysts with potential for pipeline read-through

- **Acute safety, target engagement, clinical responses**

Expanding network of academic & industry partners to enhance platform

WuXi AppTec · B-MoGen Biotechnologies Inc. · ARTISANBIO · Penn University of Pennsylvania · Children's Hospital of Philadelphia · Yale · UCDAVIS University of California

Pipeline[1] includes multiple disease targets where cure is possible

Therapeutic Area	Indication	Program	Discovery[2]	Preclinical	Phase 1	Phase 2/3
Dermatology	Mucosal Pemphigus Vulgaris	DSG3-CAART				
	Mucocutaneous Pemphigus Vulgaris	DSG3/1-CAART				
Neurology	MuSK Myasthenia Gravis	MuSK-CAART				
Nephrology	PLA2R Membranous Nephropathy	PLA2R-CAART				
Hematology	Hemophilia A w/ FVIII Alloantibodies	FVIII-CAART				

Current pipeline includes 7 programs targeting diseases affecting >80,000 patients in the US

1. Two additional undisclosed disease targets added to our pipeline portfolio through expansion of our Sponsored Research Agreement with the University of Pennsylvania are not shown.
2. In our discovery stage, we perform epitope mapping and optimize CAAR construct and design.

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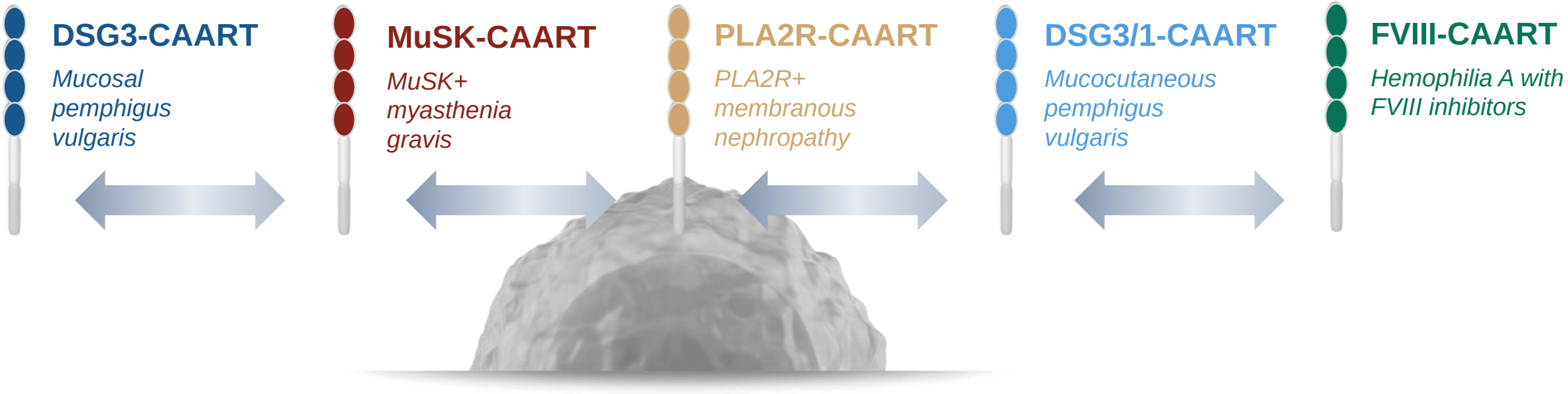
Modular platform with “plug-and-play” architecture

Technology foundation designed to enable a portfolio of programs targeting B cell-mediated diseases

Swapping the extracellular domain, or autoantigen, creates **new product candidates**



Clinically validated engineered T cell platform is the foundational technology

Data from the DesCAARTes™ trial provides read-through to pipeline

We believe the initial DesCAARTes™ data begins to de-risk the platform

Manufacturing success in clinical trial

- Strong relationship with Penn CVPF manufacturing organization
- Use of validated process from CAR T experience at Penn helps mitigate risk
- 100% success rate for DesCAARTes™ trial manufacturing to date in the first cohort

Acute safety in patients with mPV

- No DLTs or any clinically relevant toxicities observed in initial cohort through 8 days
  - DSG3-CAART was detected at low levels via qPCR in both patients evaluated to date
  - 20M DSG3-CAART cell dose administered without lymphodepletion
  - In patients with soluble circulating anti-DSG3 antibodies
- Next dosing cohort is at 100M DSG3-CAART cells
  - Plan to initiate next cohort once patient 3 completes 28 day follow up absent DLTs
  - Two cohorts higher than 100M cells are currently planned as well, if necessary

Future Data: Target engagement

- We believe biologic activity is present if DSG3 Ab titers consistently reduced by >20%
- More robust anti-DSG3 titer decline expected with greater target engagement
- Many variables to modify and strategies to maximize target engagement

