Success in Treatment of Autoimmunity with CAR T-cells: application to prevention and mitigation of immunogenicity of therapeutic proteins?

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EpiVax, Inc

Agenda

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- CD19 CAR-T cells in treatment of autoimmune diseases
  - Chimeric Autoantibody Receptor (CAART) T cells: application to autoimmune disease
- Application of Antigen Specific CAAR-T and CAR-T regs to prevention or elimination of ADA to therapeutic proteins
  - Potential applications
  - Logistical considerations
  - Safety issues for all CAR/CAAR T therapies
- Engineered CAR-Tregs
- Safety and Immunogenicity issues for all CAR T cells
- Alternative approach to antigen specific tolerance: Tregitope based therapy

CAR-T Effector Cell Therapies: from Oncology into Autoimmunity and ? Immunogenicity

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Oncology

Targets: B cell antigens CD19 and BCMA

Mechanism:
Elimination of CD19–expressing B cells (healthy and malignant) or BCMA–expressing healthy plasma and myeloma cells

Autoimmune Disease

Targets: B cell antigens CD19 and/or BCMA (using traditional CARs) or autoantigen specific expression ***on effector T cells*** "CAAR Ts" or on CAR-Tregs

Mechanism:
CD19 and BCMA CAR-T: Elimination of normal and self-reactive B cells plasmablasts (CD19+) and plasma cells (BCMA)
CAAR-T/CAR-Tregs: Antigen Specific: elimination or suppression of autoreactive B cells and autoantibody–producing plasma cells: potential to address ADA to protein therapeutics

To Suppress or Kill? Regulatory and Effector T cell Strategies to Treat Autoimmunity

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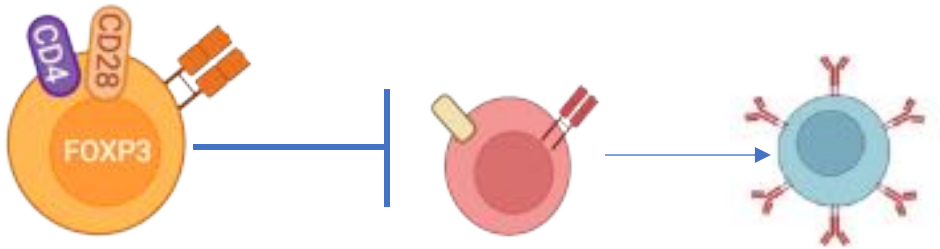
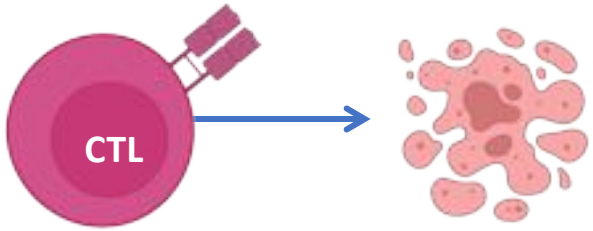
Regulatory T (Treg) cell therapies

- Harness the ***immunosuppressive capacity*** of Tregs to reduce the activity of self-reactive immune cells



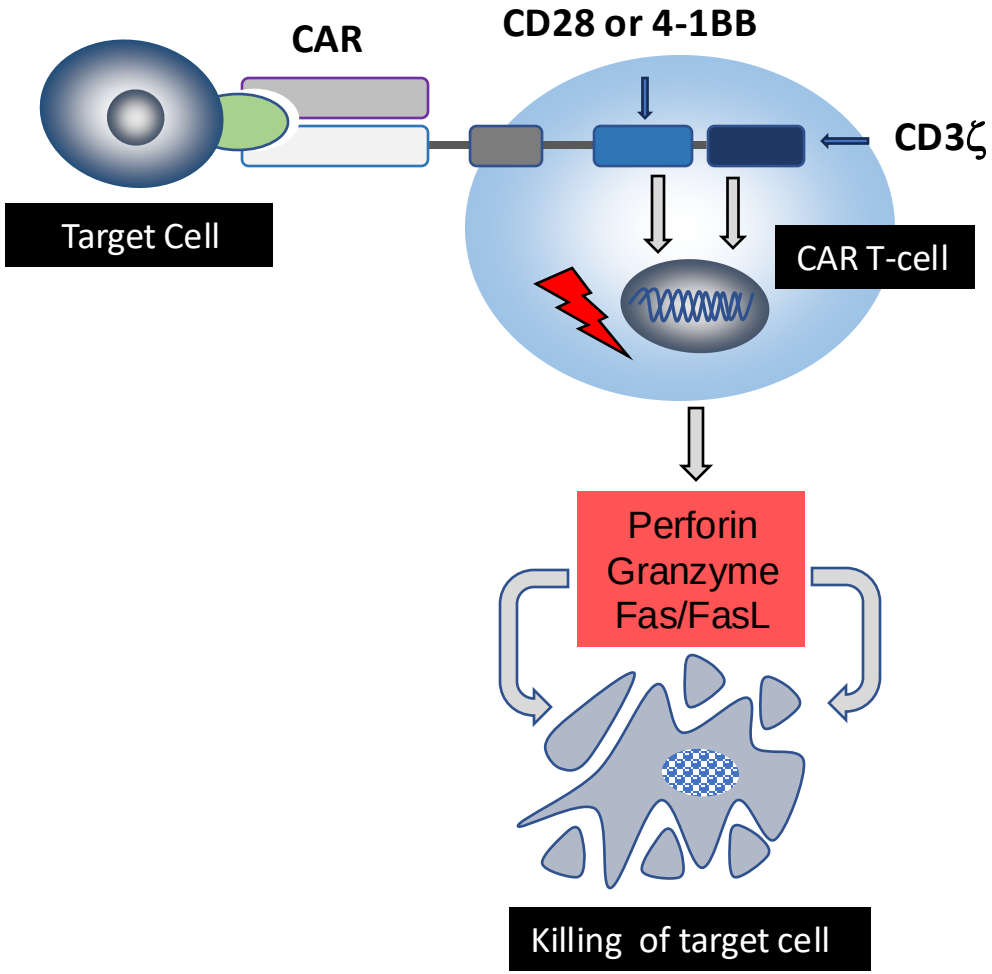
Effector T cell therapies

- Harness the ***cytotoxic power*** of T effector cells to destroy self-reactive cells



Structure of CAR-T Cells

Antigen recognition
and
effector function in
one drug



Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, June CH. Sci Transl Med. 2011;3:95ra73.
June CH and Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med 2018; 379:64-73.

Breakthrough Therapeutic: CD19 CAR-T Cells for Treatment of Autoimmune Diseases-A Magic Bullet?

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- Study: CD19 CAR-T cells for Treatment of Patients with severe SLE, Scleroderma, Inflammatory Myositis
  - ***Single infusion*** of CD19 CAR T cells: 8 patients with severe SLE, 3 patients with idiopathic inflammatory myositis and 4 patients with systemic sclerosis who received a single infusion
- Patients all preconditioned with one course of low dose fludarabine and cyclophosphamide
- Safety: No moderate- or high-grade cytokine release syndrome (some patients treated with Tocilizumab) or Immune effector Cell-Associated Neurotoxicity (ICAN) syndrome; 1 serious infection but most infections mild
- Efficacy assessed up to 2 years after CAR T-cell infusion by Clinical Disease Specific Scales: full B-cell reconstitution for up to 2 years with Drug-Free Remission/No Progression beyond one year (many >2years) except for one IIM patient requiring treatment at 15 months post-treatment.
- Much more effective than Rituximab which has poor efficacy in SLE despite recurrent dosing

Muller F et al N Engl J Med 2024;390:687-700.

CD19 CAR-T cells Eliminate Autoantibodies and Disease Benchmarks in Severe SLE over an Extended Time Frame

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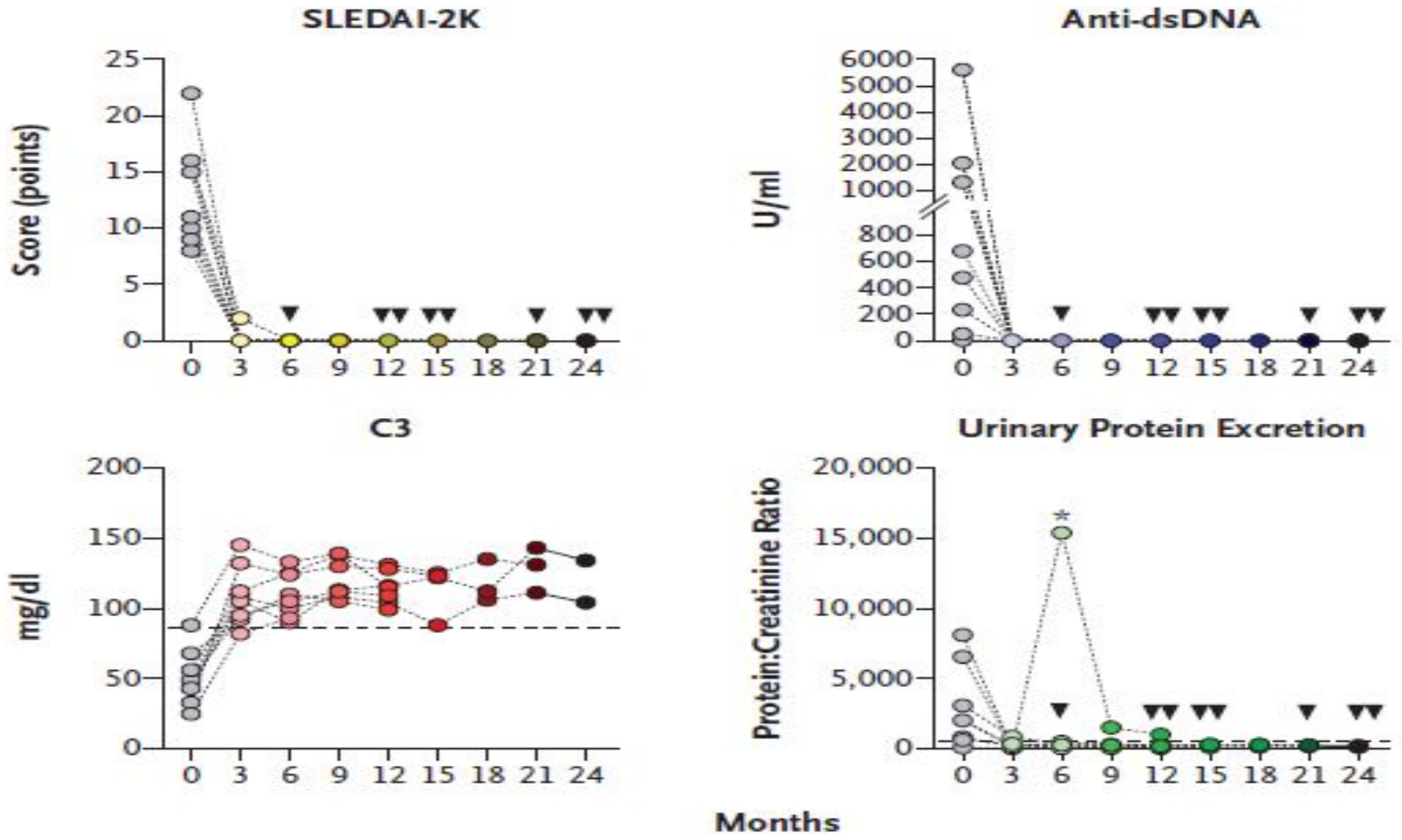

Muller F et al N Engl J Med 2024;390:687-700.

Stunning Efficacy of CD19-CART Cells: Prolonged Disease-Free Remission Across Different AIDs

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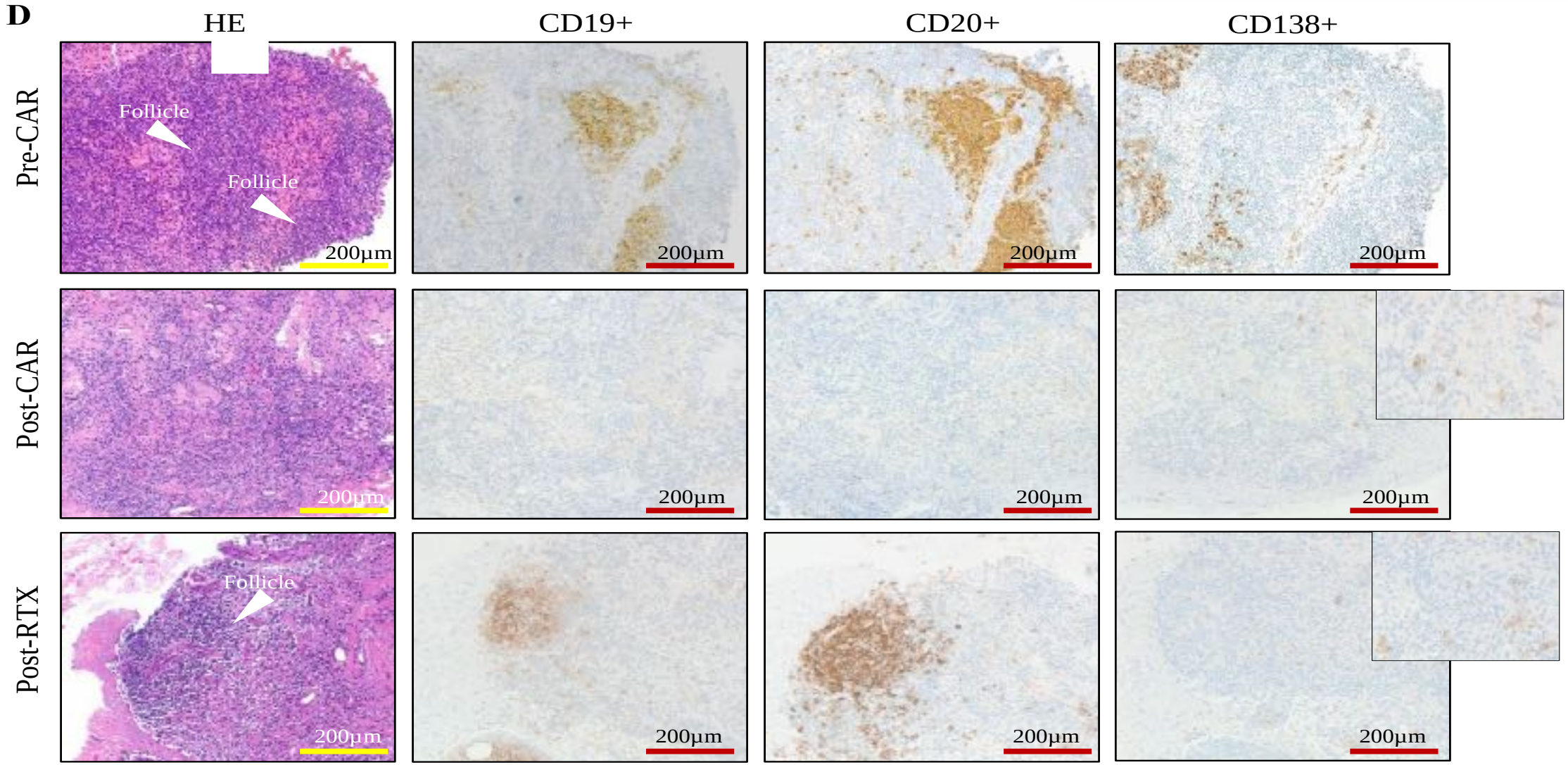
Patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
Follow-Up (months)	40	35	31	31	29	26	22	17	26	21	14	23	19	18	14
Drug-Free Remission/No Progression	+	+	+	+	+	+	+	+	+	15mo	+	+	+	+	+
Glucocorticoid-free state	+	+	+	+	+	+	+	+	+	15mo	+	+	+	+	+
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+	+	15mo	+	+	+	+	+

Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

Why Rituximab Fails and CAR-Ts Effective:CD19 CAR-Ts have enhanced tissue penetration that Rituximab fails to access



Schett G

Basis for Success of CD19 CAR-Ts: Long-Acting, Enhanced Tissue Penetration and CD19 (vs CD20) Targeting

