

MBIM735: Advanced Immunology

Treg therapy

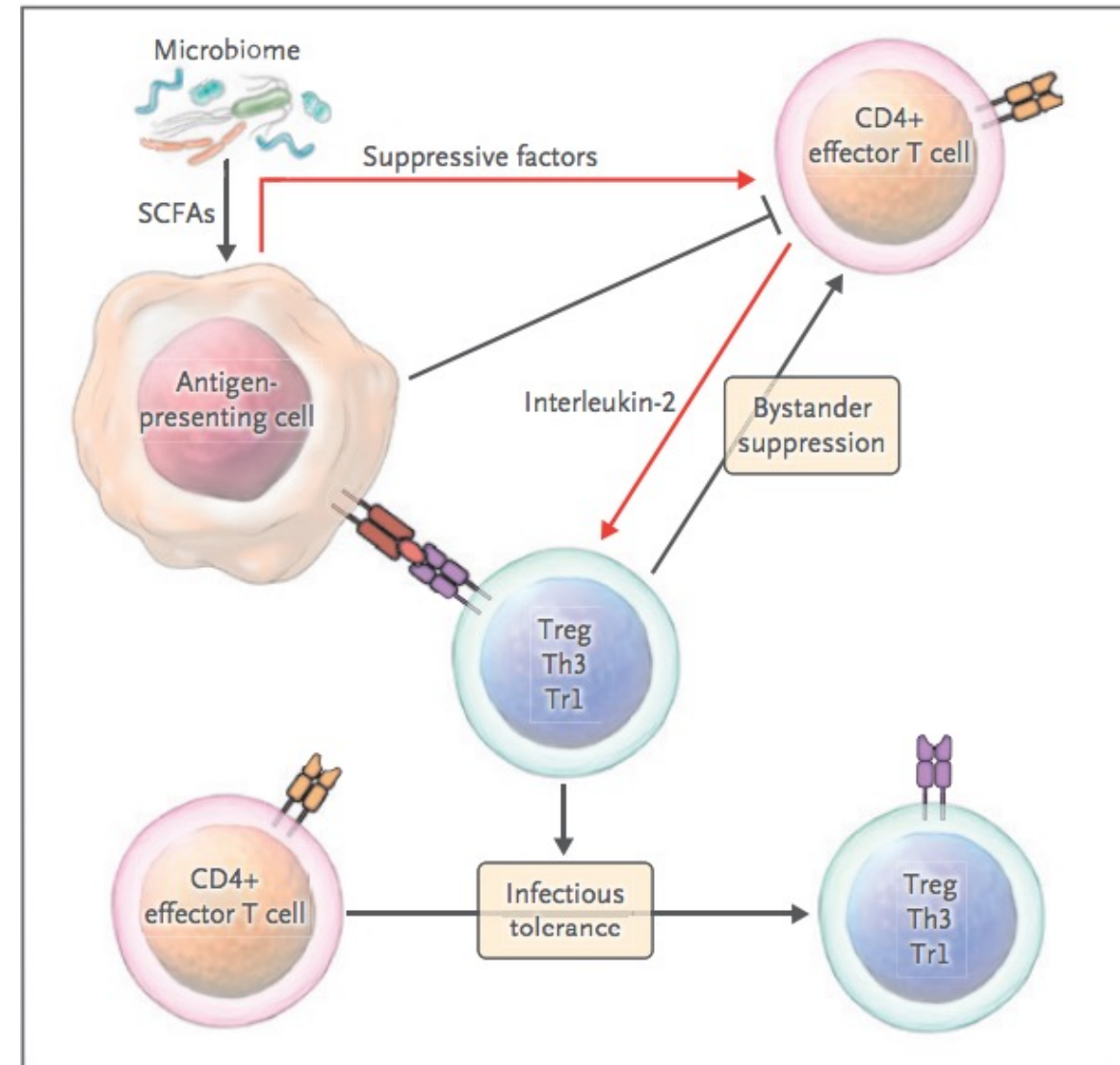
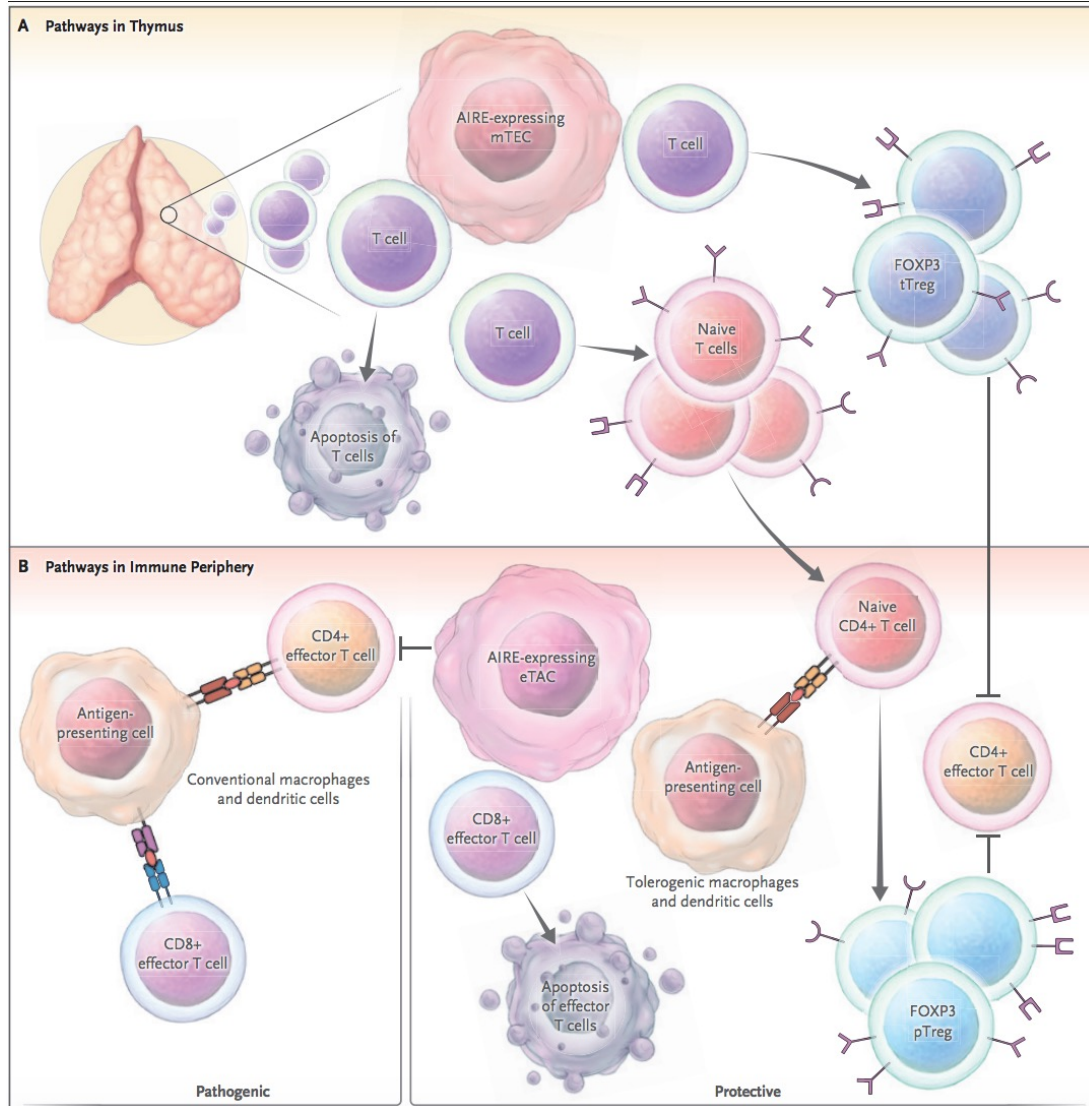
Leonardo M.R. Ferreira