Pemphigus Vulgaris: Current Treatment Options and Future Goals for Therapy

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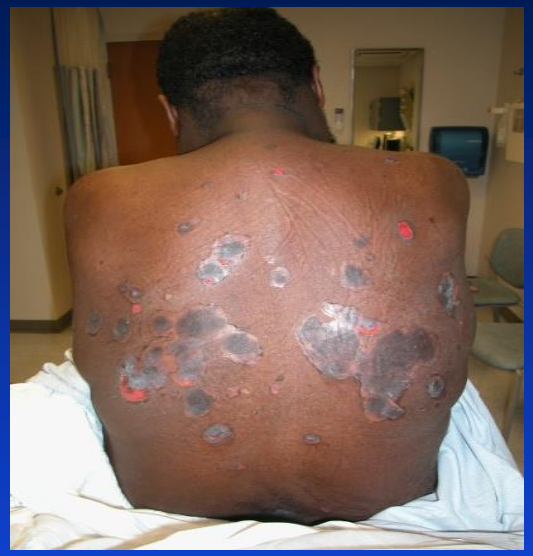
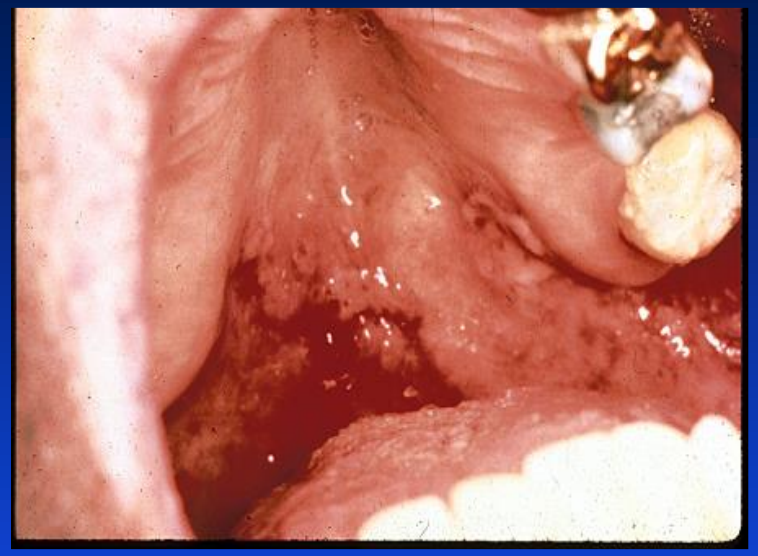
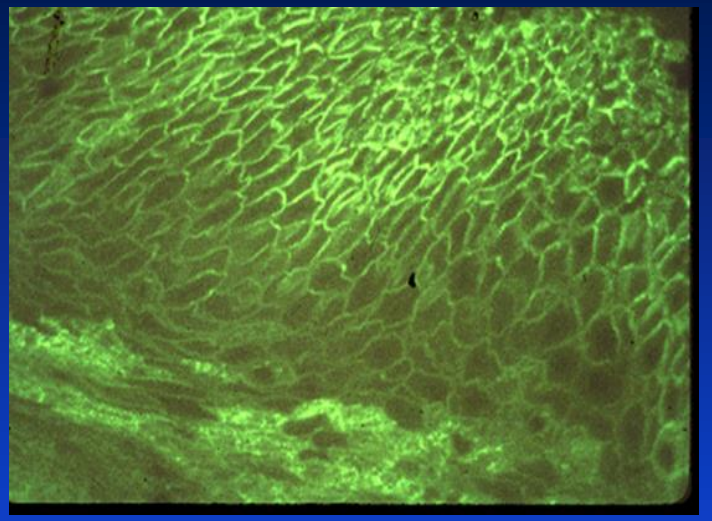
Pathogenesis Pemphigus