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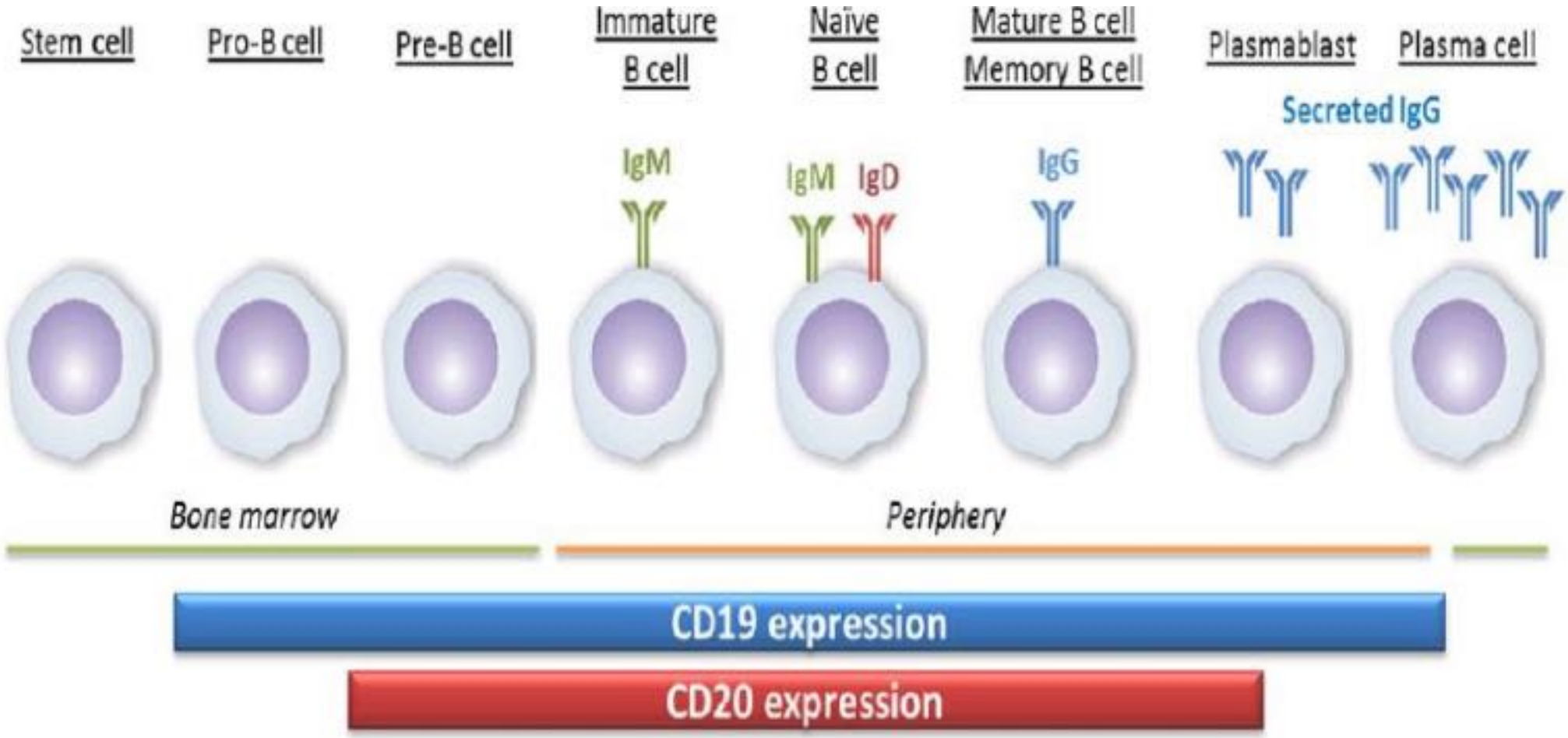
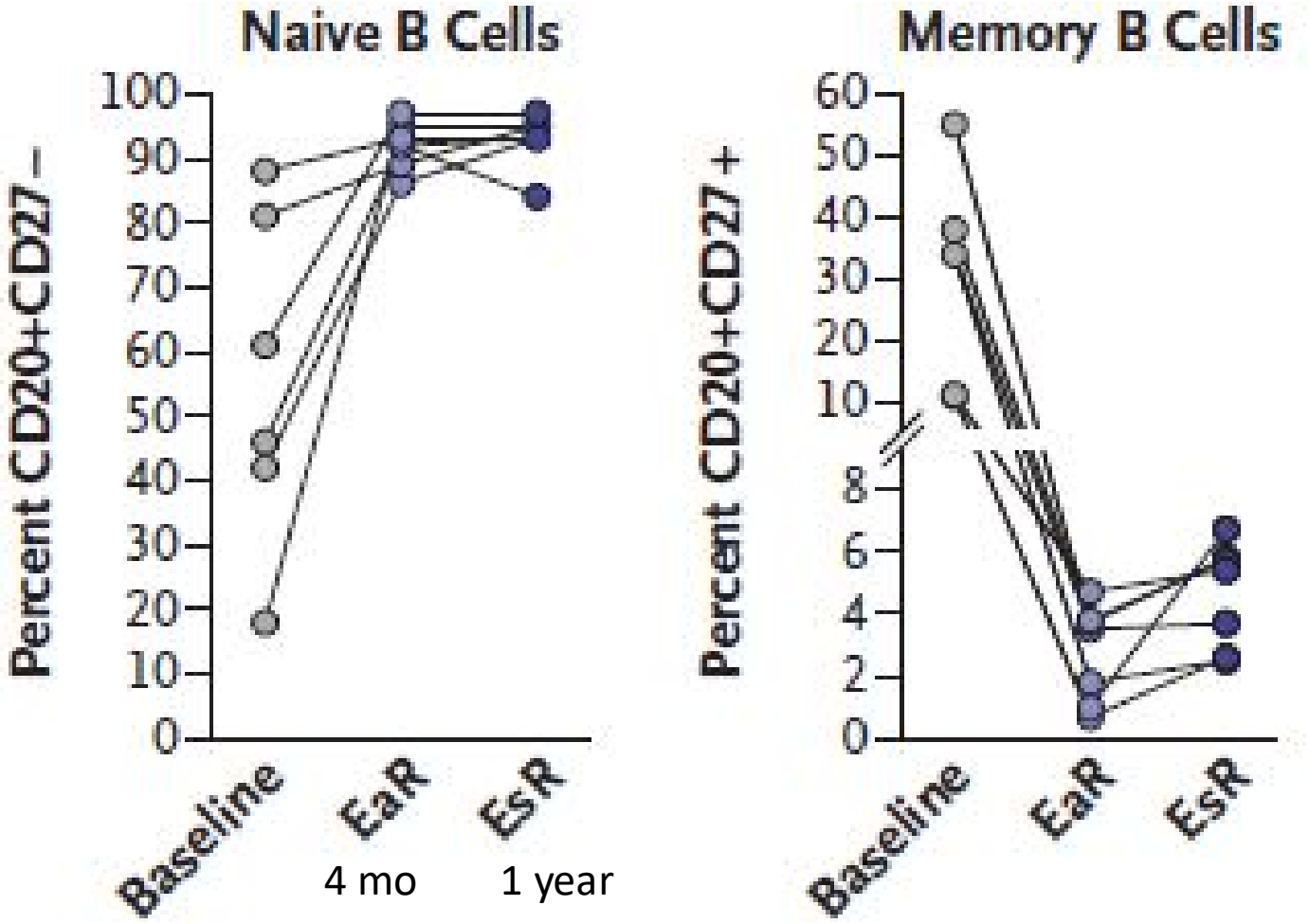


Forsthuber TG et al *Ther Adv Neurol Disord* 2018

CD19 CAR-Ts Reset the Stage! Prolonged Depletion of Memory B Cells- Rapid Return of Naïve B Cells Under Immunomodulatory Conditions



Are Tregs/Bregs induced under these conditions?

Muller F et al N Engl J Med 2024;390:687-700.

Safety of CD19 CAR-Ts: Maintenance of Childhood Vaccine Immunity by Long Lived CD19-neg Plasma Cells

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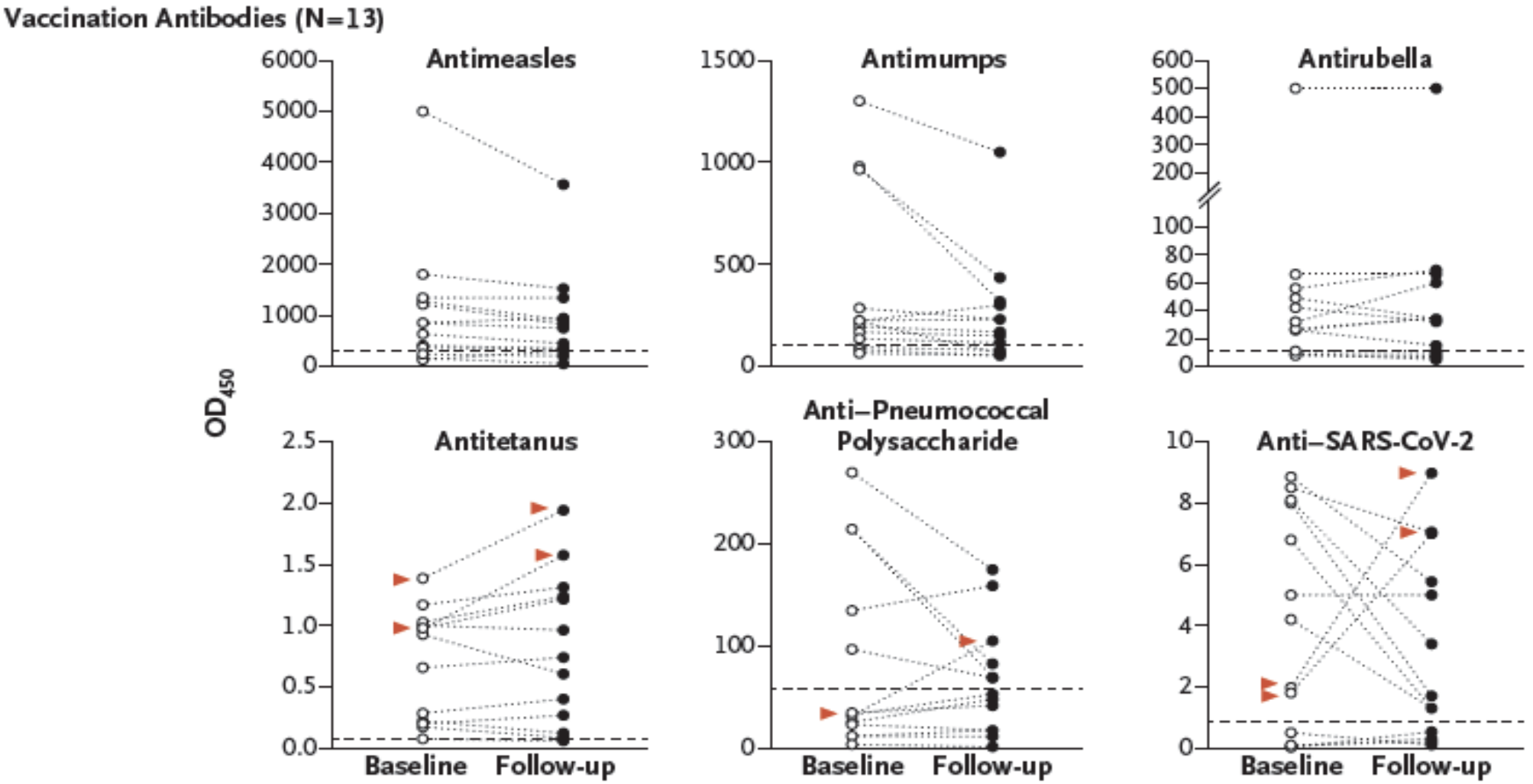

And generation of de novo vaccine responses-

Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

Key Questions: is Immune Tolerance Induced? Disease Cured?

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- **Does a single course of preconditioning plus CD19 CAR-T induce tolerance in autoimmune disease, cure disease or only prolong remission?**
  - Very prolonged remission-up to 40 months suggests it may be curative in some patients
- **If so, what is the mechanism(s) of immune tolerance: *Essential to Define Mechanism***

  1) **Active Immune Tolerance Mediated by Tregs, Bregs**?

  2) **Anergy**: immune checkpoint molecule expression on autoreactive T cells?

  3) **Deletion** of autoreactive cells; prevention of subsequent generation?
- **Which CD19+ B cell populations are essential to deplete for disease remediation? Tolerance?**
  - Pre and naïve B cells; B memory cells, plasmablasts, tissue resident plasma cells
- **If tolerance, is tolerance concomitantly induced to "innocent" or pathogenic bystanders?**
- **Durability: effects of intercurrent infection or trauma?**

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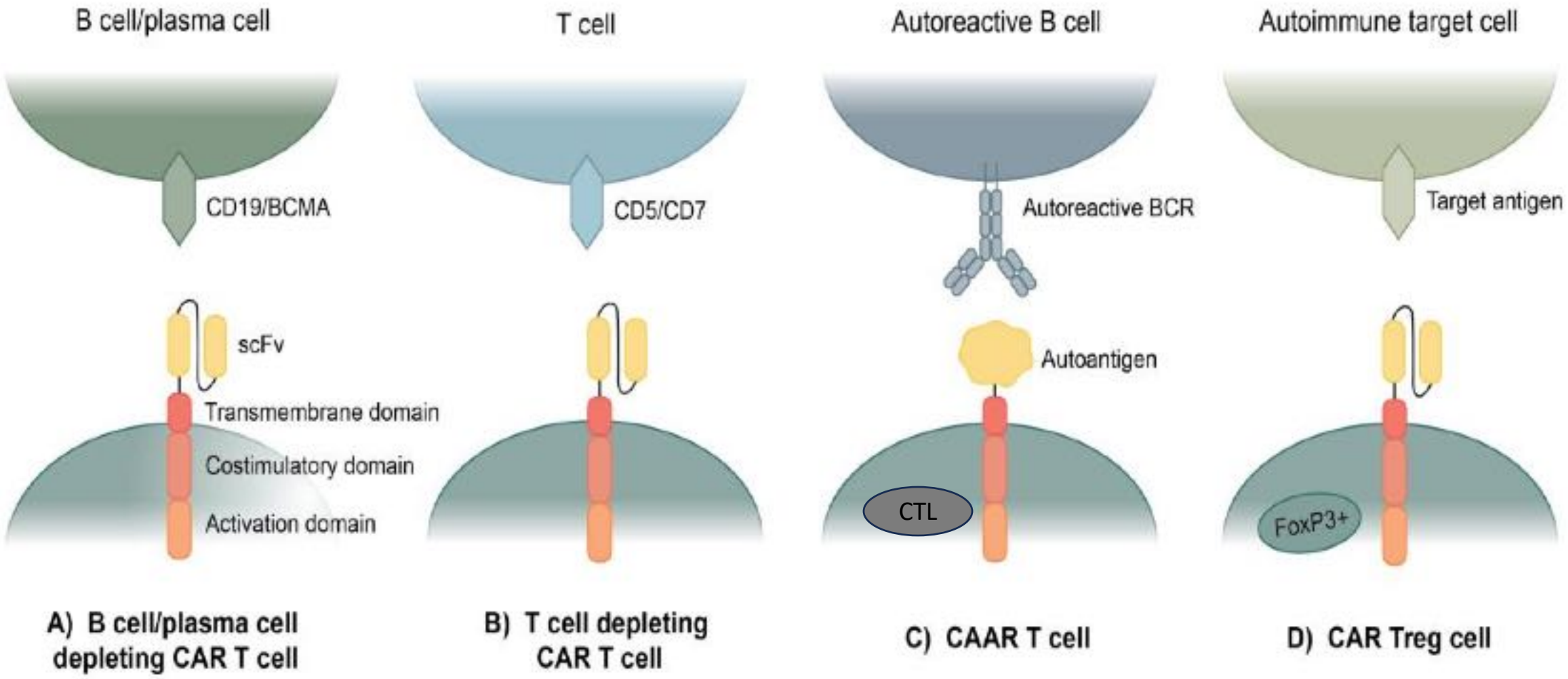
CAR Ts Made Antigen Specific! Antigen Specific CAAR-T and CAR-Treg Spare Irrelevant B Cell Populations



Cheever A et al Front. Immunol. 15:1465191

Studies of CAAR-T for Autoimmune Disease: A Model for Preventing/Eliminating ADA to Therapeutic Proteins?