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Hollings Cancer Center

Medical University of South Carolina

Immune tolerance



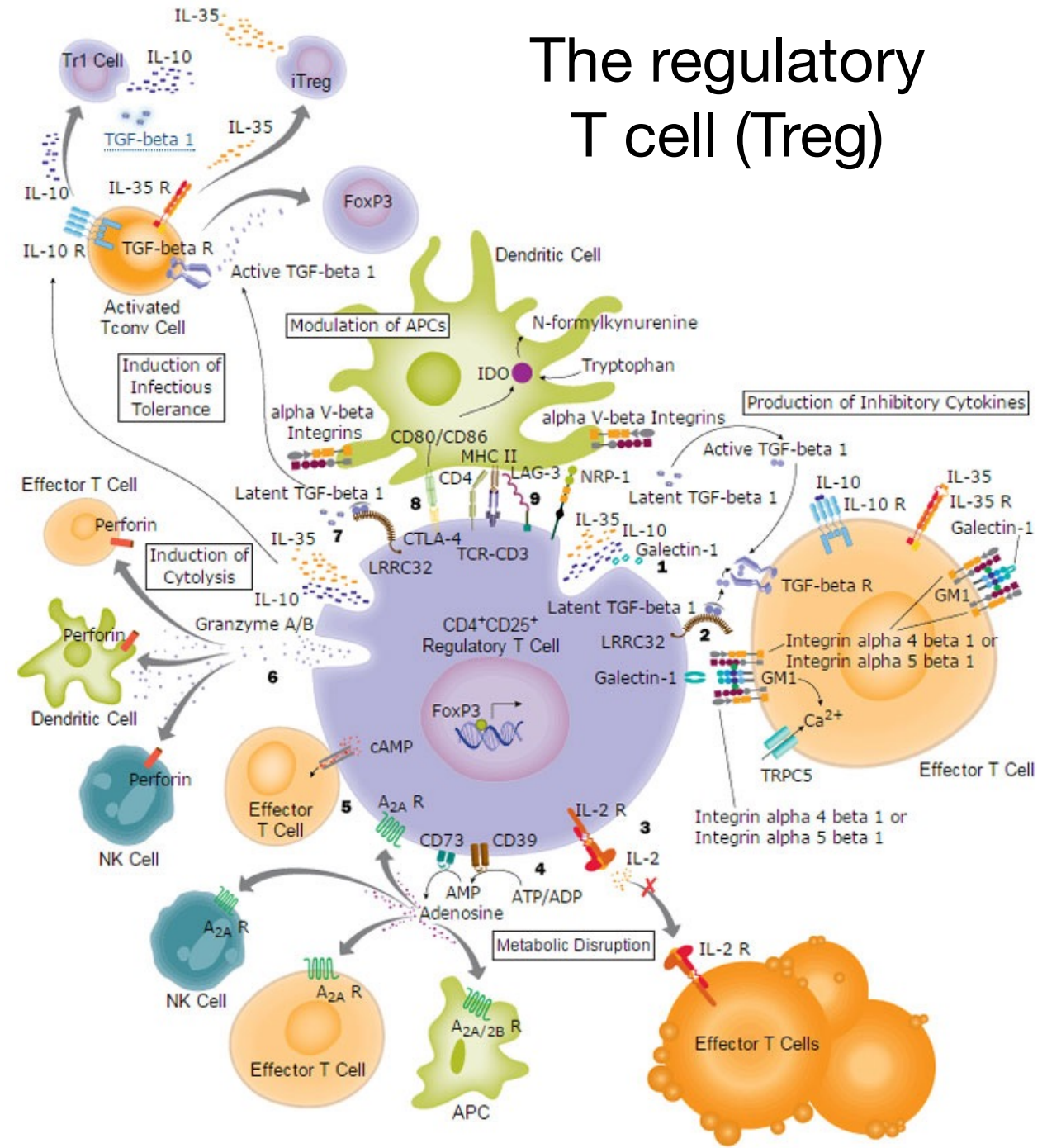
The regulatory T cell (Treg)

Versatile

Multi-faceted

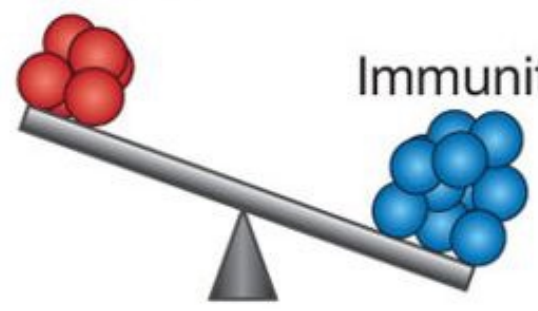
Many suppressive mechanisms

A therapy?



Regulation

Immunity



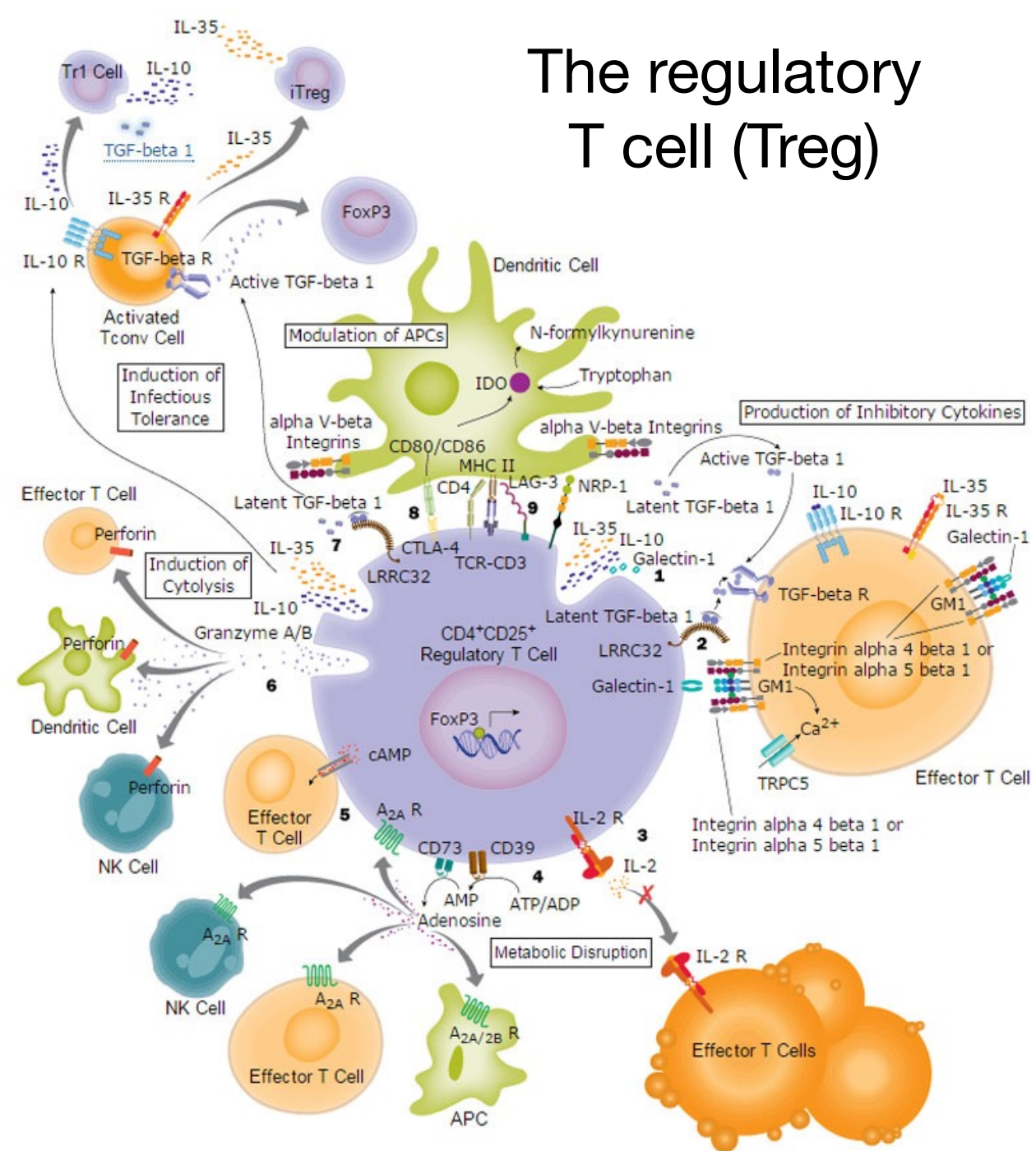
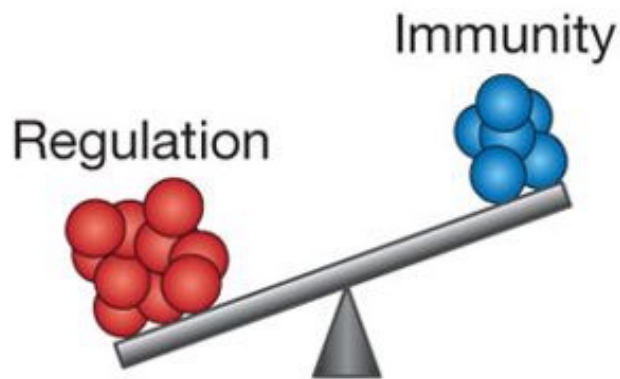
The regulatory T cell (Treg)