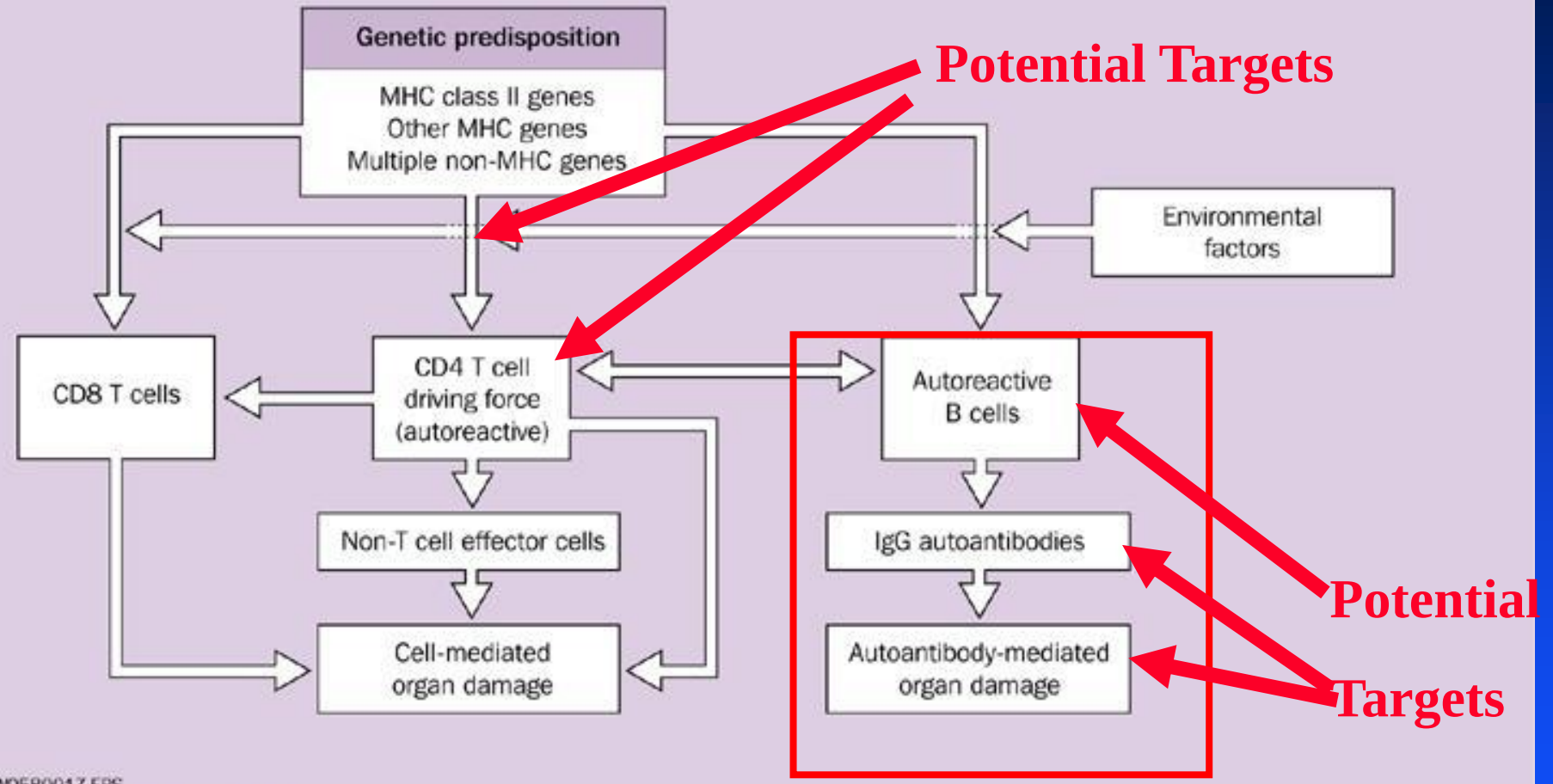


Pemphigus Vulgaris

- IgG autoantibodies directed against DSG1 and DSG3 (PV with mucosal and skin), **DSG3 (PV mucosal dominant)** and DSG1 (PF)
- Auto-antibodies found deposited on keratinocyte cell surface in skin and circulating in the serum
- Autoantibodies pathogenic in animal models
- Autoantibody levels related to disease activity

Kasperkiewicz M, et al, Nature Reviews, 3 :17026, 2017

Steps involved in the pathogenesis of autoimmune disease



Long term Goal
Treatment of Pemphigus

- Long term remission of disease with little or no need for long term/repeated treatments
- Minimal short term adverse events (serious and minor)
- No long term serious adverse events
- Corticosteroid “FREE” treatments
- Control of disease occurring within in the first two weeks of starting treatment

Murrell DF et al J Am Acad Dermatol, 82:576,2020

Joly et al. JEADV, 34:1900,2020

Rituximab Therapy in Pemphigus

- **Randomized control trial of Prednisone plus rituximab vs Prednisone**
  - **Prednisone + Rituximab (treated 0, 12, 18 months)**
  - **Prednisone alone**
- **Rituximab treated subjects**
  - **Increased rate of complete remission off therapy at 24 months (Ritux: 89%; Prednisone 34%)**
  - **Decreased time to complete remission off therapy**
    - **Ritux: 277 Days, Range 177-751 d**
    - **Prednisone Therapy: 677 Days, Range 420-713**
  - **<u>24% of Ritux treated patients relapsed by month 24</u> (9% Severe)**

Joly P et al, Lancet 389: 2031-2040, 2017)

Rituximab Therapy in Pemphigus

- 50% of patients relapse after first rituximab treatment by 18 months, requiring repeat 2-6 treatments

  Nosrati et al, *Dermatology 2021*

- Rituximab treated subjects with RA 9.5 yrs followup (3,194 patients; 11,962 patient yr)
  - Serious Infection: 3.94/100 patient years
  - Low IgM level greater than 4 months : 22.4%

    Van Vollenhoven et al *Ann Rheum Dis 2013*

- Long term impact of repeated rituximab infusions with B cell depletion on new and repeat immunizations not known

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Murrell DF et al J Am Acad Dermatol, 82:576,2020

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DesCAARTes™ Trial Data Update

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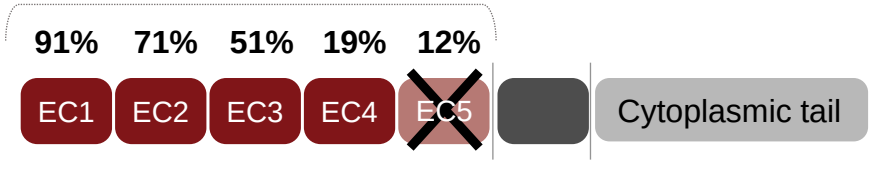
DSG3-CAART is designed to bind all known pathogenic autoantibodies