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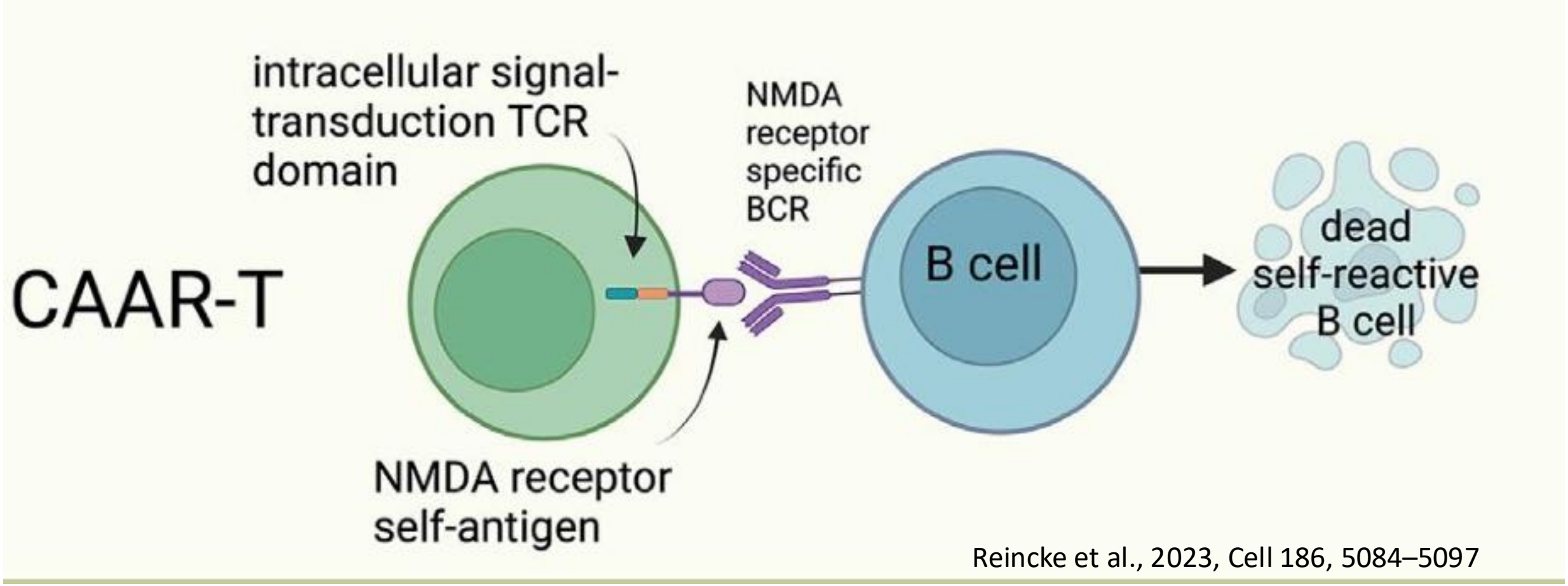
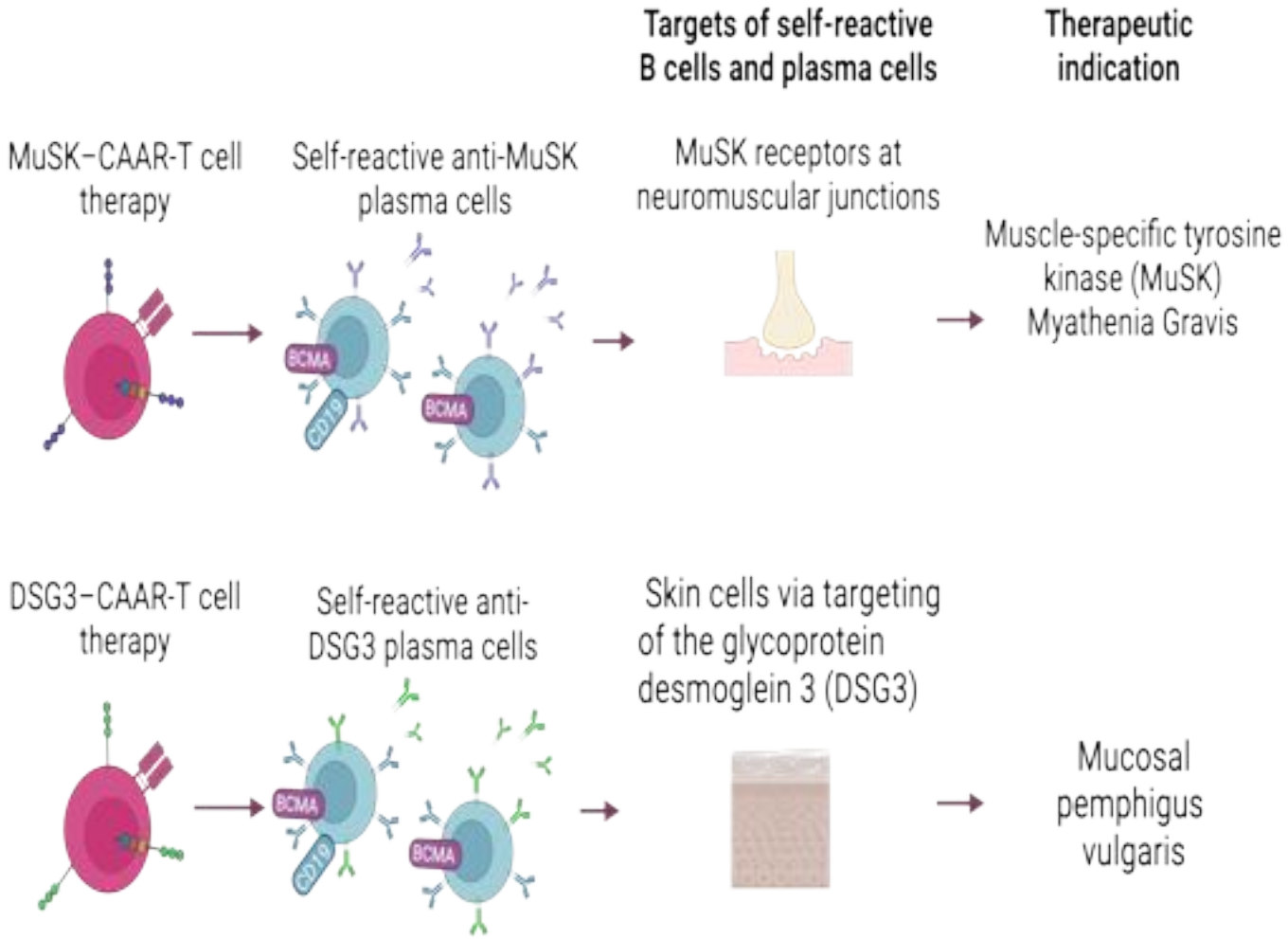
Autoimmunity: anti-N-methyl-D-aspartate (NMDA) receptor encephalitis



Reincke et al., 2023, Cell 186, 5084–5097

Autoimmune Conditions Under Investigation for Treatment with CAAR-T Cell Therapy



MuSK-CAART infusion *without preconditioning* in patients with Myasthenia Gravis (MuSCAARTesTM trial): patients had low levels of autoantibodies

Aimee Payne (Columbia/Cabaletta Bio)

CAAR-T/CAR-Tregs Have Potential to Address Multiple Clinical Scenarios Featuring Antigen Specificity

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Potential Clinical Scenarios

- For life saving therapeutic proteins such as enzyme replacement therapy for Pompe Disease; Also, for ERT for other Lysosomal Storage Diseases with less urgent need for tolerance induction
- For severe allergy: eliminate IgE producing B cell populations: administer after prophylaxis for anaphylaxis ie omalizumab
- For highly effective but immunogenic mAbs for which target CDRs are well defined.
- For highly conserved but immunogenic human growth factors and receptors in common autoimmune diseases: ie thyroid stimulating hormone receptor

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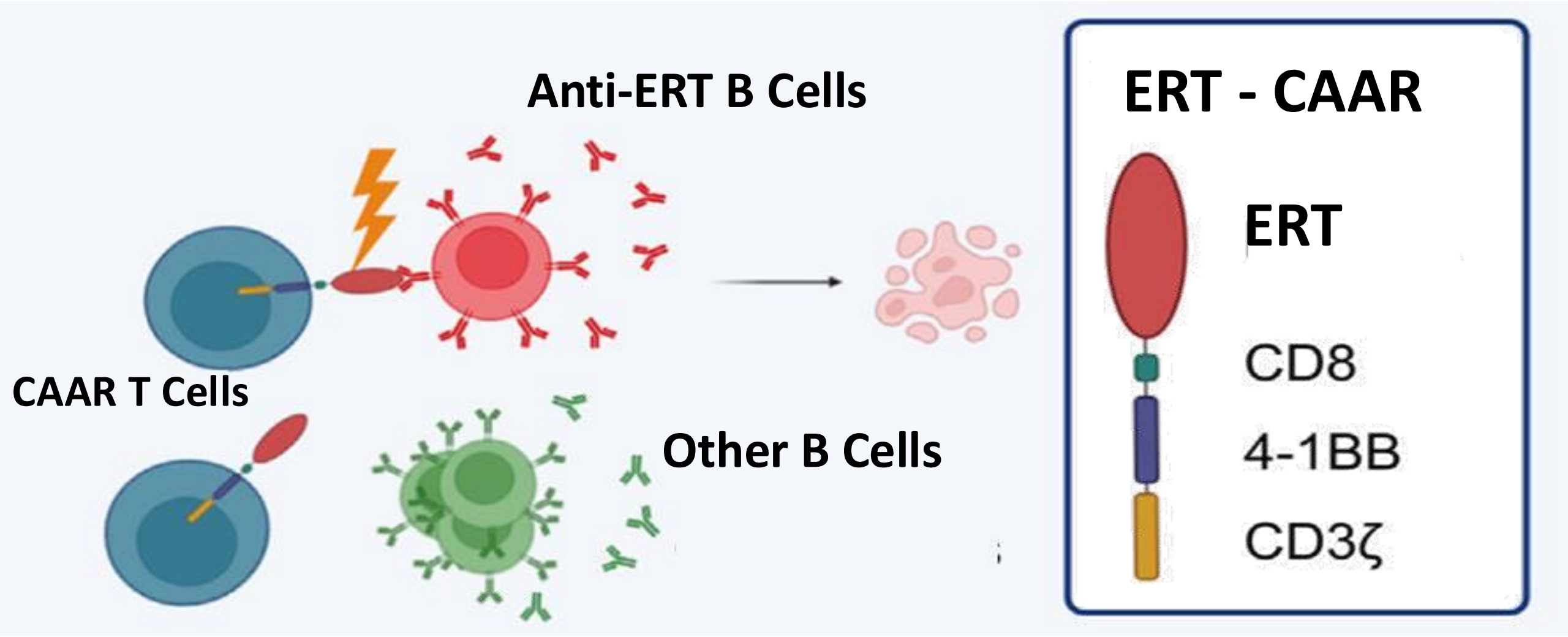
Anatomy of a CAART Cell for Preventing ADA to a LifeSaving Enzyme Replacement Therapy (ERT)



Case Example: Urgent Need for Immune Tolerance Induction to ERT in Infantile Onset Pompe Disease

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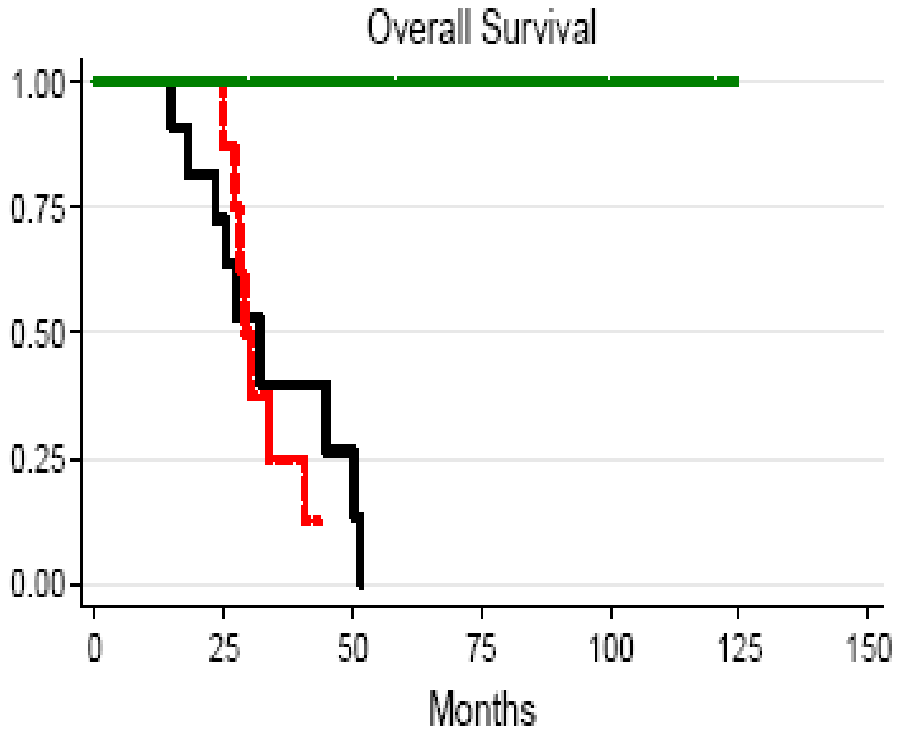
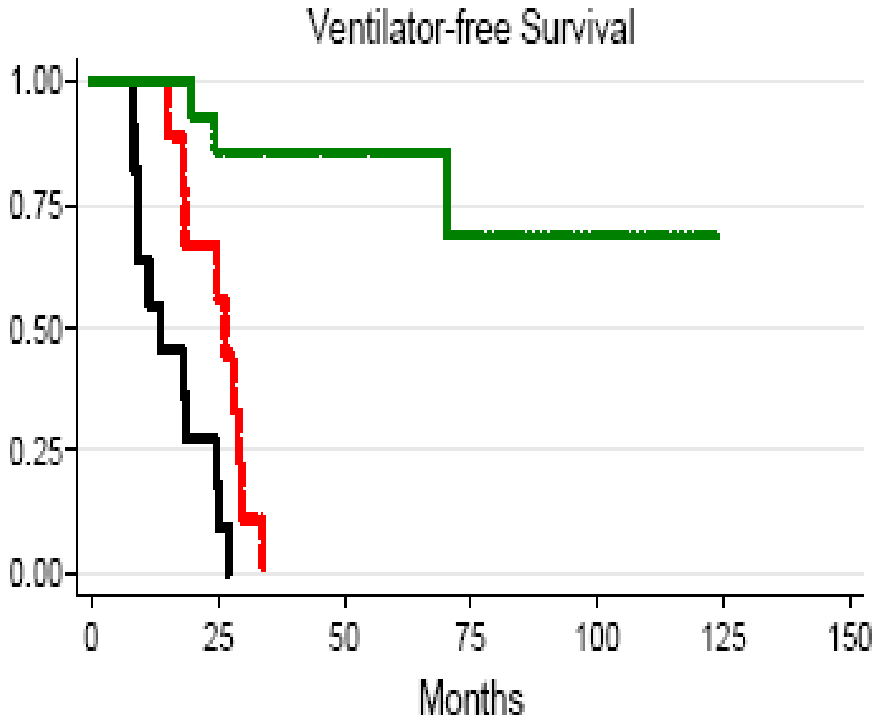
ADA Neutralize Life Saving Enzyme Replacement Therapy alpha-glucosidase in Pompe Disease





High Titer ADA CRIM+

Low Titer ADA CRIM+

High Titer ADA CRIM-

Kishnani PS et al 2011

Prophylactic Tolerance Induction for ERT in Pompe: requires multiple immune suppressive agents recurrently administered

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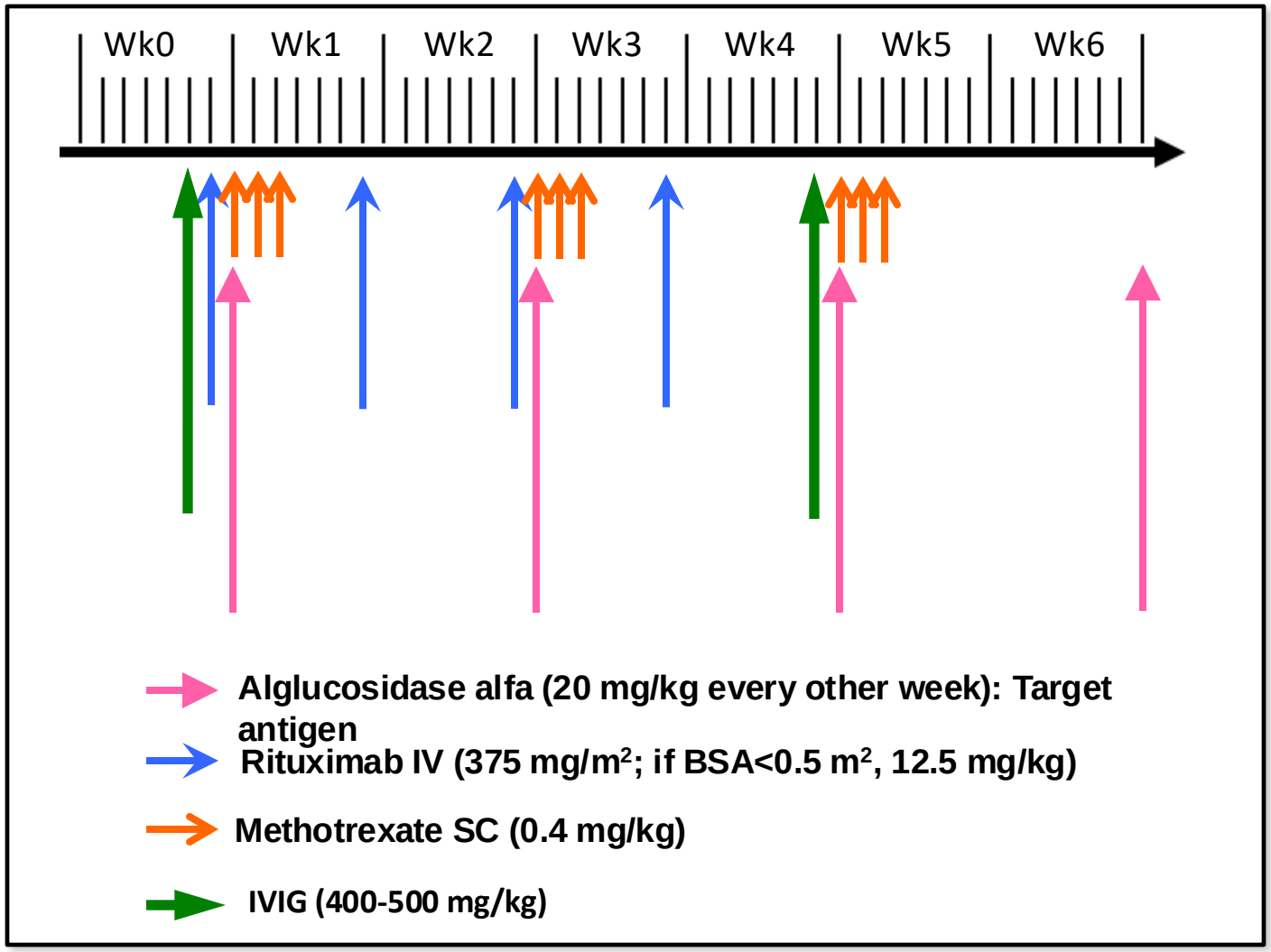