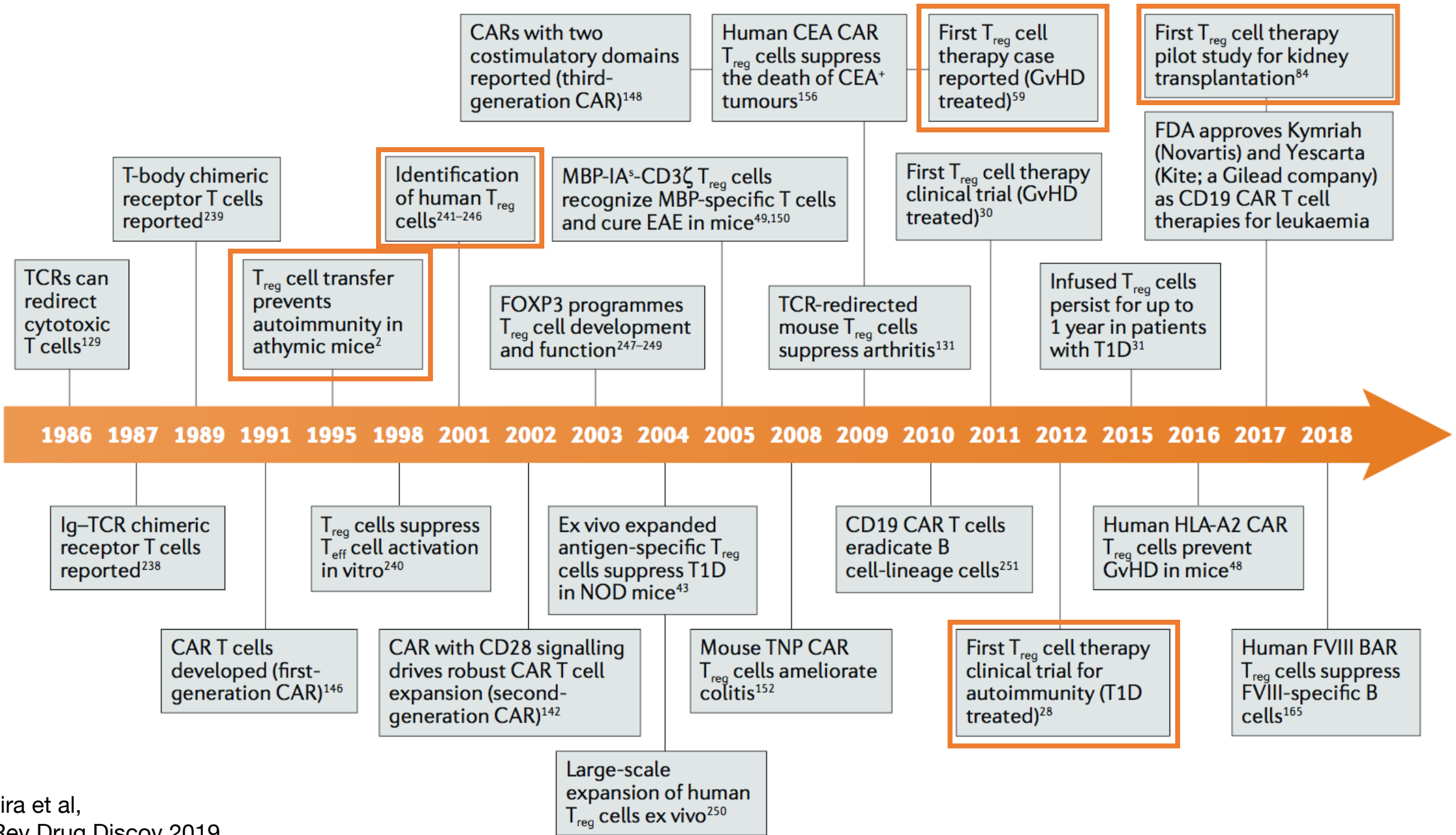
Versatile

Multi-faceted

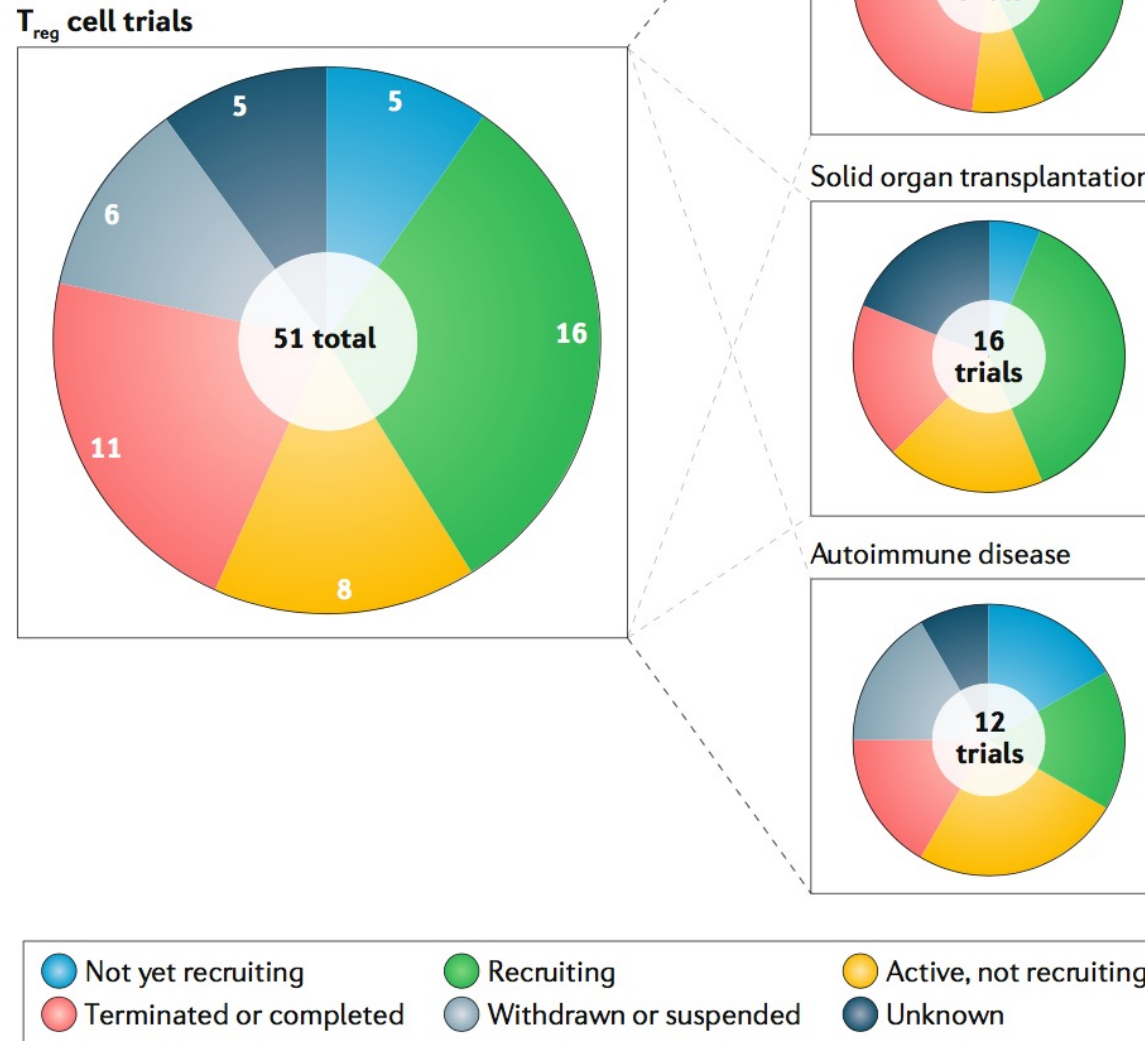
Many suppressive mechanisms

A therapy?