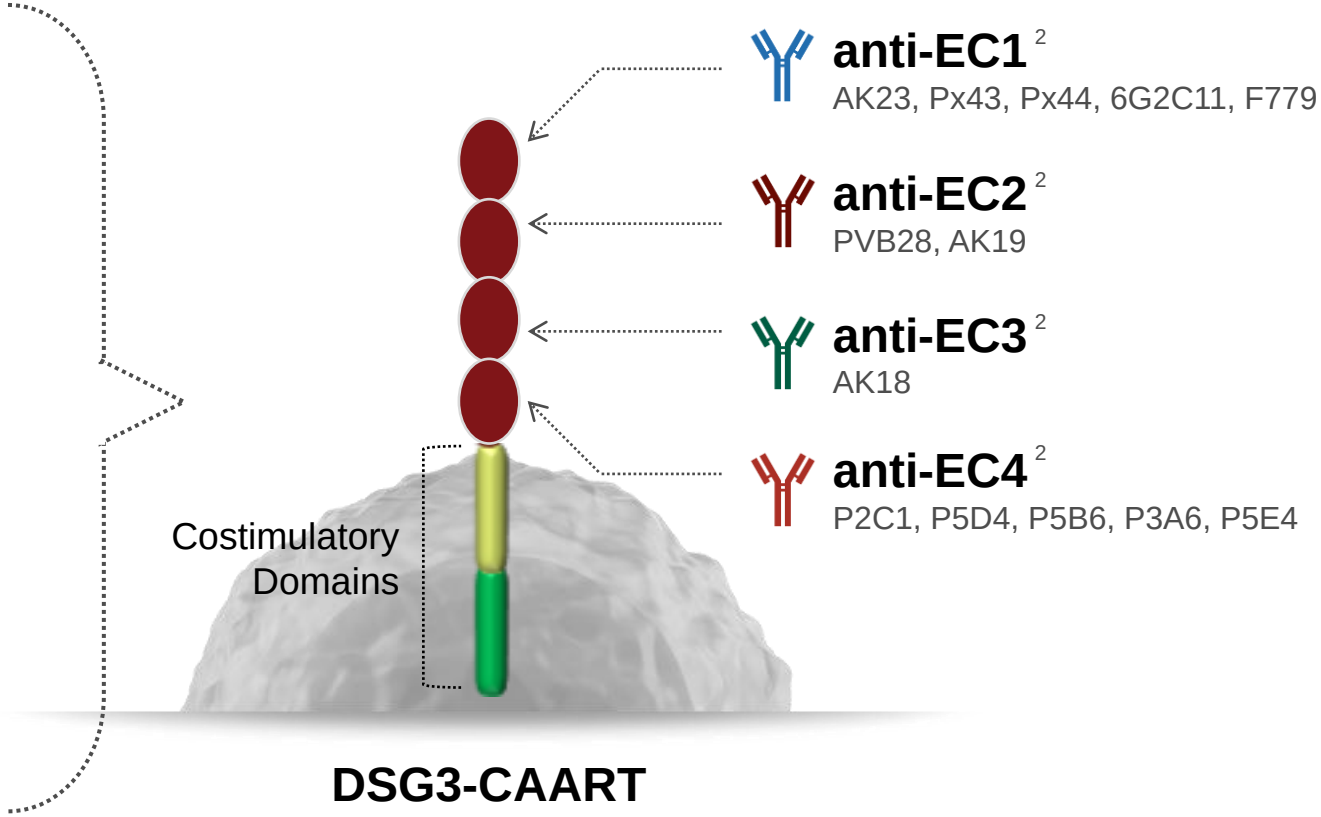
Inclusion of all disease-relevant epitopes enables a ‘one-size-fits-all’ approach for patients with mPV

% of PV sera targeting each domain[1]



DSG3 Protein

EC5 directed antibodies are not known to be pathogenic



DSG3-CAART

1. Ohyama, Bungo, et al. "Epitope spreading is rarely found in pemphigus vulgaris by large-scale longitudinal study using desmoglein 2–based swapped molecules." Journal of investigative dermatology 132.4 (2012): 1158-1168.
2. Antibodies that target the specific extracellular domain are shown below each extracellular domain.

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

SCREENING PERIOD → **TREATMENT PERIOD** (1-3 WEEKS) → **FOLLOWED** (2-4 WEEKS) → **Next Patient**

Part	Cohort	# Subjects
A – Dose Escalation Fractionated infusion at increasing dose levels	A1-A4	3 (+3) per cohort
B – Dose Consolidation Consolidating selected dose fractions into a single infusion	B1-B2	3 (+3) per cohort
C – Expansion[1] Expanded subject enrollment at final selected dose	C	~12
	Total	**~30 (+18)**