Rituximab: Reduces B cells

- Diminished generation of antibody producing plasma cells;
- Diminished antigen presentation by B cells

Methotrexate: T Cells

- Cytostatic; halts proliferation at G_1
- Inhibits cytokines by activated T-cells
- Restores Treg cell function

IVIG

- Anti-inflammatory
- Anti-microbial
- Induction of Tregs

Messinger YH et al Genet Med. 2012
Banugaria S et al PlosOne 2013

Not All Patients Tolerize with One Round of Treatment Requiring 2nd Course

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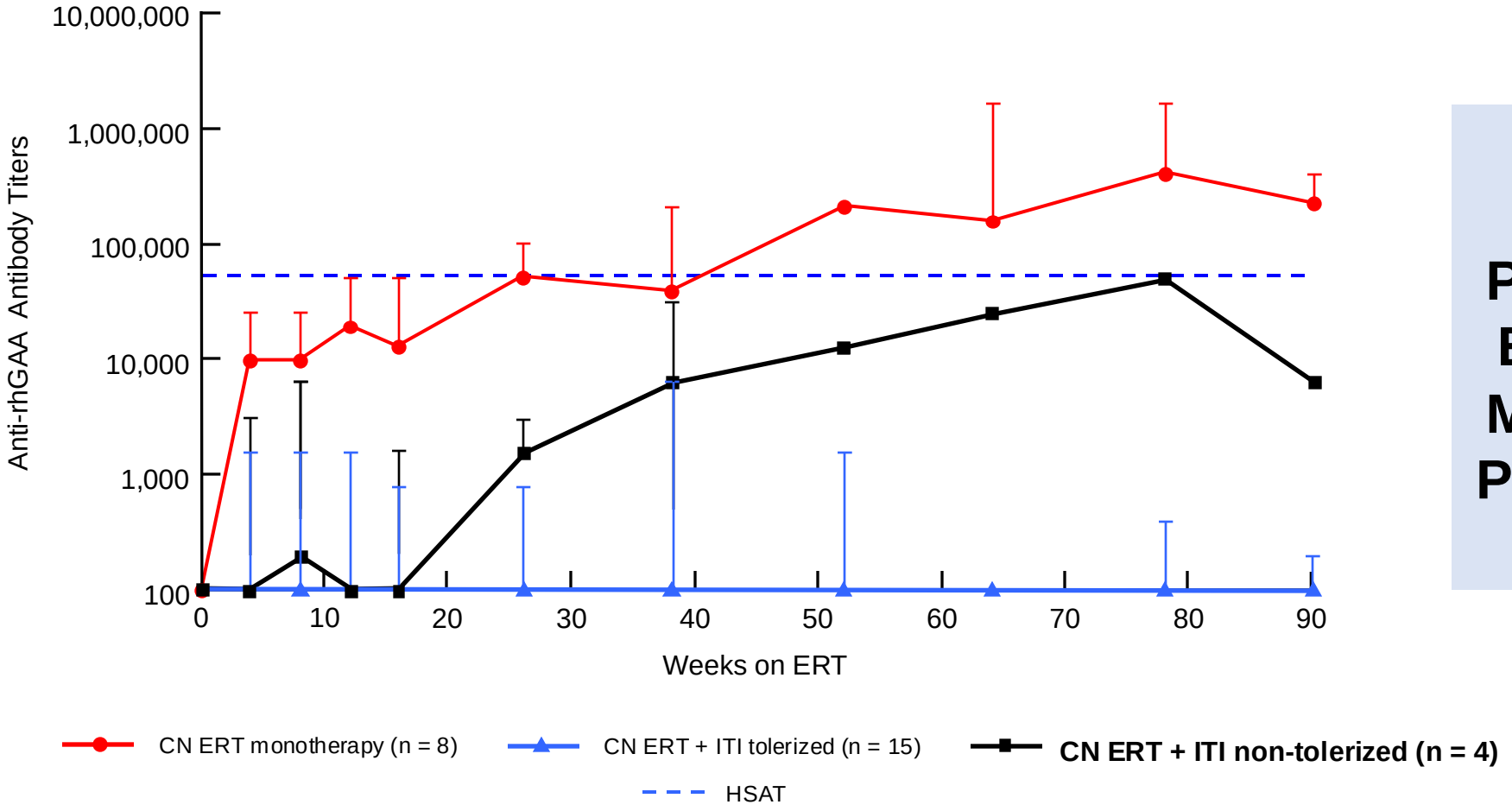
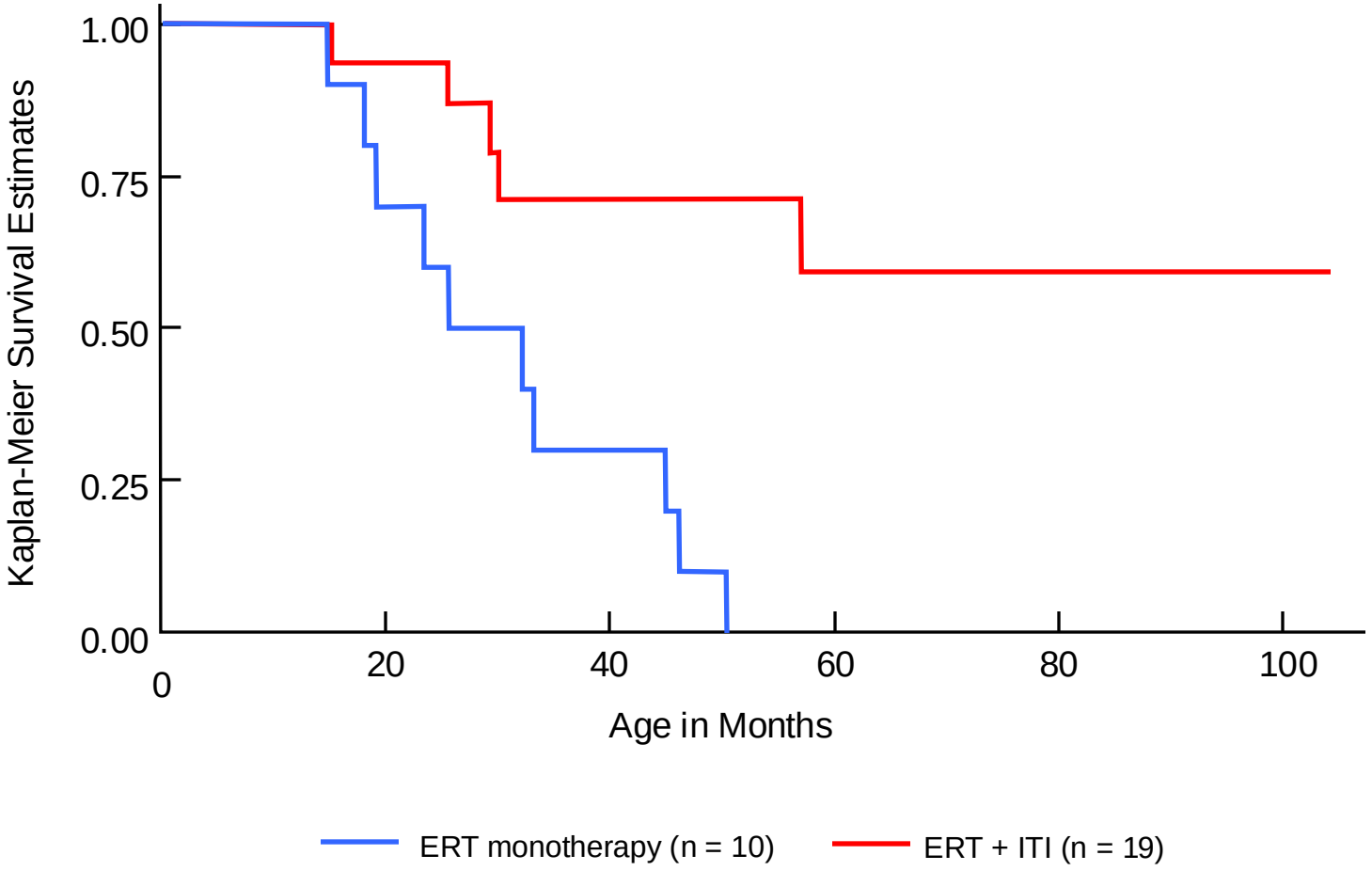


CRIM-negative Patients Treated Prophylactically with ERT+ITI versus ERT Monotherapy: Not all Patients Tolerize With Round 1

(Kazi ZB et al JCI Insight 2017)

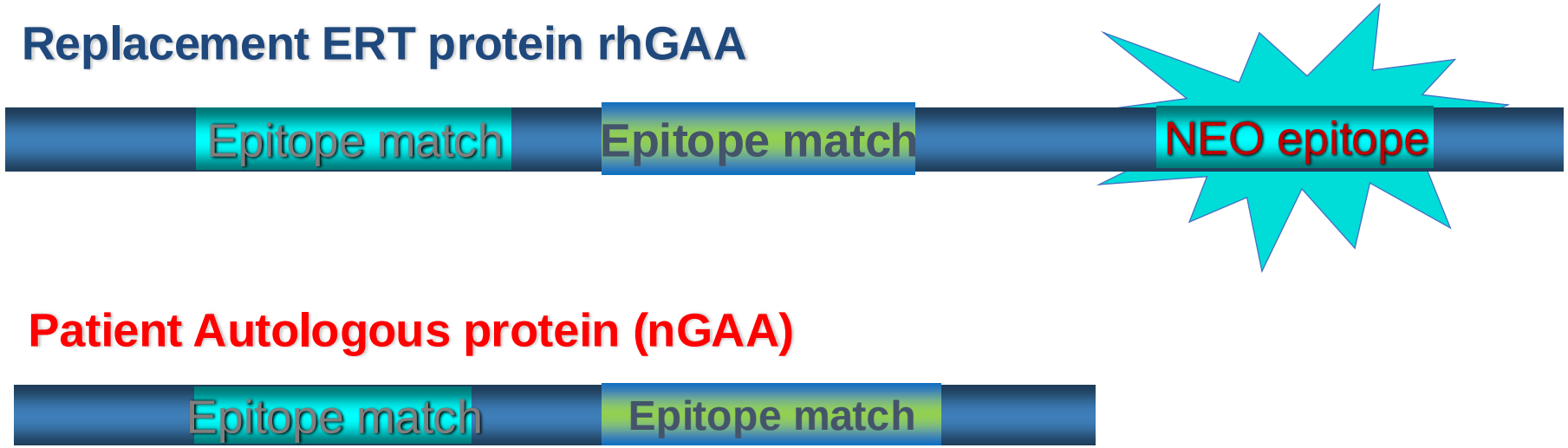
Enhanced Survival in IOPD Patients Tolerized to ERT but Critical Need for Better Tolerizing Treatment



Could CAAR-T/CAR-Tregs at onset of treatment be safer and more effective than highly immune suppressive regimen? *Will it induce tolerance to the ERT?*

(Kazi ZB et al JCI Insight 2017)

1st Challenge: Define the Target ERT Neoepitope(s) of ADA then Express them in CAAR-T or CAR-Tregs



Critical domains of the ERT are the Uptake and Catalytic Domains
Uptake domain is the more common target of ADA

CAAR-T Cells Expressing NEO epitopes of Life Saving Enzyme Replacement Therapy to Preclude or Eliminate ADA

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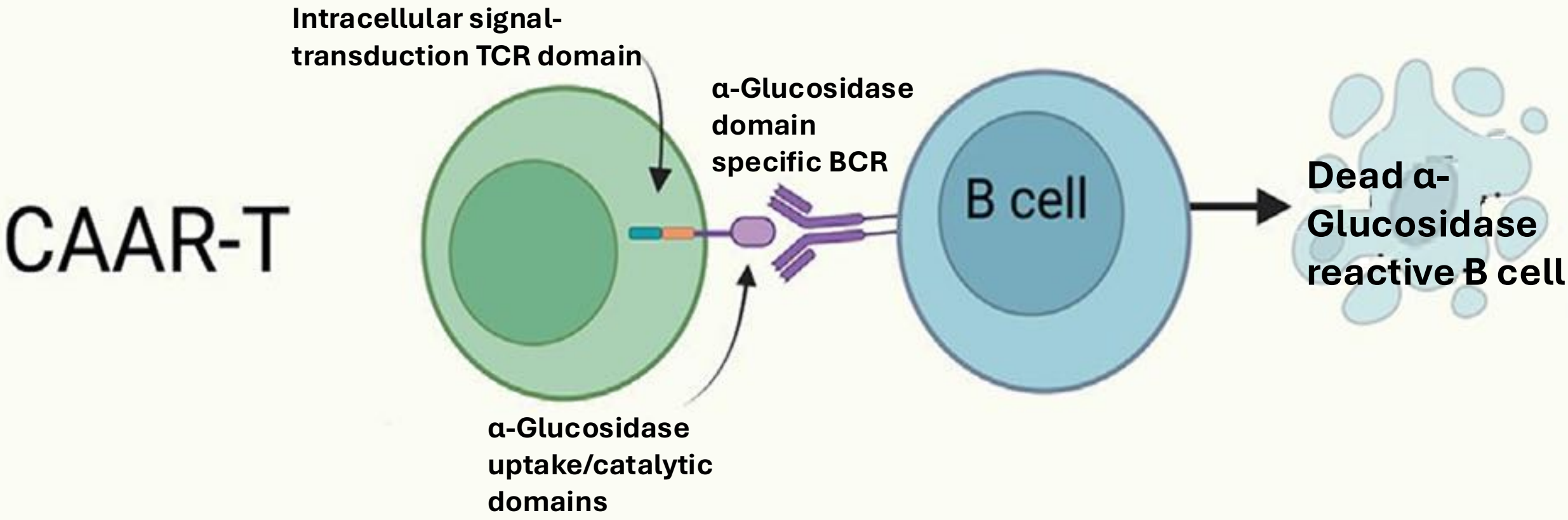

Logistical Considerations for CAAR-T and CAR-Treg Cell Therapies for Urgent Indications

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- For Pompe, ERT must start immediately given muscle wasting; time to generate autologous CD19 CAR-T, CAR-Tregs or CAART > 2 weeks. Clear need for off the shelf CAR-T, Tregs, or CAART:
  - Allogeneic CD19 CAR-T cells deimmunized by deleting TCR, MHCI, MHCII under development: HLA-E transgene to deter NK activity (Schett Lab); apply same to CAART, CAR-Tregs
  - Begin ERT immediately then follow with CAAR or CAR-T
  - Autologous CAR-Treg and CAAR-T approaches can be used when elimination of ADA not urgent as for other Lysosomal Storage Diseases including Fabry, and for other therapeutic proteins

- Need for depletion of endogenous T cell populations for engraftment: chemotherapeutic agents used for cancer and severe autoimmune disease, albeit at low doses, are problematic in neonates and young children: alternatives?
  - T cell cytopheresis with reinfusion following CAAR T treatment?
  - Expression of receptor for cytokine or growth factor on CAAR T or CAR-Tregs and administration of the factor to trigger and enhance their expansion.
  - *Preconditioning may not always be essential;* No preconditioning for treatment of MuSK MG with CAAR-T MuSK EC Domain*.