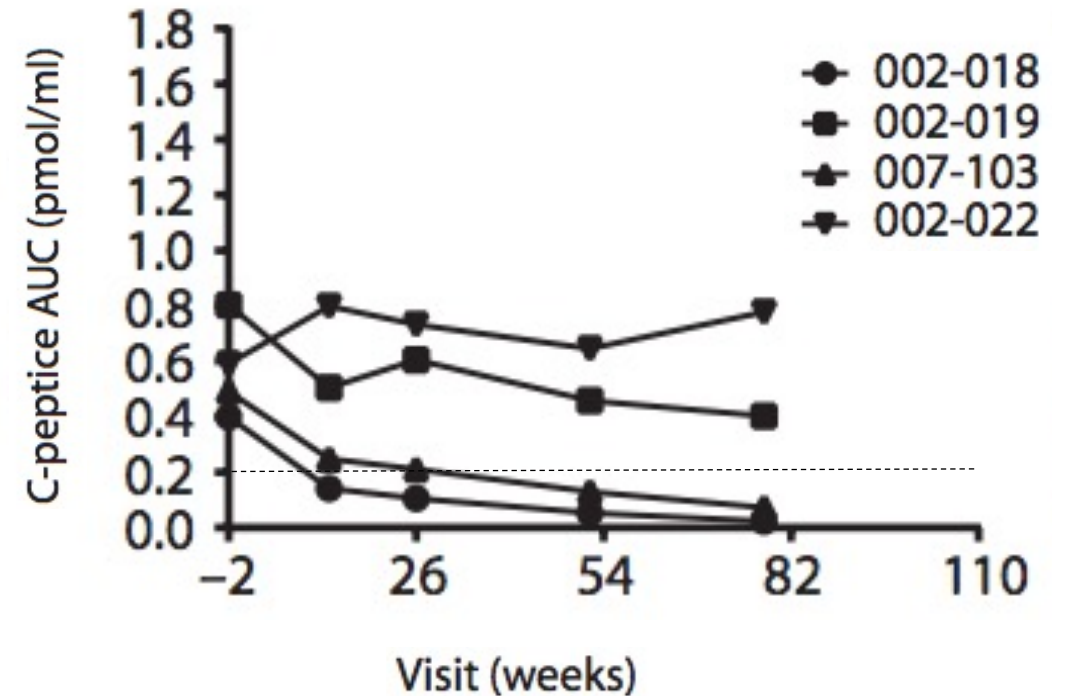
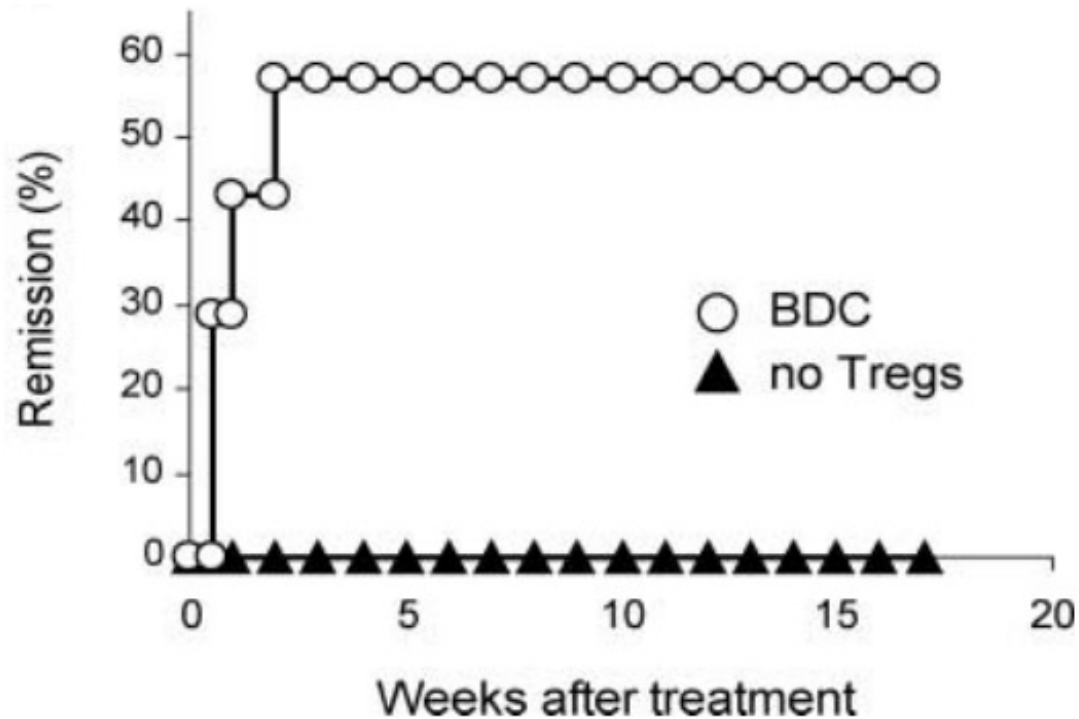
Clinical trials with Tregs



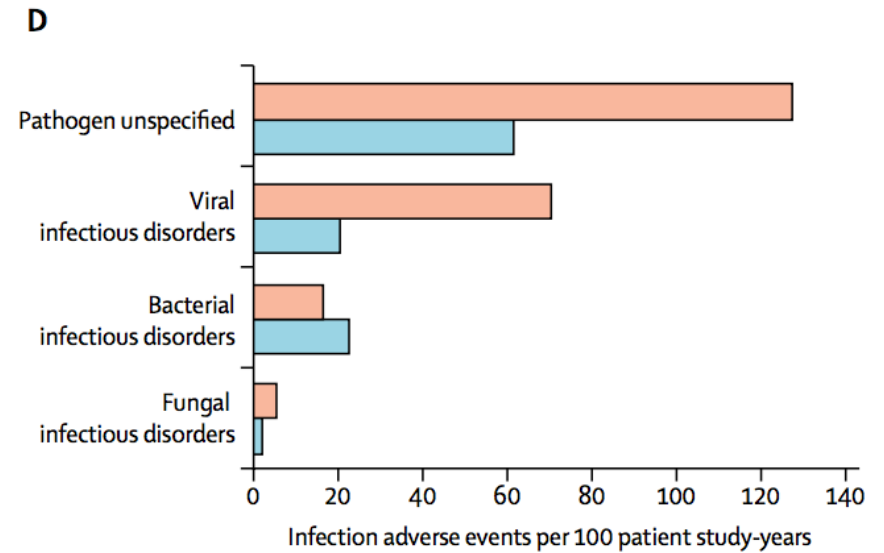
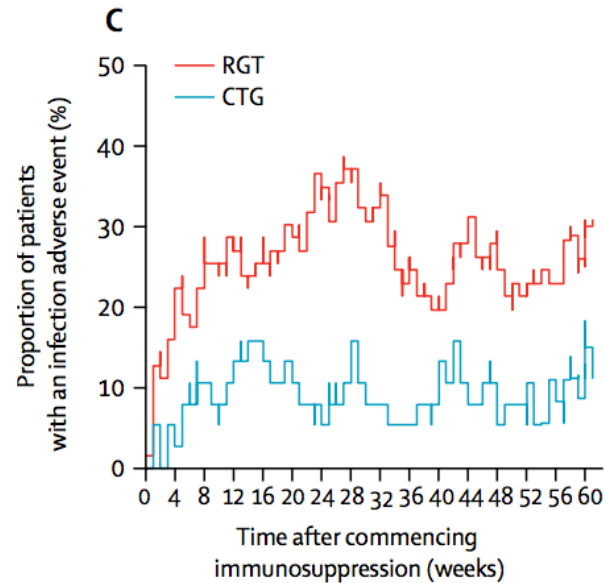
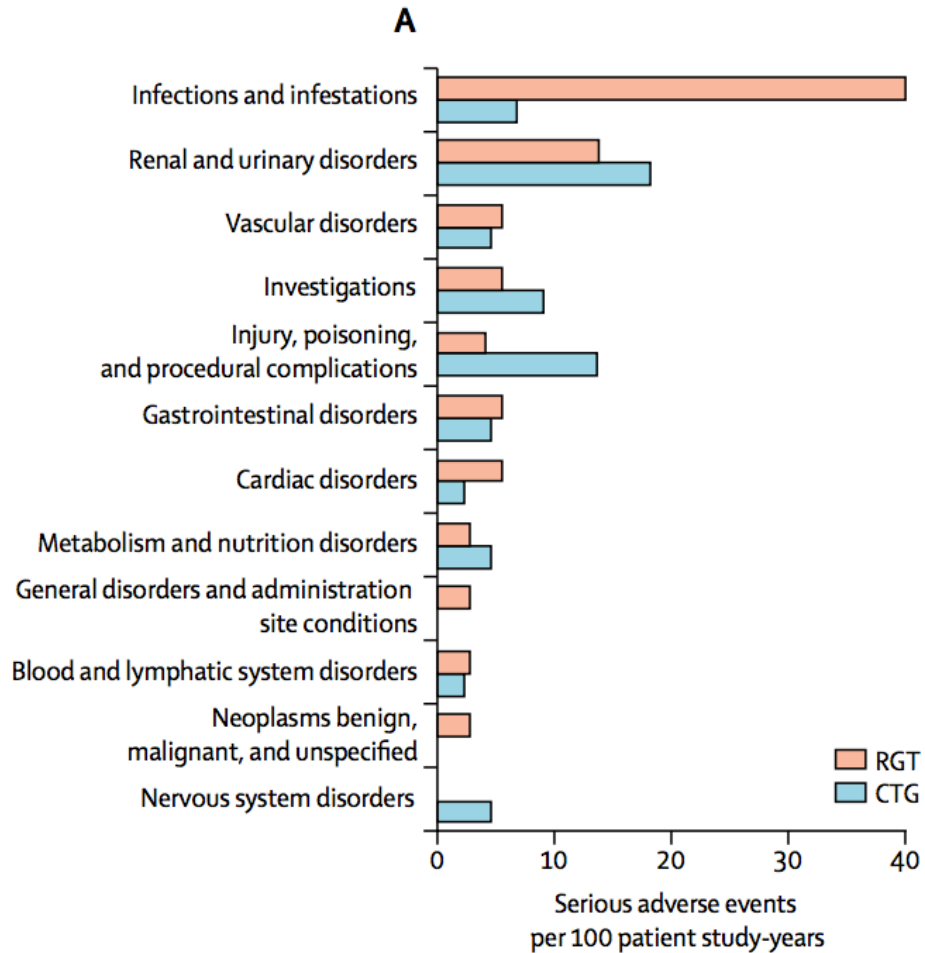
Treg therapy for type 1 diabetes