Study Endpoint & Objectives

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

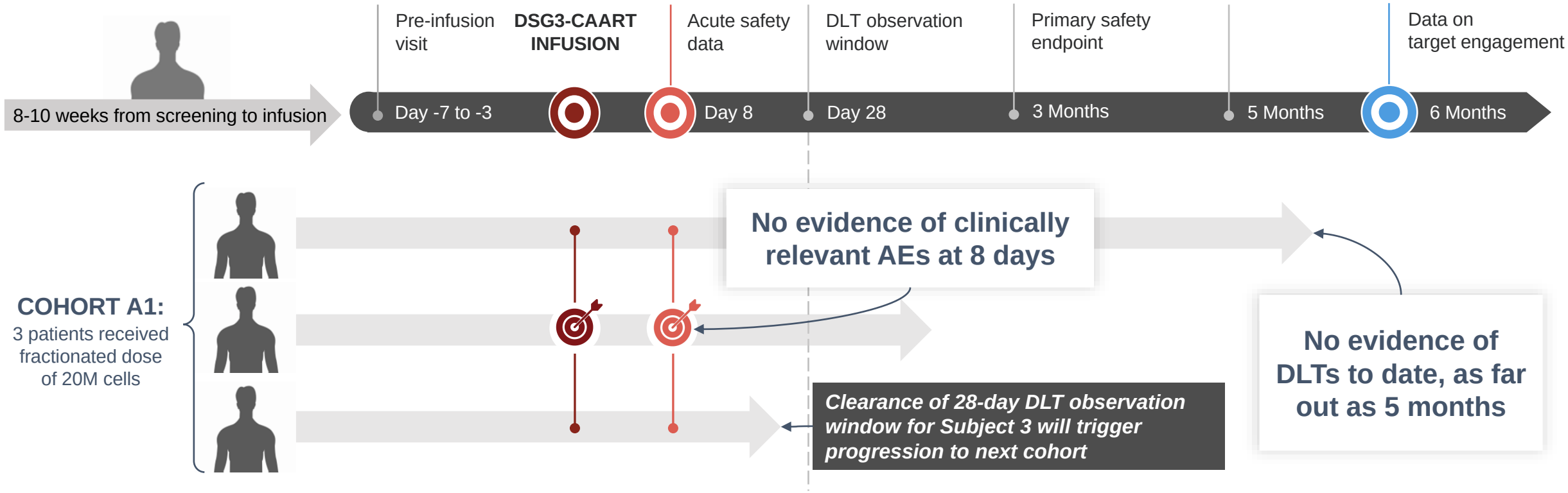
- DLTs include any grade 3 or 4 CRS or neurotoxicity, or any grade 2 CRS or neurotoxicity that failed to improve to ≤ Grade 1 or baseline within 7 days

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

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 advice, the submission of part A data is not gating to planned enrollment in part B.

No DLTs observed to date in 1st cohort of DesCAARTes™ trial

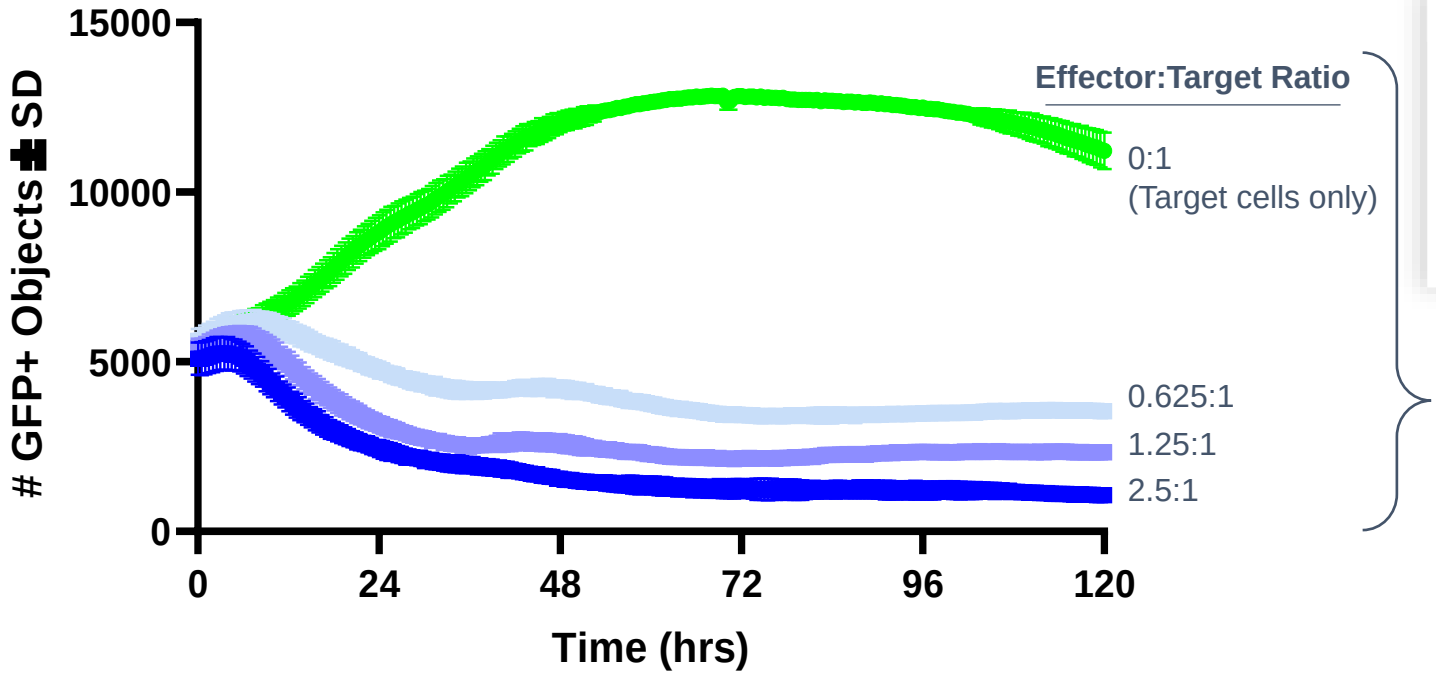
Promising initial safety profile for all 3 patients dosed with DSG3-CAART in the 1st trial cohort



No clinically meaningful adverse events in any subject to date

Manufactured DSG3-CAART cells exhibit target elimination *in vitro*

100% success rate for manufacturing of DSG3-CAART cells in DesCAARTes™ trial to date



DSG3-CAART cells successfully engage & eliminate DSG3 antibody expressing target cells *in vitro*

Samples run in triplicate

1 × 10^5 target cells per well

Manufacturing partnership with Penn is delivering necessary quality & capacity for the clinical trial requirements