- Potential need to deplete ADA or autoantibodies at high titer via plasmapheresis to allow CAAR-T cells access to B cell populations in tissue sites

*Poster presentation-JR Volkov et al Cabaletta Bio ESGCT Annual Congress 2024

Caveats for all CAR T and CAART Therapies

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- Rare malignancies in patients treated with CD19 CAR-T cells. CAART and CAR-Tregs also generated with lentiviral vectors with potential for insertion site mutagenesis. CRISPR-Cas directed approach to better assure “safe haven”?

- Immunogenicity of CD19 CAR Ts in cancer treatment documented in some cases. Also a concern for CAART and CAR-Tregs but tolerogenicity may have mitigating effects.

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CAAR T regs in the Spotlight! Chimeric Antibody Receptor Tregs to Prevent or Eliminate ADA

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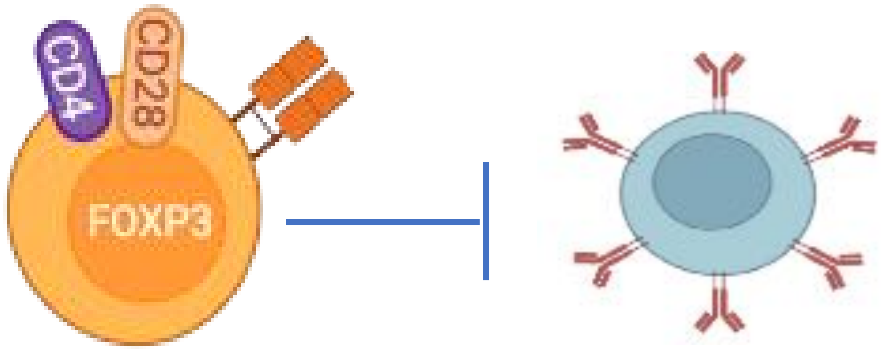
CAAR-Tregs Specific for Drug Specific B cells

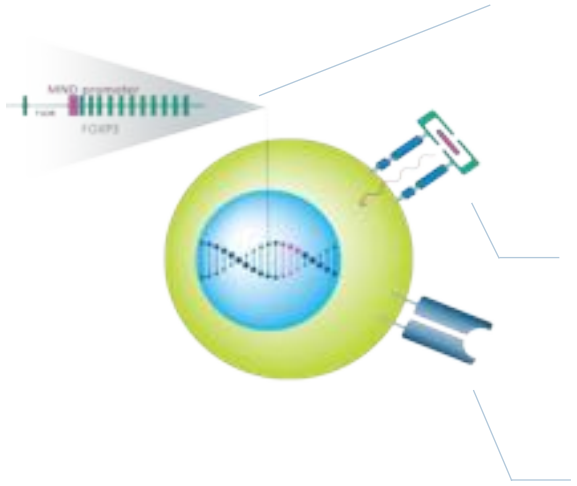
Harness the immunosuppressive capacity of CAAR Tregs to block maturation and activity of ADA specific B cells: Difference in efficacy/safety of suppressive mechanisms vs killing of effector cells?



Addressing Key Challenges for Treg Therapy by Engineering Optimal Tregs

ENGINEERED Treg PLATFORM SOLUTION: GentiBio Approach

GOAL: Scalably engineer targeted Tregs from bulk CD4 cells that are highly stabilized and functional in the inflammatory disease environment



Lock in Treg stability
constitutive, high-level expression of the Treg master regulator, FOXP3

IL-2 signaling support:
lock in Treg stability. Promote activity, expansion and long-term engraftment

Tissue/B cell targeting
via CAR, TCR, or upregulation of chemokine receptors for optimal homing, efficacy, and safety

Addressing the three challenges has clear potential for ADA prevention or elimination: off the shelf Tregs would add to advantage

The Field is Exploding with Novel Engineered Tregs!

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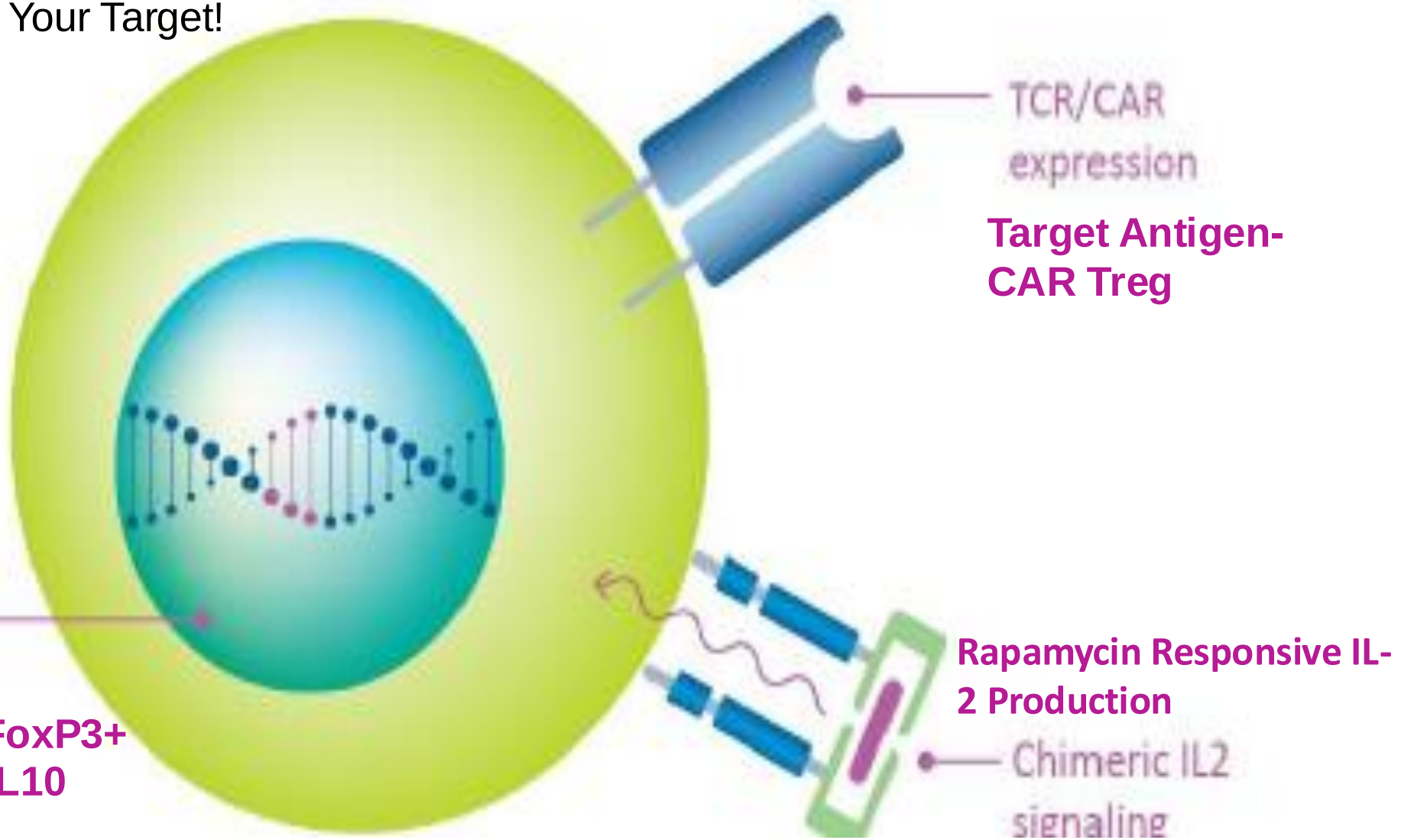
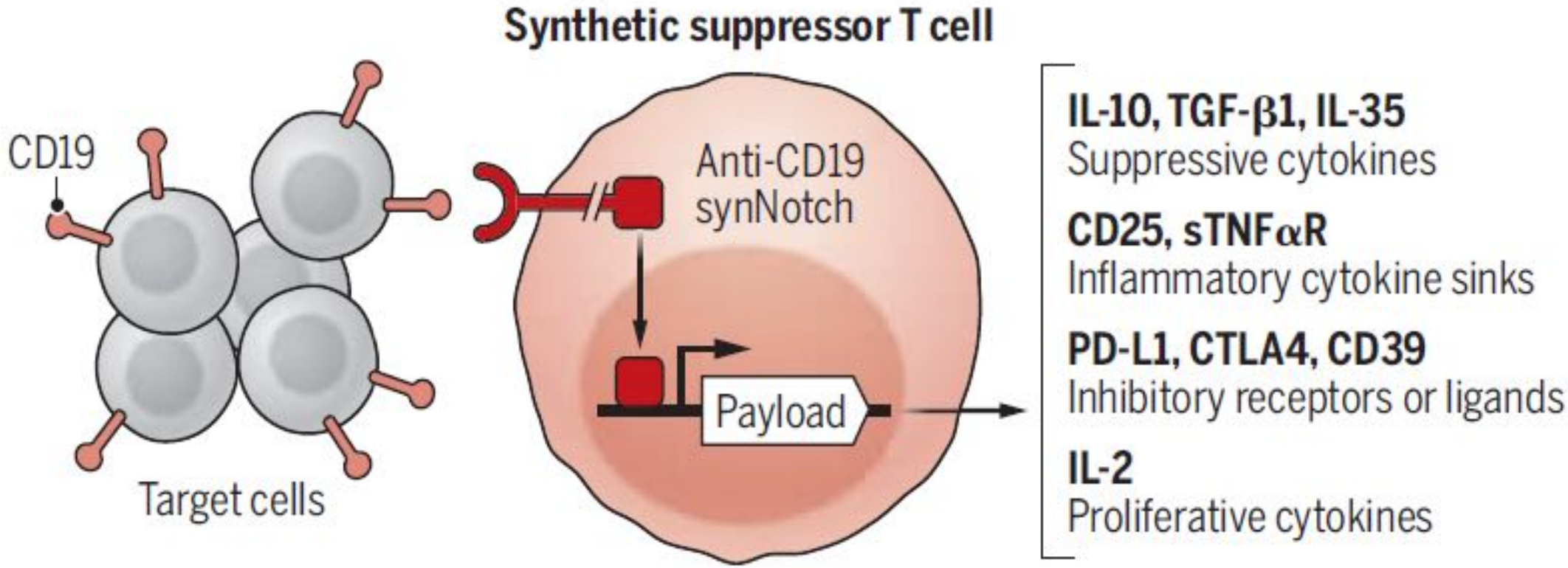
GentiBio's Platform: Choose Your Target!



Recently Reported: Treg Platform Based on "Synthetic" Gene Circuits Engineered for Efficient Treg Activity



Davila ML and Brentjens R Science Dec 6 2024

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Safety Issue for CAR-T Cells: T cell Malignancies Following Treatment with CD19-CAR T Immunotherapies

In November 2023, the FDA posted a safety communication to provide information about reports of T cell malignancies including CAR-positive lymphoma in patients who received treatment with BCMA- or CD19 autologous CAR T cell immunotherapies (for cancer). Reports were received from clinical trials and/or post-marketing adverse event data sources. 22 cases/27K doses as of 12/2023

- "FDA has determined that the risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T cell immunotherapies". Boxed Warning
- Post-marketing requirements include conducting 15-year follow-up observational safety studies to assess the long-term safety and the risk of secondary malignancies occurring after treatment.

In the February 6 edition of NEJM, a brief report described a CD4+ T cell lymphoma harboring a CAR integration in TP53 in a patient previously treated for refractory MM with BCMA-CAR-T cells (Perica K et al NEJM Feb 6 2025)

In the February 13 edition of NEJM a Brief Report was published regarding CAR+T cell Lymphoma after anti-BCMA CAR T Therapy for Relapsed or Refractory Myeloma in two patients (Harrison SJ et al NEJM Feb 13;2025)

Potential Contributing Factors to Development of Malignant CAR-T T Cell Lymphomas

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- The recent reports of T cell malignancies following CAR-T therapy were in patients treated for multiple myeloma who have significant risk factors: elevated risk for all lymphomas as a second primary malignant neoplasm

- The role of insertional mutagenesis (lentiviral vector) was uncertain in these patients

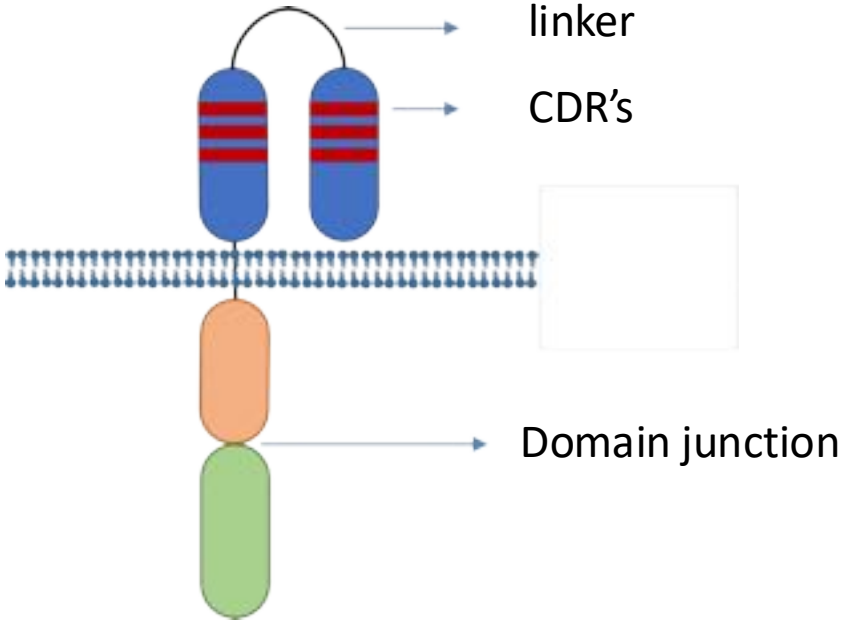
- Transduction of preexisting low level TET2-mutated T cells in CAR-T manufacturing a potential major contributing factor

Harrison SJ et al NEJM 2025 392: 677-685

Is Immunogenicity a Concern for CAR-T cells Given Extensive Elimination of B (but not T) cell Populations?

Receptor construct:

- Non-human sequences can be presented on HLA class I/II
- Murine vs fully human ScFv
- CDRs can be recognized as non-self
- Linker peptides
- Domain junctions



Residual production related proteins:

- Viral (AAV/Lentiviral) proteins
- Expansion mAbs / streptavidin
- CRISPR (Cas9) / Talen proteins
- Host Cell Proteins
- Preexisting reactivity for residual proteins?

Allogenic CAR-T

- GVH and HVG risk due to HLA mismatch

V. Jawa BMS

Immunogenicity *can* be a Significant Problem for CD19 CAR-T Cells

CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients

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BACKGROUND. T cells that have been modified to express a CD19-specific chimeric antigen receptor (CAR) have antitumor activity in B cell malignancies; however, identification of the factors that determine toxicity and efficacy of these T cells has been challenging in prior studies in which phenotypically heterogeneous CAR–T cell products were prepared from unselected T cells.

METHODS. We conducted a clinical trial to evaluate CD19 CAR–T cells that were manufactured from defined $CD4^+$ and $CD8^+$ T cell subsets and administered in a defined $CD4^+$:$CD8^+$ composition to adults with B cell acute lymphoblastic leukemia after lymphodepletion chemotherapy.