In mice: 2×10^6 BDC2.5 Ag-specific Tregs together with syngeneic islet transplant revert autoimmune diabetes

In humans: 2×10^9 polyclonal Tregs are safe for type 1 diabetes patients but do not ameliorate disease



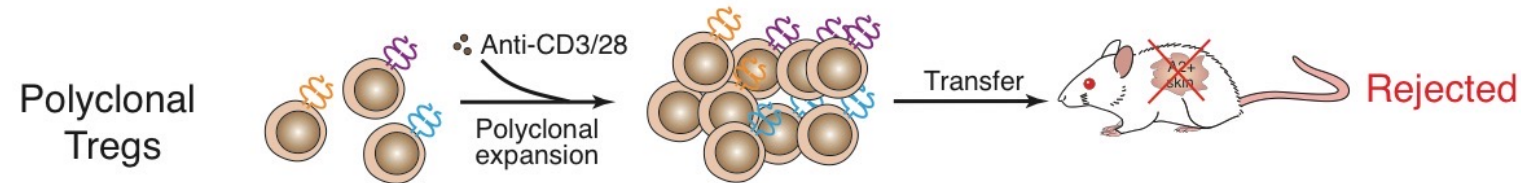
Treg therapy for organ transplant



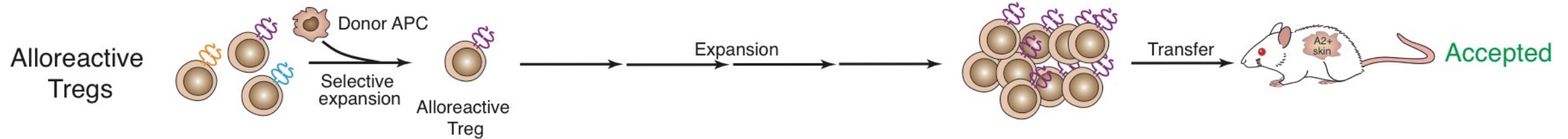
Regulatory cell therapy allows for lower doses of immunosuppressive drugs and leads to less infections

How can we put Treg therapy in the fast lane?

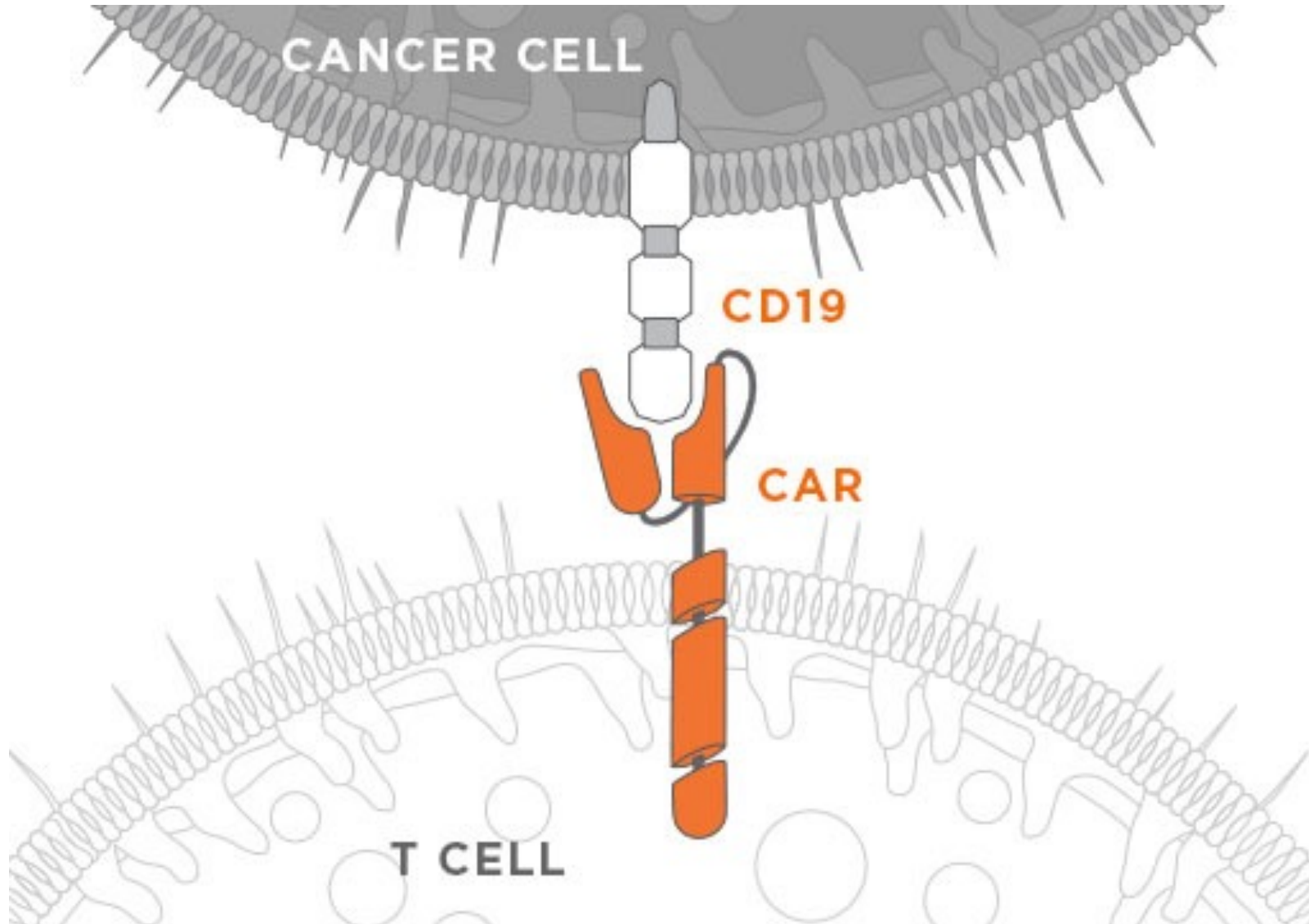
A



B

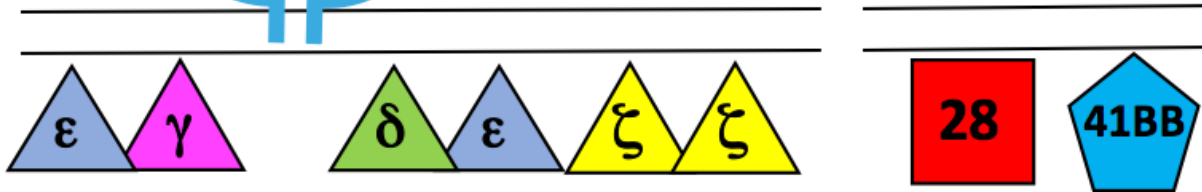


Chimeric antigen receptor (CAR)