Initial clinical safety profile in 1st cohort informed by several factors

No DLTs or clinically relevant toxicities in 1st three patients to date

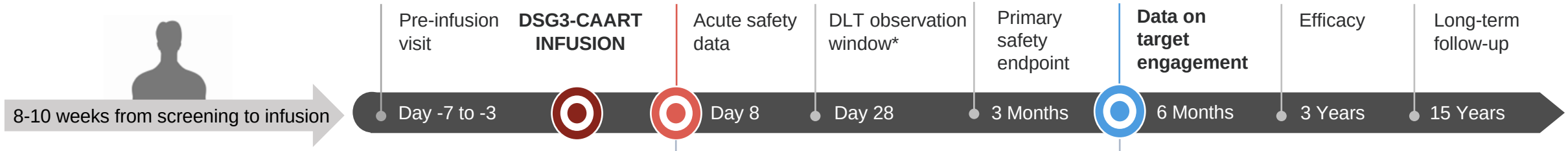
- At a 20 million cell dose, in the absence of lymphodepletion
- Circulating anti-DSG3 antibodies present in all patients at infusion
- Patients 1 and 2 have completed the 28-day DLT monitoring period
  - DSG3-CAART was observed at low levels via qPCR in both patients
- Patient 3 has completed the acute safety period (1st 8-days post-infusion)
  - Evaluation for DSG3-CAART has not yet occurred

Future topline target engagement data to be disclosed on a cohort-by-cohort basis

- Target engagement in the 1st cohort possible, but not expected
- Topline target engagement data on 1st cohort to be reported in 2H21

DesCAARTes™ clinical trial assessments and timeframes

Safety assessed acutely (Day 8) and at 3 months, with data on potential target engagement by 6 months



Day 8 acute safety data

Monitors for key risks:

- CRS / neurotoxicity
- Impact of soluble antibody
- Other adverse events

Primary safety endpoint at 3 months

Potential for disease flare during planned steroid taper

Target engagement to be assessed by declining anti-DSG3 titers[1,2]

- We believe initial signal would be evidenced by a consistent ~20% or more reduction in anti-DSG3 titers within a patient. More robust decline expected with greater target engagement
- Translational program evaluating potential for *in vivo* expansion and threshold dose effect[3,4]

Other key potential efficacy measures[2]

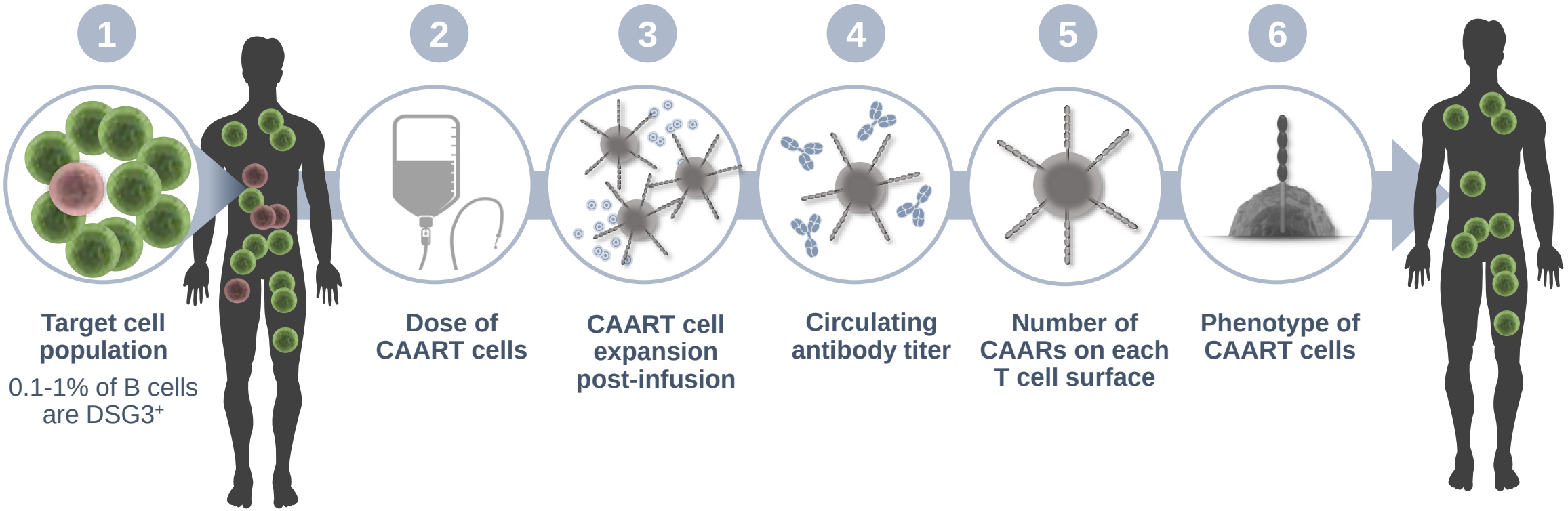
- Disease activity (clinical)
- Steroid / immunosuppressive use

** Clearance of 28-day observation window without DLTs required to initiate next dosing cohort.*

1. Spindler, Volker, et al. "Mechanisms causing loss of keratinocyte cohesion in pemphigus." Journal of Investigative Dermatology 138.1 (2018): 32-37.
2. This information represents data that we believe can be used to inform potential efficacy endpoints in future clinical development.
3. Dasyam, Nathaniel, Philip George, and Robert Weinkove. "Chimeric antigen receptor T-cell therapies: Optimising the dose." British journal of clinical pharmacology 86.9 (2020): 1678-1689.
4. Raje, Noopur, et al. "Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma." New England Journal of Medicine 380.18 (2019): 1726-1737.