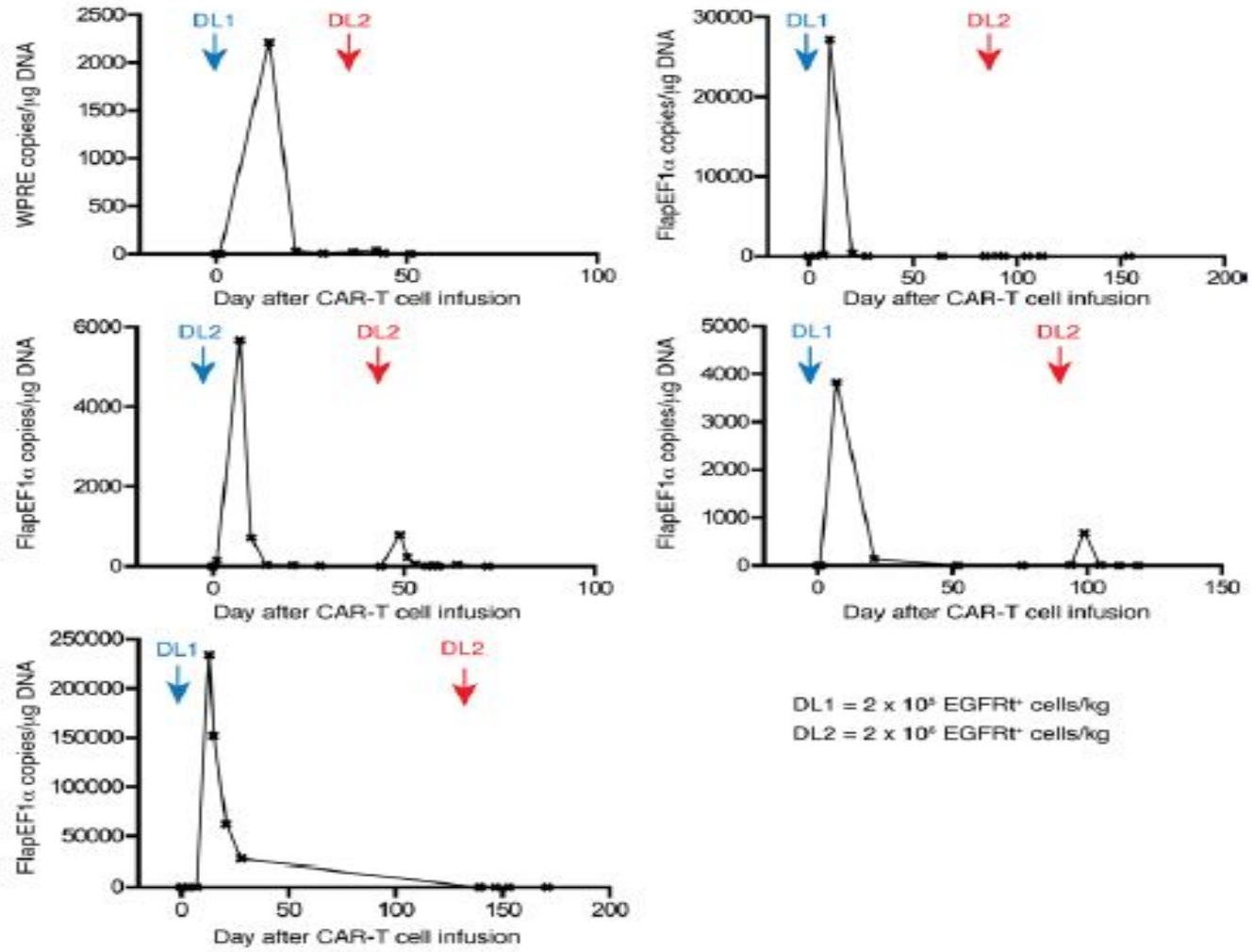
RESULTS. The defined composition product was remarkably potent, as 27 of 29 patients (93%) achieved BM remission, as determined by flow cytometry. We established that high CAR-T cell doses and tumor burden increase the risks of severe cytokine release syndrome and neurotoxicity. Moreover, we identified serum biomarkers that allow testing of early intervention strategies in patients at the highest risk of toxicity. Risk-stratified CAR-T cell dosing based on BM disease burden decreased toxicity. $CD8^+$ T cell–mediated anti-CAR transgene product immune responses developed after CAR-T cell infusion in some patients, limited CAR-T cell persistence, and increased relapse risk. Addition of fludarabine to the lymphodepletion regimen improved CAR-T cell persistence and disease-free survival.

CONCLUSION. Immunotherapy with a CAR-T cell product of defined composition enabled identification of factors that correlated with CAR–T cell expansion, persistence, and toxicity and facilitated design of lymphodepletion and CAR–T cell dosing strategies that mitigated toxicity and improved disease-free survival.

CD8+ T cell–mediated anti-CAR transgene immune responses developed after CAR–T cell infusion in some patients,… limited CAR–T cell persistence and increased relapse risk

J Clin Invest. 2016;126(6):2123–2138

Loss of CAR-T Due to Cytotoxic Response to CAR T Elements: could this have been predicted?



- **Five patients with persistent leukemia or relapse received a second infusion of CAR-T cells (Red arrows)**
- **Study found no "expansion or persistence of CAR-T cells or demonstrable antitumor activity in any of these 5 patients"; loss of CAR T cell population**
- **Anti-CAR-T specific CD8 responses detected in all 5 patients; % specific lysis increased with second infusion**

Turtle CJ et al JCI 2016

Tools for Immunogenicity Risk Evaluation of CAR-T Cells Same as those for Therapeutic Proteins and Gene Therapies

EpiVax

Immunogenicity Risk Assessment Assays and Tools

Immunogenicity tools and assays developed for biologics can be modified to cellular therapeutics

***In Silico* tools**

- MHC Class I and II binding
- Novel tools predicting antigen processing and presentation and tolerance

***In vitro* assays**

T cell proliferation assay

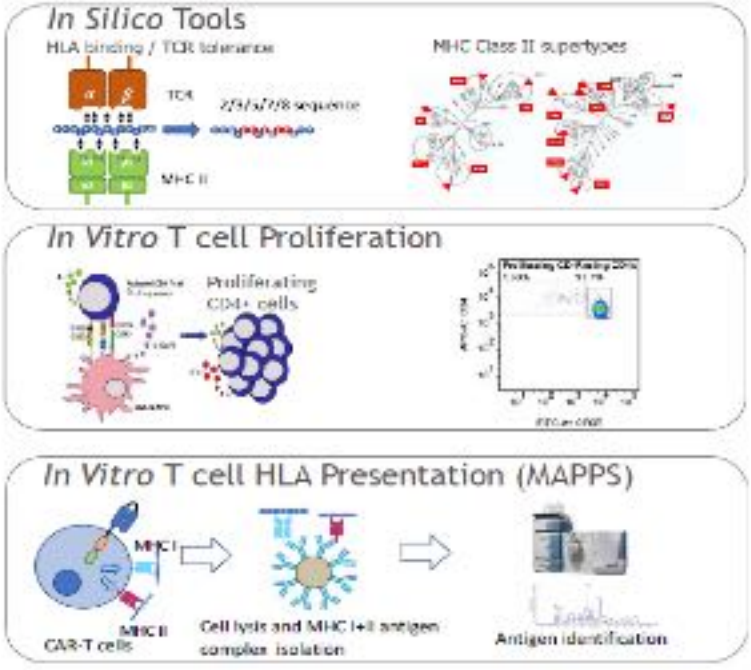
- Extracellular vs whole construct (challenge to recombinantly express whole receptor)
- Overlapping peptides of CDRs/linkers/domain junctions

MAPPS assay

- MHC I and II presented peptides processed and presented peptides
- Can be used to design peptides for clinical ELIspot /CTL assay
- Can be used for algorithm development

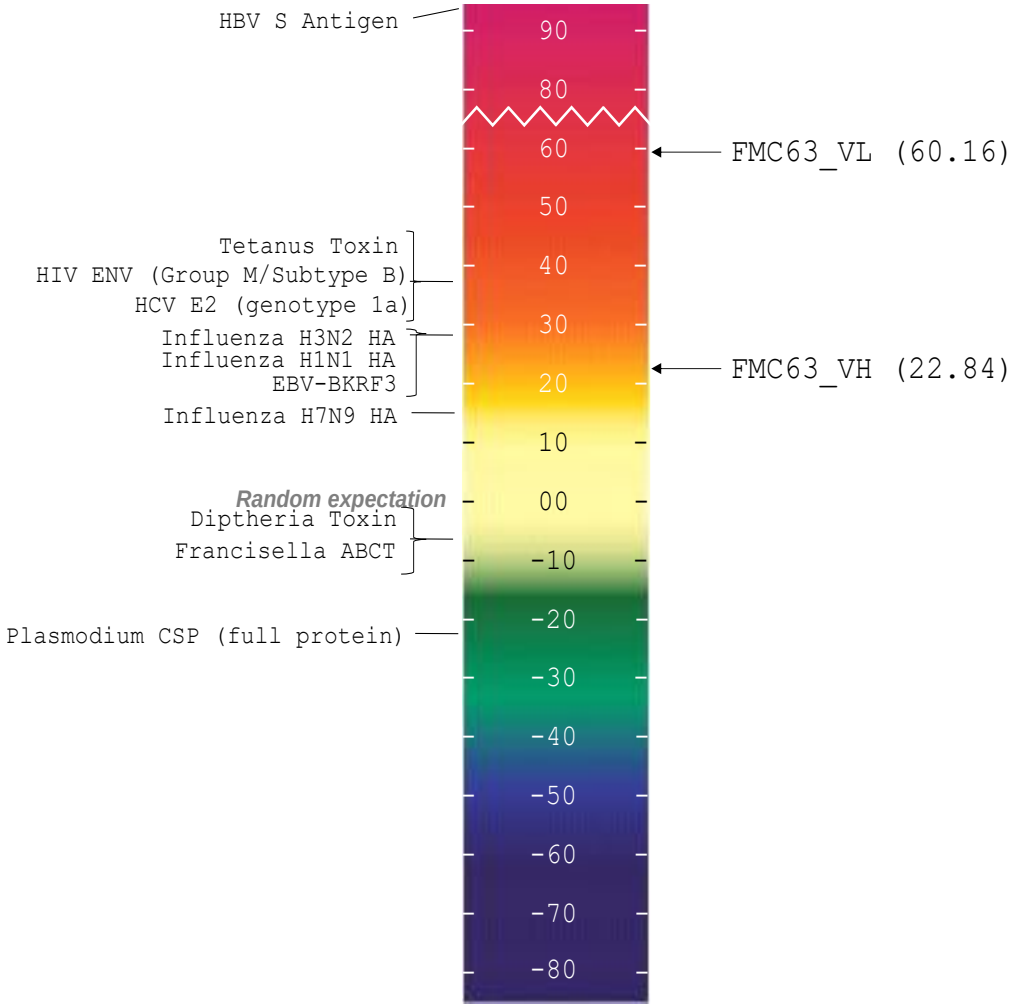
Innate activation assay

- Residual process related proteins
- Whole blood / PBMC / engineered TLR cell line



Gokemeijer J et al Novel Modalities WG of Translational ADME Leadership Group Presentation 2022

InSilico Assessment of Class I HLA/scFv Peptide 9mers in CAR-T via ISPRI: Numerous HLA Class I Epitopes Detected



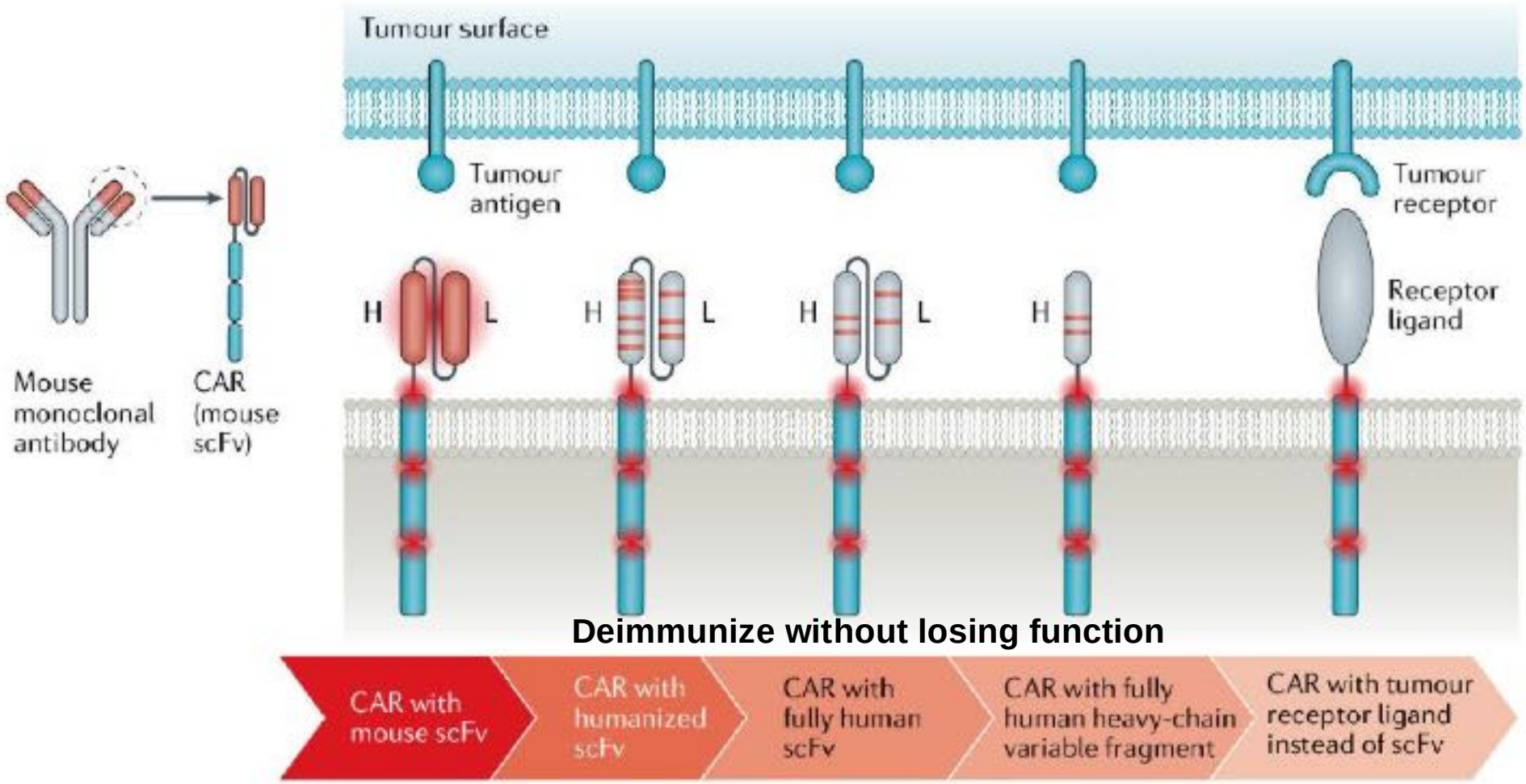
Protein Label	Length	Assessments	EpiMatrix Hits	EpiMatrix Score
FMC63_VH	123	690	43	22.84
FMC63_VL	120	672	55	60.16

Summarized Results	A0101	A0201	A0301	A2402	B0702	B4403	Total
FMC63_VH, by 9	10	5	8	8	5	7	43
FMC63_VL, by 9	14	8	7	13	8	5	55

FMC63 sequence contains many putative Class I epitopes

FMC63 sequence obtained from Nicholson et al. 1997

Remediation- Assess Immunogenicity of CAR-T Domains: Deimmunize Without Loss of Function



Wagmer DL et al Nat Rev Clin Oncol. 2021

Conclusions

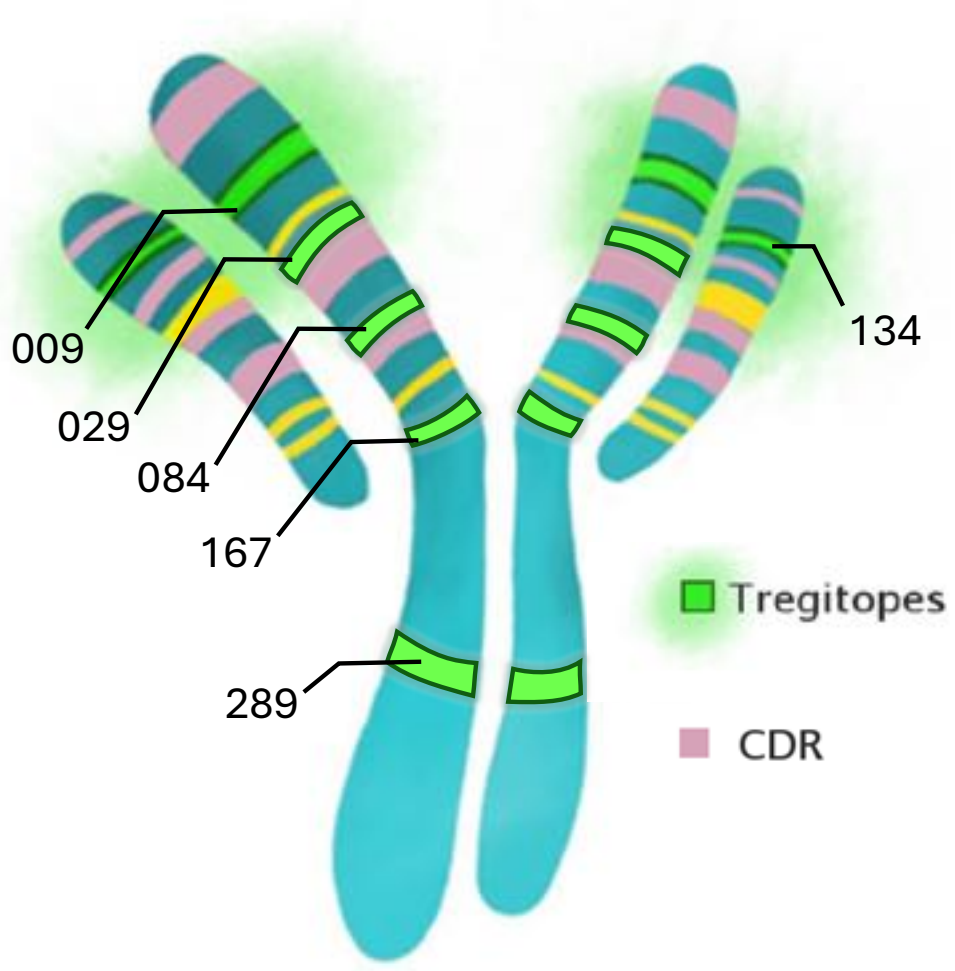
- Although there are many logistical concerns, antigen specific T cell therapies should be further investigated and developed for prevention or mitigation of devastating immune responses to protein, gene, and cellular therapies.
- Safety issue of T cell malignancies including CAR-positive lymphoma of particular concern for all but especially treatment of children; requires further investigation of factors predisposing to their generation and elimination of risk
- Immunogenicity issues remain a significant concern particularly in the absence of immune depleting pre-treatments. Deimmunization strategies may reduce efficacy impacting immunogenicity.