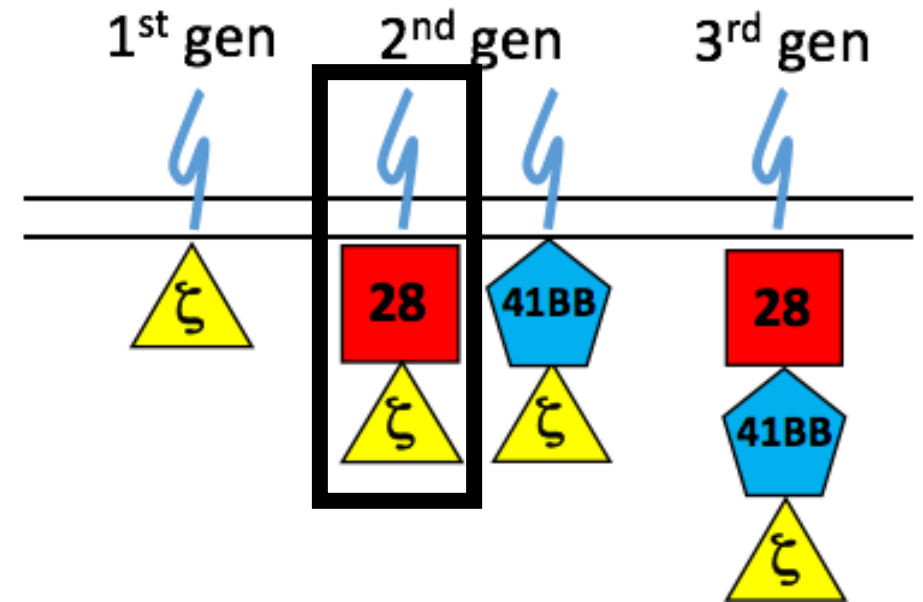
TCR



TCR/CD3
complex

Co-stimulatory
receptors

CAR

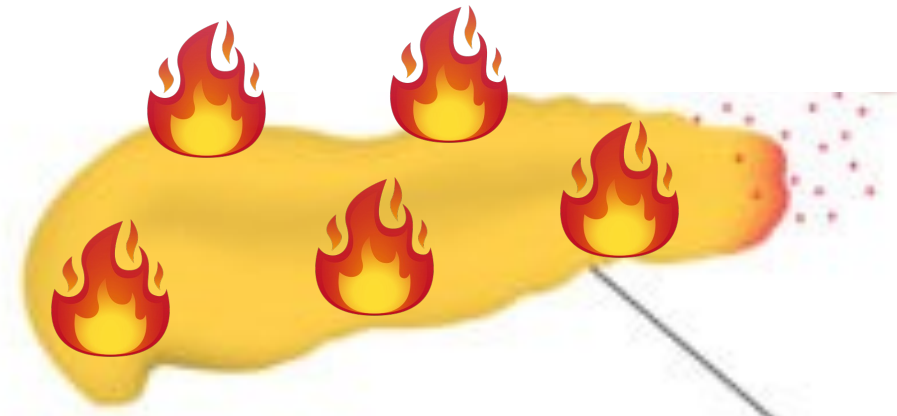


1st gen

2nd gen

3rd gen

Type 1 diabetes



Autoreactive T cells destroy the pancreas

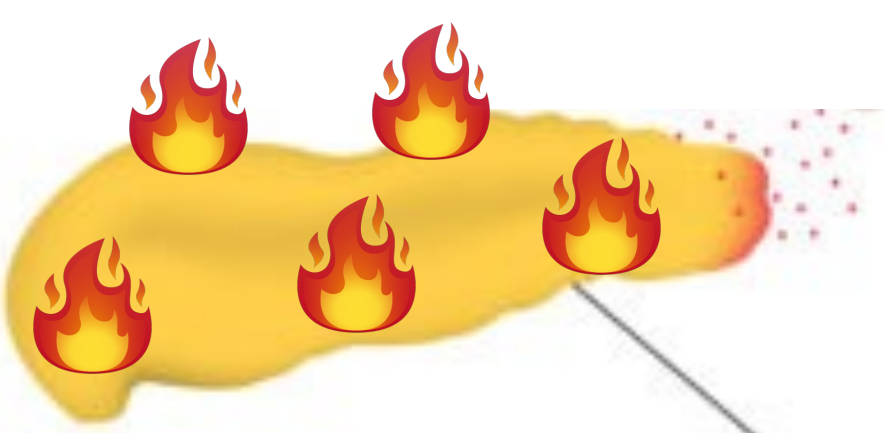
Pancreas cannot produce insulin



More glucose in the blood



Treating type 1 diabetes using CAR Tregs



Pancreas cannot produce insulin



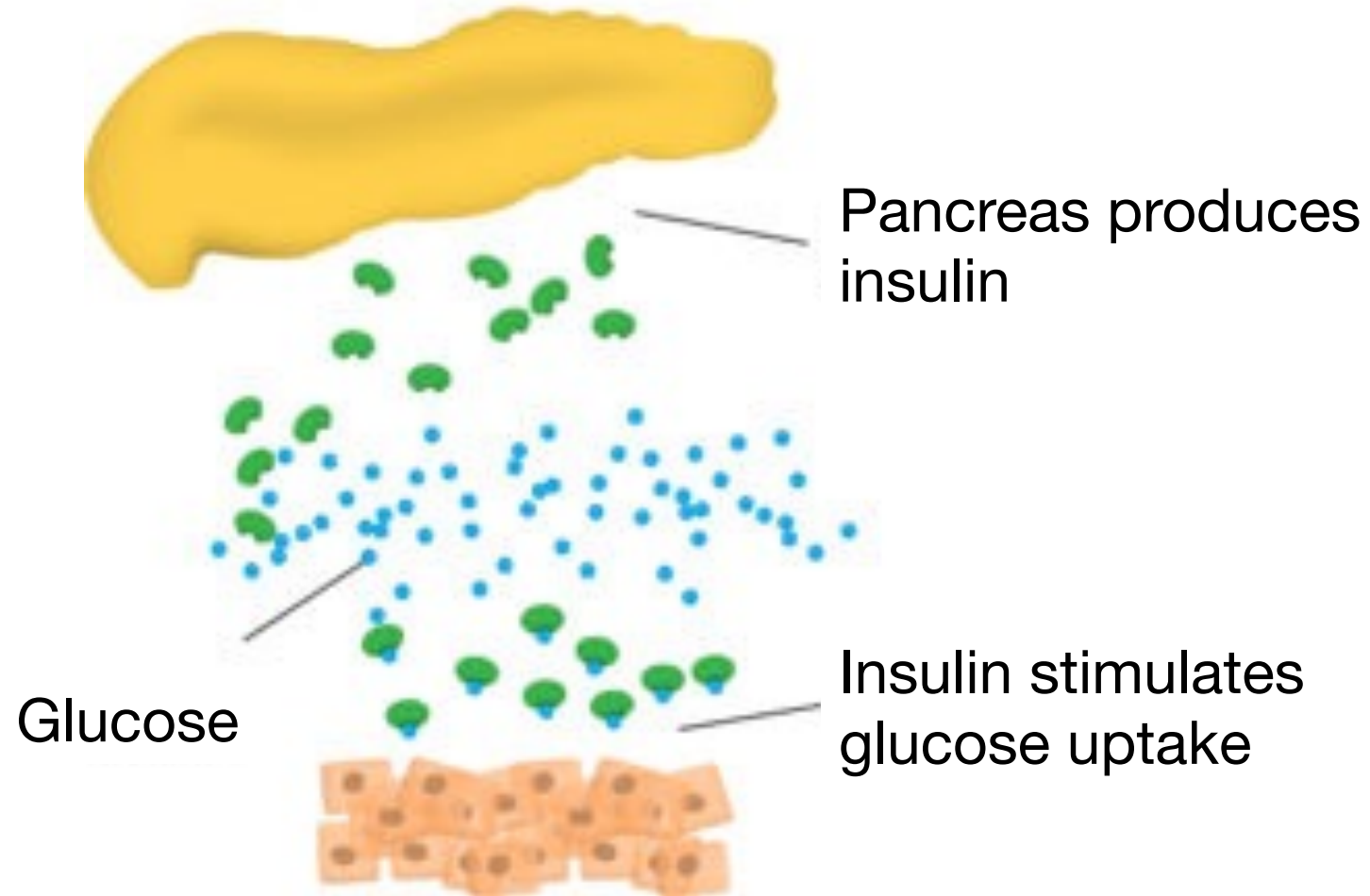