Potential drivers of target engagement in autoimmune disease

Range of strategies to consider for targeted cell therapy approaches in patients with autoimmune diseases



Many options exist to enhance signals of target engagement

CAART cell

Pathogenic autoreactive B cell

Healthy B cell

Accelerating timelines for DesCAARTes™ trial

Strong interest by study sites, with three sites actively enrolling and many more working to open

- Growing clinical site network with high investigator engagement
  - Penn — University of Pennsylvania
  - Stanford Medicine
  - UC Davis — University of California
- Expanding relationships with patient advocacy organizations
  - ippf — International Pemphigus & Pemphigoid Foundation
  - NORD — National Organization for Rare Disorders
  - mg — Myasthenia Gravis Foundation of America
- Opportunities to accelerate development
  - Orphan Drug
  - Fast Track

DSG3-CAART: Data from DesCAARTes™ Trial

- *Acute Safety*
- *Target Engagement*

Milestone	1Q 2021	2Q 2021	3Q 2021	4Q 2021
1st cohort[1]	COMPLETED			
2nd cohort[1]				2
3rd cohort[1]				

Accelerating development & learnings from DesCAARTes™ trial to inform MuSK-CAART & future programs

1. Assumes no dose-limiting toxicities are observed during cohort and uninterrupted enrollment occurs in the trial.
2. Expect to report in 4Q21 or 1Q22.

PLA2R-CAART Introduction

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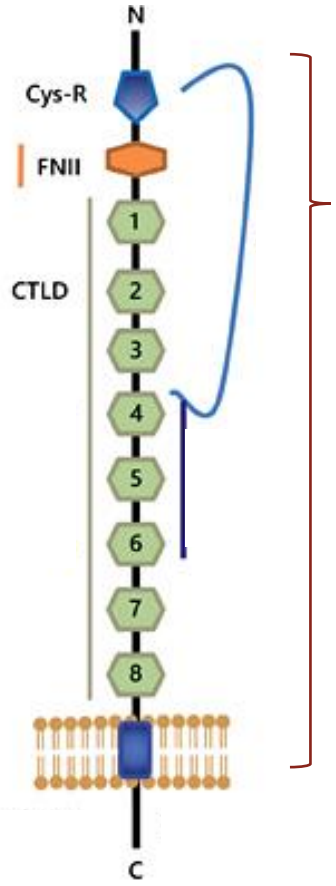
Discovery-stage CAART program in membranous nephropathy

Primary MN is an immune-mediated kidney disease with anti-PLA2R antibodies in ~75% of patients

Membranous nephropathy (MN) is a type of glomerular disease that causes nephrotic syndrome and may lead to kidney failure

Accumulating evidence of a correlation between PLA2R antibodies and disease activity, remission and relapse in primary MN

1. PLA2R autoantibody levels routinely used as diagnostic and prognostic markers
2. Autoantibody titer shown to precede and rise rapidly before clinical manifestations
3. Co-localization of antigen & PLA2R antibodies at site of damage in kidney



PLA2R+ MN is attractive for CAAR development

- Single pass transmembrane protein with distinct immunogenic regions
- Epitopes are well-defined
- IgG4-dominant disease, similar to PV and MuSK MG

Multiple lead candidates containing the main immunogenic epitopes demonstrate specific target engagement and cytolytic activity; lead product candidate being confirmed

Changing treatment paradigm highlights the role of B cells in disease

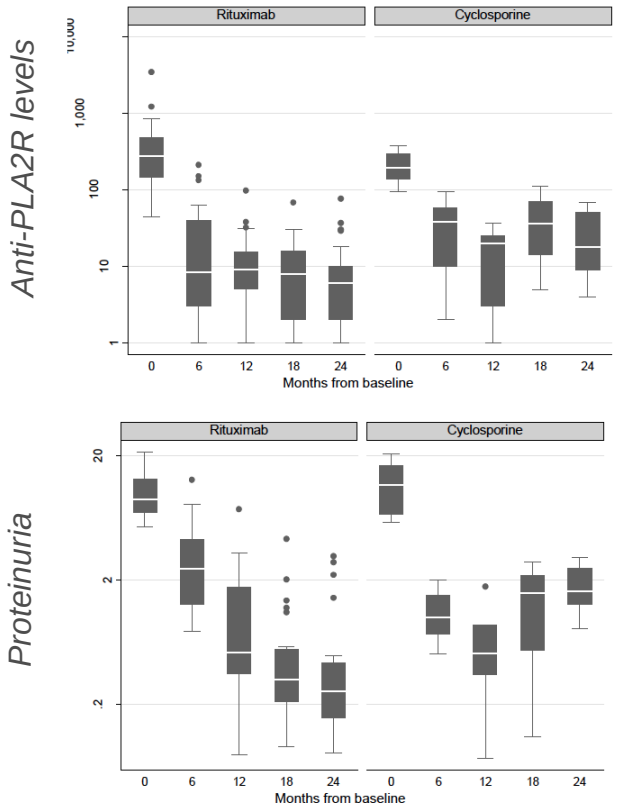
Opportunity to develop antigen-targeted therapy to address significant unmet need