Agenda

- CD19 CAR-T cells in treatment of autoimmune diseases
  - Chimeric Autoantibody Receptor (CAART) T cells: application to autoimmune disease
- Application of Antigen Specific CAAR-T and CAR-T regs to prevention or elimination of ADA to therapeutic proteins
  - Potential applications
  - Logistical considerations
  - Safety issues for all CAR/CAAR T therapies
- Engineered CAR-Tregs
- Safety and Immunogenicity issues for all CAR T cells
- Alternative approach to antigen specific tolerance: Tregitope based therapy

Regulatory T cell epitopes (Tregitopes) an Alternative Approach to Antigen Specific Immune Tolerance Induction

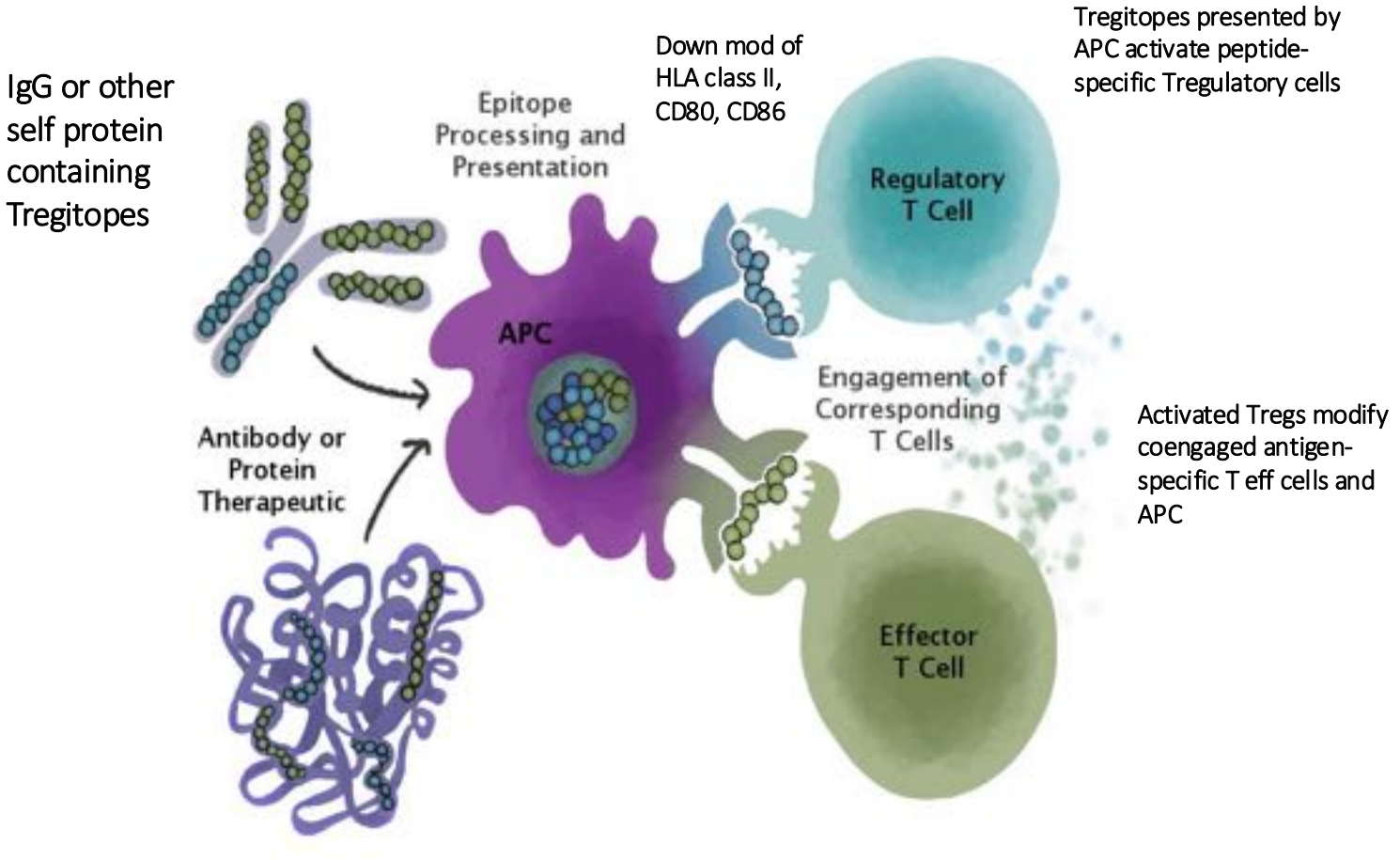
EpiVax



- 15-20 amino acid peptides in conserved IgG regions
- Presentation of Tregitopes is HLA-restricted
- Tregitopes are presented by multiple HLA
- Highly conserved among IgG molecules
- Induce natural Tregs to modify immune response

Tregitope	Sequence
009A	VQPGGSLRLSCAASG
029B	WVRQAPGKGL
084	FTLTISSLQ
088	YLQMNSLRAEDTAVY
134	FYPREAKVQWKVDNALQS
167	LQSSGLYSLSSVVTVPSSSL
289	YNSTYRVVSVLTVLH

Tregitopes Activate Regulatory T cells, Induce Tolerogenic APCs, and Convert Teff to Tregs



De Groot A.S., et al., Activation of Natural Regulatory T cells by IgG Fc-derived Peptide "Tregitopes". Blood, 2008,112: 3303.
http://tinyurl.com/ASDeGroot-Blood-2008

- **Tregitopes- Short, linear peptide sequences that bind to HLA and activate *regulatory T cells***
- **Identified by Epivax immunoinformatics searching on epitopes that are homologous to human genome at the TCR face**
- ***Can be co-formulated or attached to immunogenic proteins to provide antigen-specific tolerance***
- **Wide range of therapeutic applications**
- **Two mechanisms of action**:
  - **Effects directly on Tregs**
  - **Effects on APC**

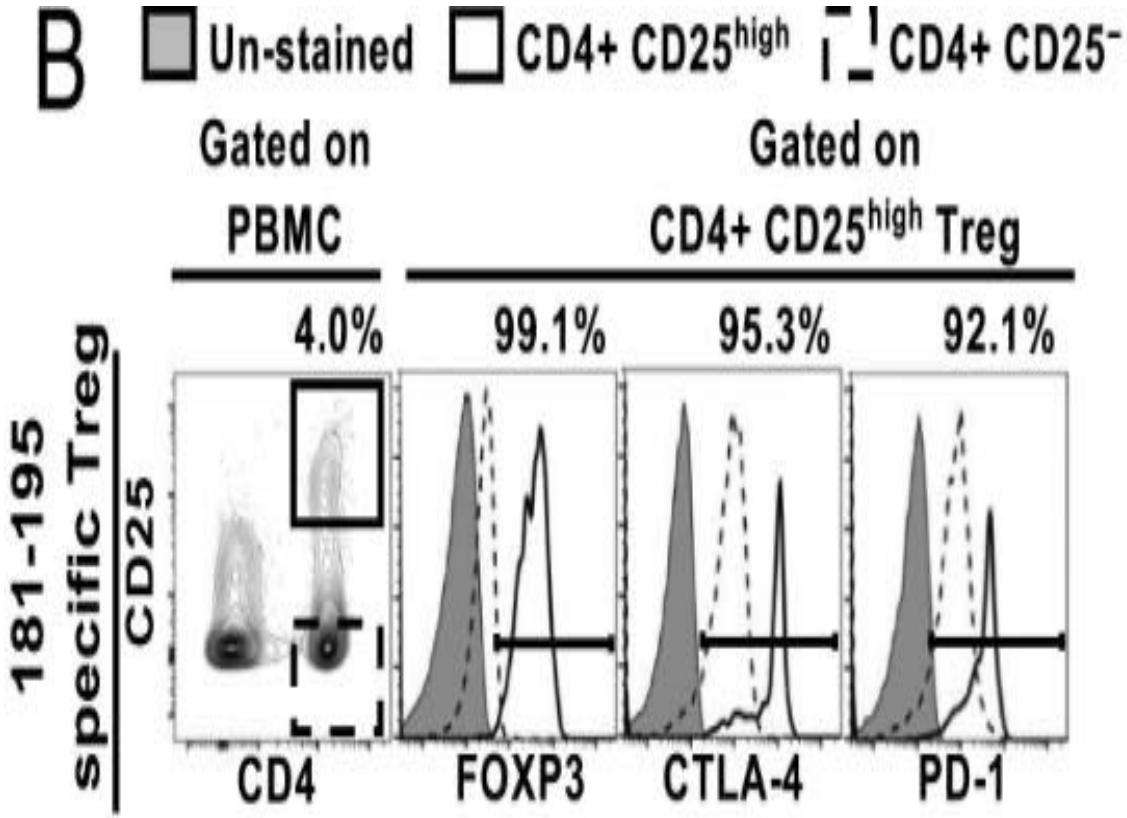
IgG-derived Fc peptide Tregitopes are Presented by Bcells and Induce Tsuppressor Phenotype

Fc position	Sequence
21 - 35	TAALGCLVKDYFPEP
26 - 40	CLVKDYFPEPVTVSW
31 - 45	YFPEPVTVSWNSGAL
36 - 50	VTVSWNSGALTSGVH
51 - 65	TFPAVLQSSGLYSLS
56 - 70	LQSSGLYSLSSVVTV
61 - 75	LYSLSSVVTVPSSSL
66 - 80	SVVTVPSSSLGTQTY
121 - 135	SVFLFPPKPKDTLMI
126 - 140	PPKPKDTLMISRTPE
181 - 195	TYRVVSVLTVLHQDW
186 - 200	SVLTVLHQDWLNGKE
271 - 285	NNYKTTPPVLDSDGS
276 - 290	TPPVLDSDGSFFLYS
301 - 315	QGNVFSCSVMHEALH
306 -320	SCSVMHEALHNHYTQ

De Groot, Martin
Tregitopes
Discovered 2008

Tregitope 167
PAVLQSSGLYSL
SSVVTVPSSSLGTQ

Tregitope 289
EEQYNSTYRVV
SVLTVLHQDW

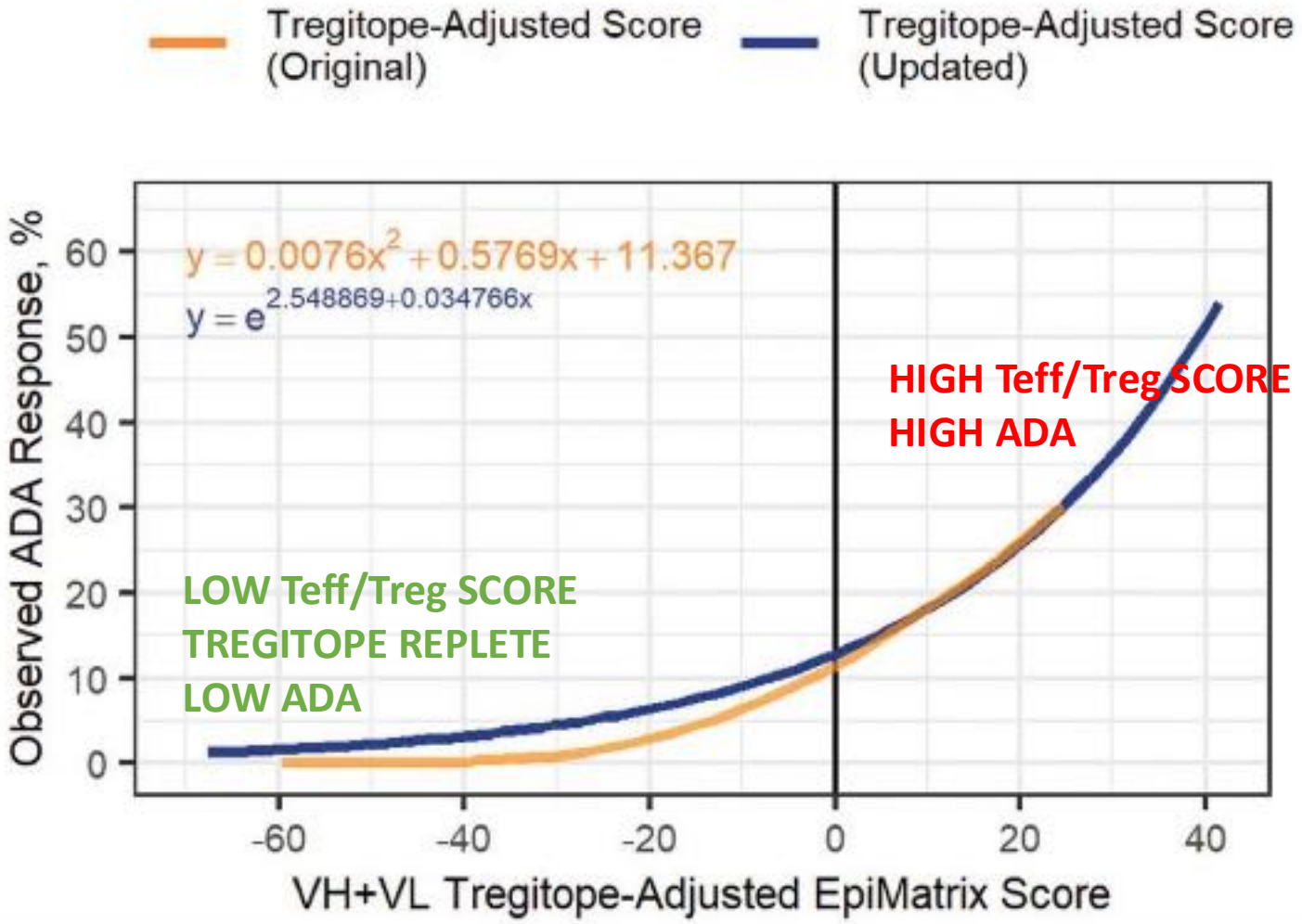


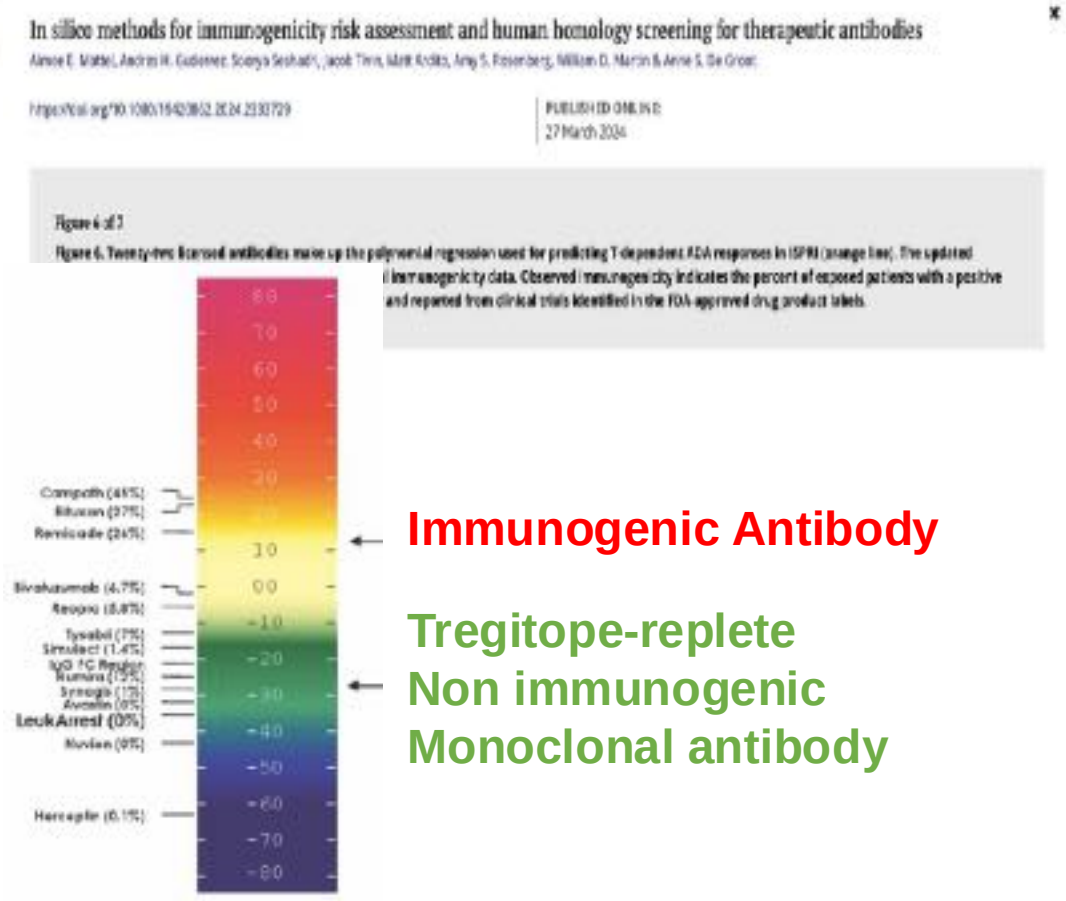
Presented peptides include Tregitopes 167 and 289