CAR Tregs suppress autoreactive T cells



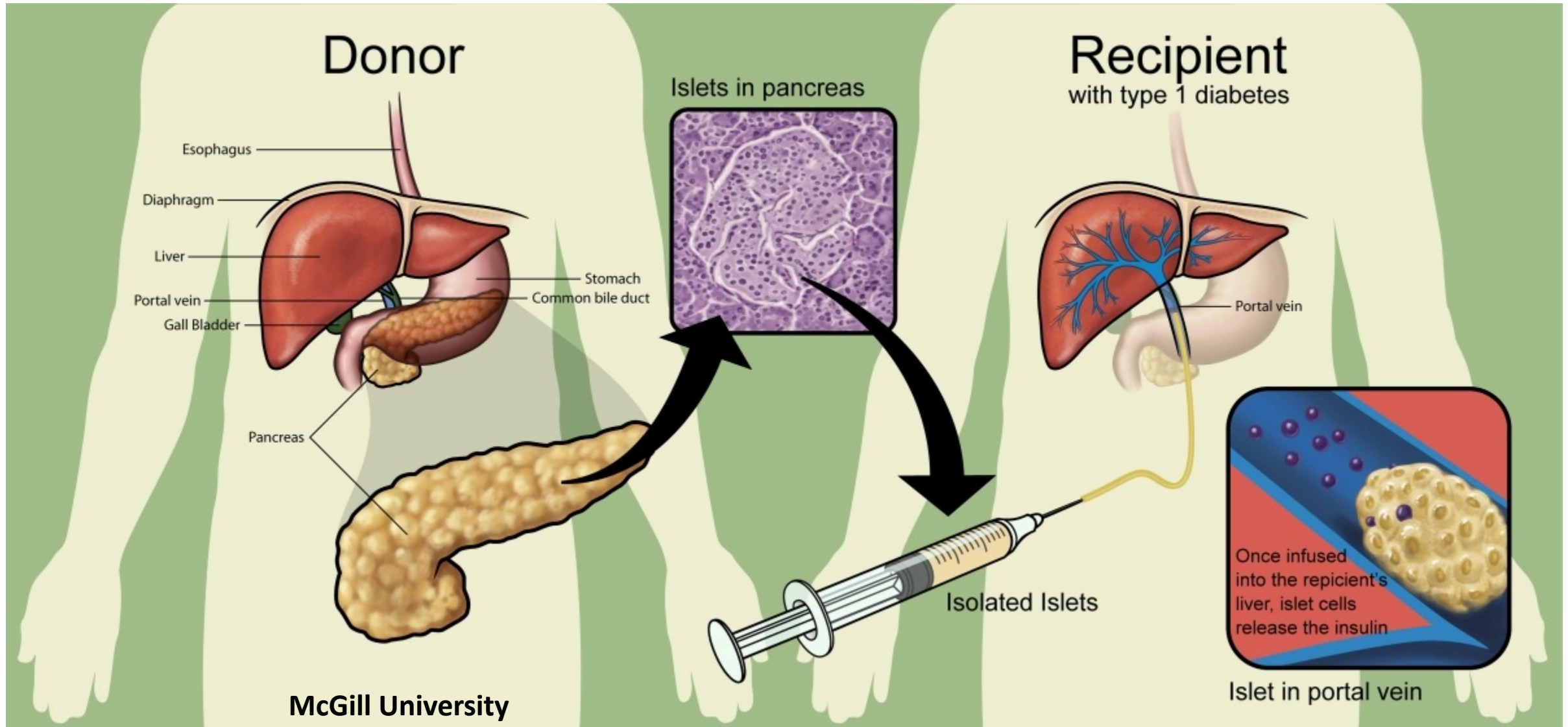
More glucose in the blood



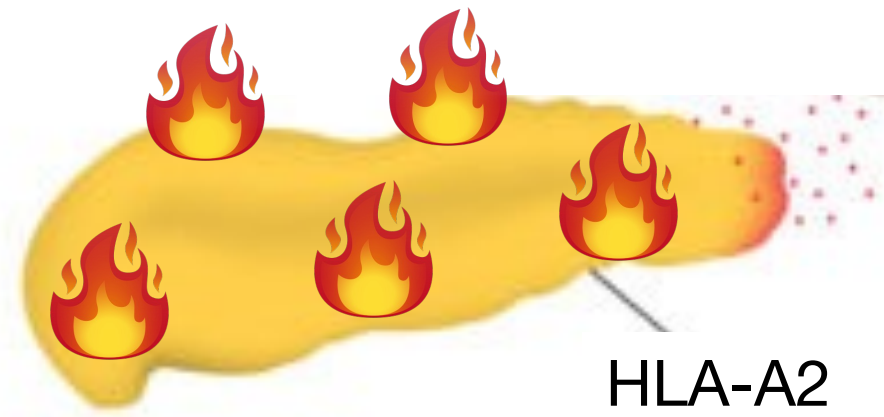
Treating type 1 diabetes using CAR Tregs



Islet transplant as a treatment for T1D



Anti-HLA-A2 CAR Tregs for HLA-A2⁺ islets transplants to treat T1D



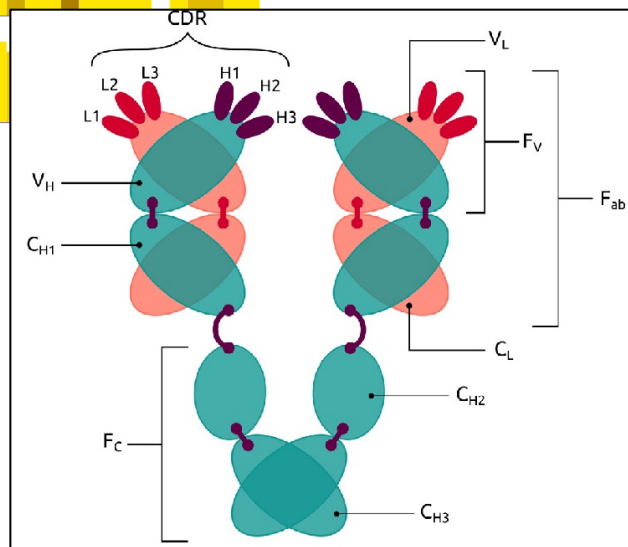
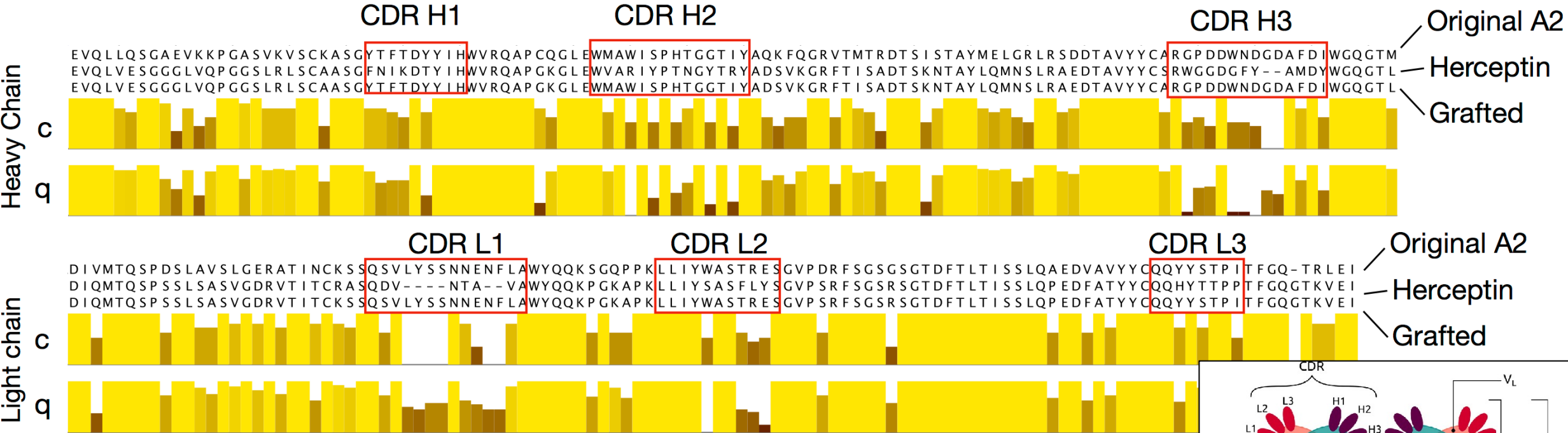
Alloreactive & autoreactive T cells destroy the islets