High unmet need despite B cell-depleting therapies

- Rituximab increasing 1st line for medium to high-risk pts
  - 1/3 cure; 1/3 relapse; 1/3 fail[1]
  - Relapse of nephrotic syndrome occurs within 2-4 years
  - Preceded by return of B cells & PLA2R autoantibodies
- Patients with higher anti-PLA2R levels at baseline and with epitope spreading less likely to respond to rituximab
- Up to 30% of diagnosed patients develop ESRD

MENTOR trial results:

Antibody levels & proteinuria by group in patients with complete or partial remission at month 24



PLA2R antibody levels correlate with proteinuria, a commonly used surrogate endpoint

1. Accelerated rituximab clearance secondary to renal damage in patients with MN thought to be a major driver of limited drug effect.

Consistent progress on PLA2R-CAART program

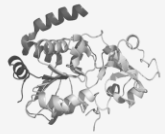
Rapid advancement through CABA development engine with near-term planned interactions with FDA

Scientific, clinical and commercial assessment

to inform product candidate development

Epitope mapping

to determine regions targeted by autoantibodies



Optimize CAAR construct / design

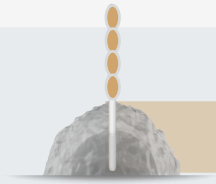
with the goal of selectively ablating reactive B cells

Preclinical *in vitro* and *in vivo* testing

to evaluate efficacy and safety

Vector & Clinical Cell manufacturing

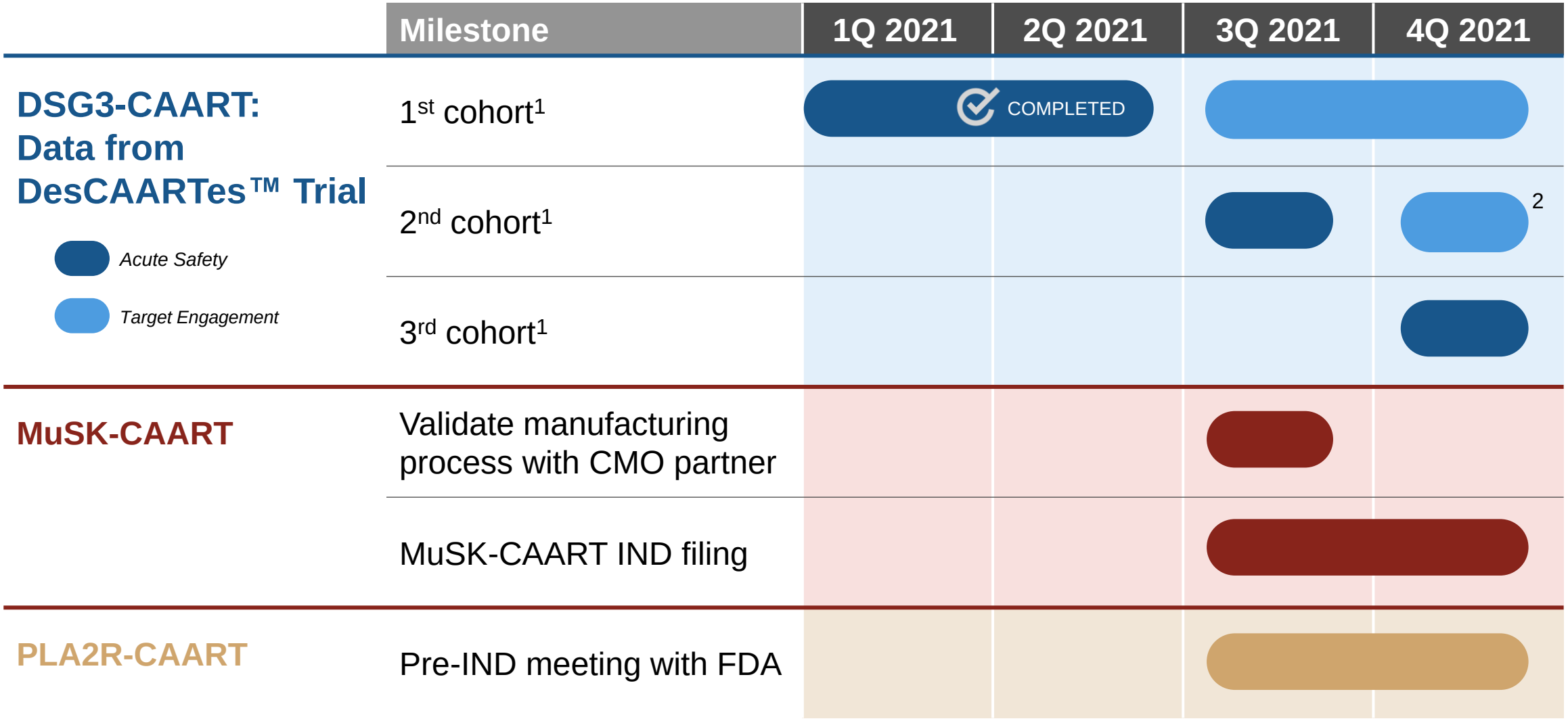
Clinical trials



PLA2R-CAART

Pre-IND meeting with FDA planned in 2H 2021

Updated 2021 anticipated milestones



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