IgG1 Fc peptides tested for Treg recognition

A Franco et al J. Immunol 2021

Tregitope Content Correlates with Immunogenicity of mAbs: more plentiful in non-immunogenic monoclonal antibodies





Mattei et al. 2024

Preclinical studies involving Tregitopes to validate *in vivo*

In vivo Model	Immunogen	Delivery	Clinical application	Findings	Publication
C57BL/6	OVA	DMSO	**Tolerance induction**	Suppress Ag-specific T cell proliferation	Cousens et al Human immunology 2014
C57BL/6	MOG	CFA	**MS**	Induce Tregs, Reduce of EAE symptoms	Elyaman et al Neur Res Int 2011
NOD /ShiLtJ	PPI	Liposome	**T1D**	Reduce incidence of Type 1 diabetes when co administered with PPI	Cousens et al J of diabetes Research 2013
Balb/C	none	IFA	**T1D**	Suppress CD4+ response and are not immunogenic	Su et al JLB 2012
NOD /ShiLtJ	none	IFA	**T1D**	Reduce Type 1 diabetes after onset	Cousens et al J of diabetes Research 2013
D011.10 TCR Tg	OVA	IFA	**ERT**	Suppress Ag-specific T cell proliferation and induce Ag specific Treg	Cousens et al J of diabetes Research 2013
ABM TCR tg	bm12	DMSO	**Tolerance induction**	Induce Ag-specific Tregs	Cousens et al Human immunology 2014
HLADR4 Tg	HDM	saline	**Allergy**	Suppress immune response to the antigen	De Groot et al Blood 2008
C57BL/6	AAV	encoded	**gene therapy**	Reduce immune response to AAV capsid	Hui et al Mol Ther 2013
Balb/C	AAV	encoded	**inflammatory colitis**	Reduce severity of the disease, increase Treg infiltrates in colon	Van der Marel et al,World J Gastroenterol 2012
C57BL/6	OVA	DMSO	**asthma**	Reduction airway reactivity, Treg induction	Dembele et al Front Immunol 2021
NOD /ShiLtJ	N/A	HSA-fusion	**T1D**	Decrease T1D associated mortality when co-administered with PPI (ASATI)	De Groot et al Sci Rep 2019

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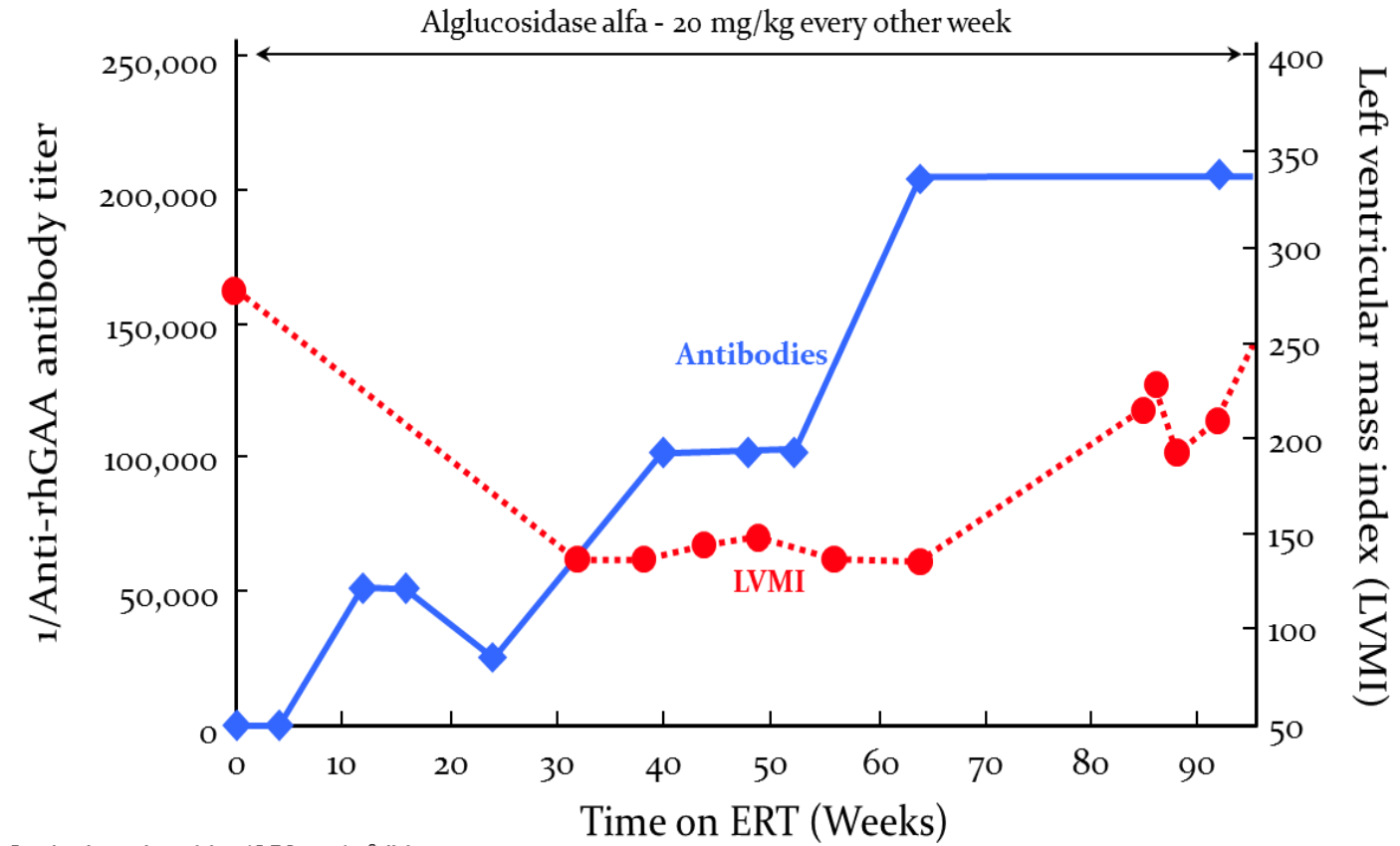
- Corey Iacono, BD Associate EpiVax, Inc
- Herve Lebrec, Sonoma Biotherapeutics
- Tiffany Chen, Gentibio

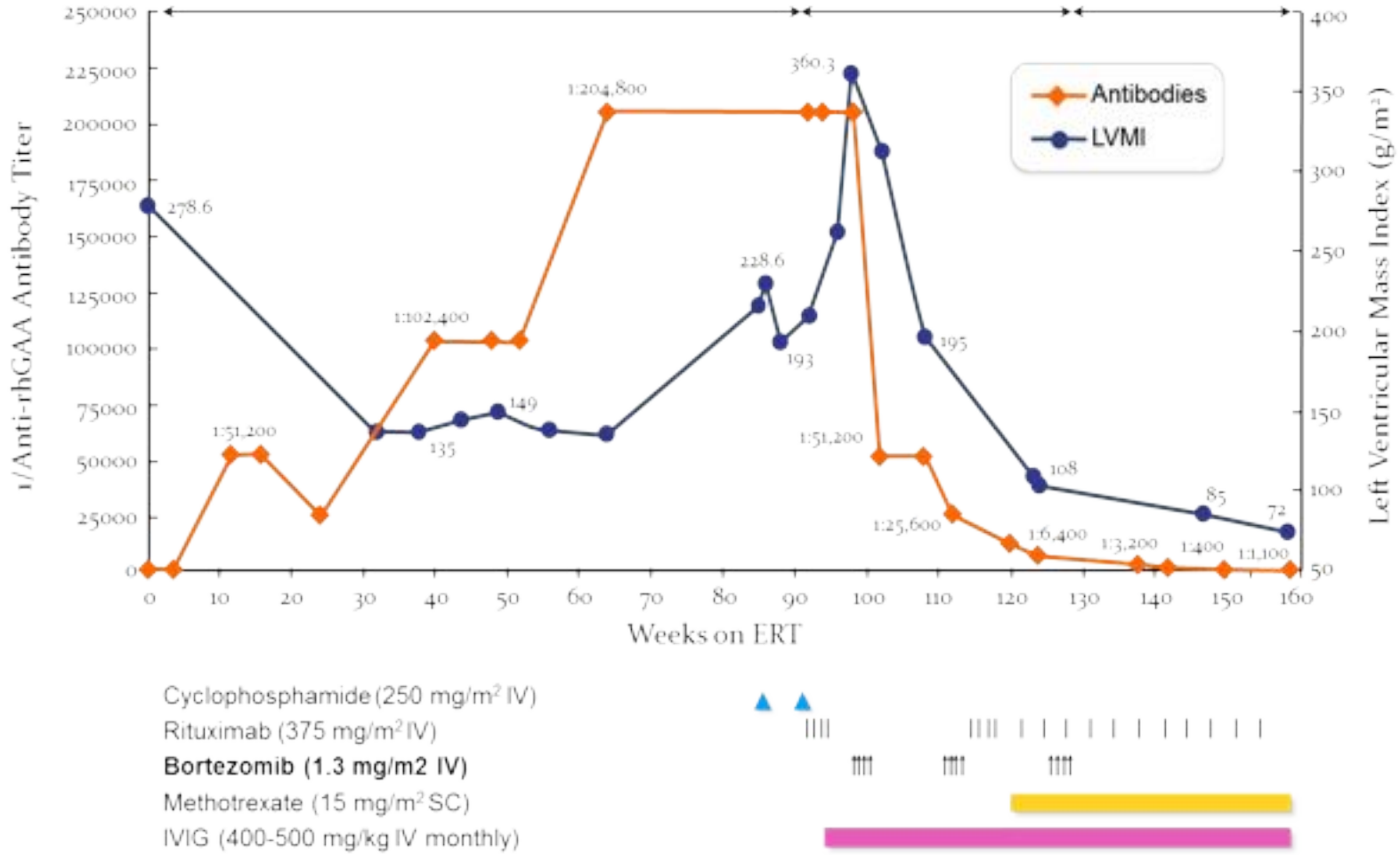
In Pompe: when the Prophylactic ITI Regimen is Ineffective ADA Surge with Rapid Clinical Deterioration



IOPD patient in profound Heart Failure due to high titer and sustained antibody responses to enzyme replacement therapy

(Banugaria SG et al Genet Med 2013)

In Patients who Fail to Tolerize: Targeting Plasma Cells Reduces ADA Can a CAAR-T Approach Supplant the Prolonged Highly Immune Suppressive Cocktail ?



Tolerance induction requires not only elimination of plasma cells but continued treatment with Rituximab, Methotrexate and IVIG over a prolonged time frame

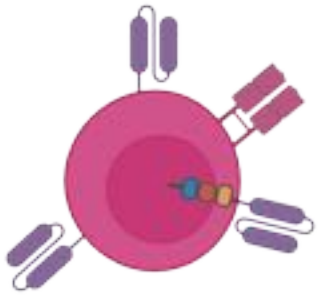
(Kishnani PS et al 2012)

B Cell Maturation Antigen (BCMA) CAR-Ts to Eliminate Long Lived CD19neg ADA Secreting Plasma Cells

EpiVax

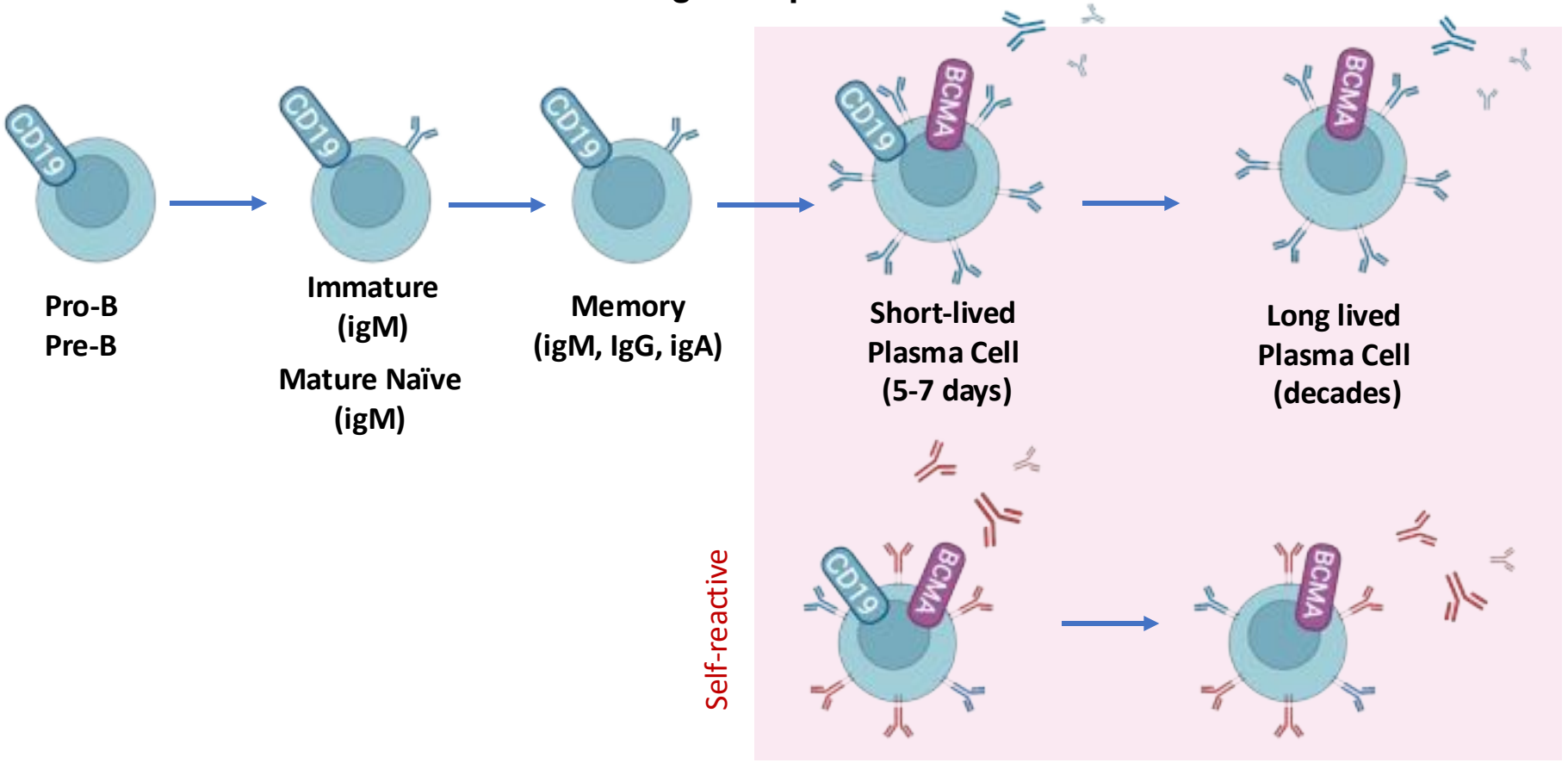
Targets BCMA on Short and long lived antibody secreting plasma cells

BCMA–targeted CAR-T



Naïve B cells

Antigen-experienced B cells



Pro-B
Pre-B

Immature
(igM)

Mature Naïve
(igM)

Memory
(igM, IgG, igA)

Short-lived
Plasma Cell
(5-7 days)

Long lived
Plasma Cell
(decades)

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EpiVax

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