The icon depicts a cluster of various colored T cells (grey, purple, blue, red) with a large black circle and a diagonal slash over them, indicating inhibition or destruction.



A2-CAR Tregs suppress aggressive T cells

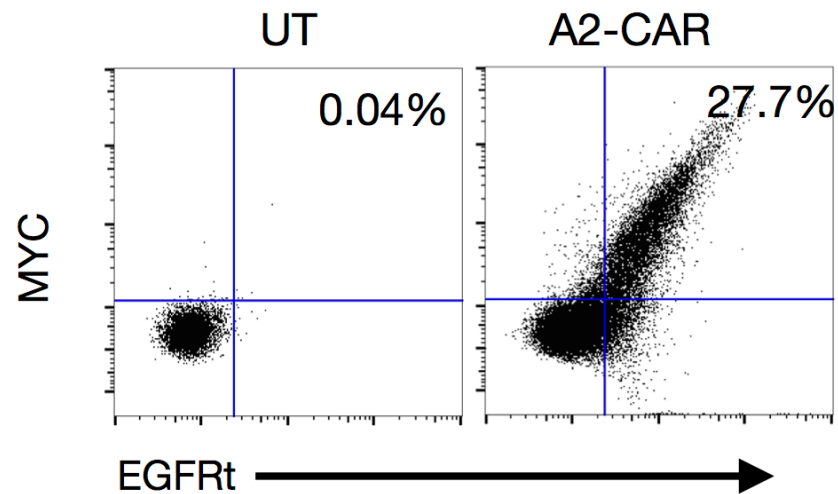
Grafting A2-CAR scFv specificity



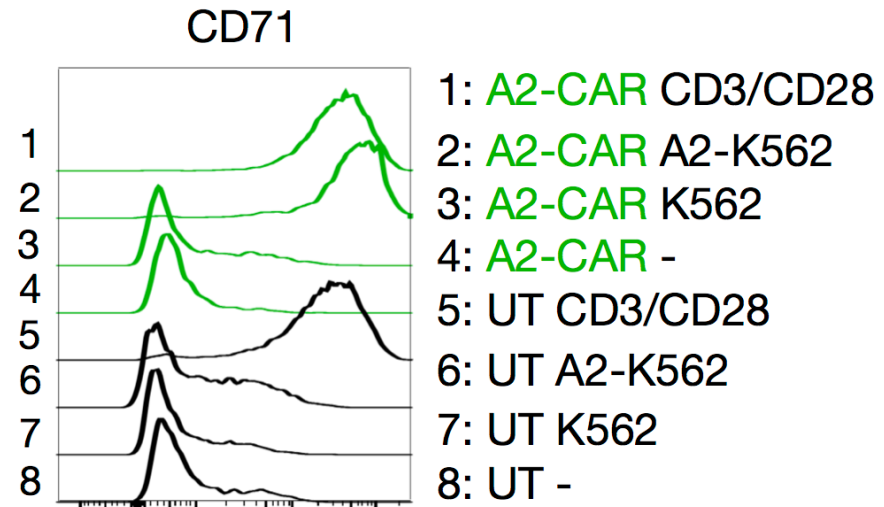
A2-CAR Tregs recognize HLA-A2



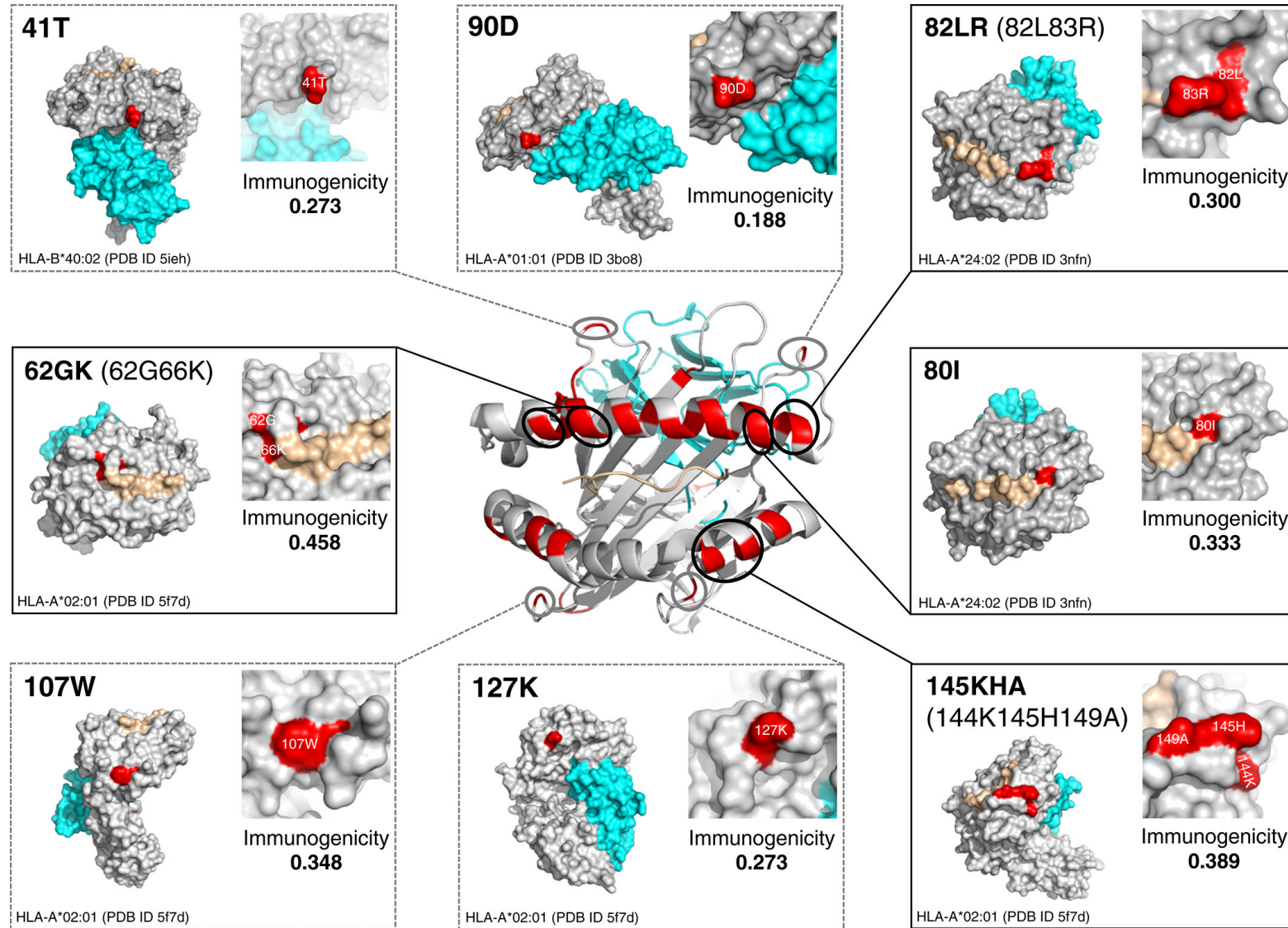
CAR expression



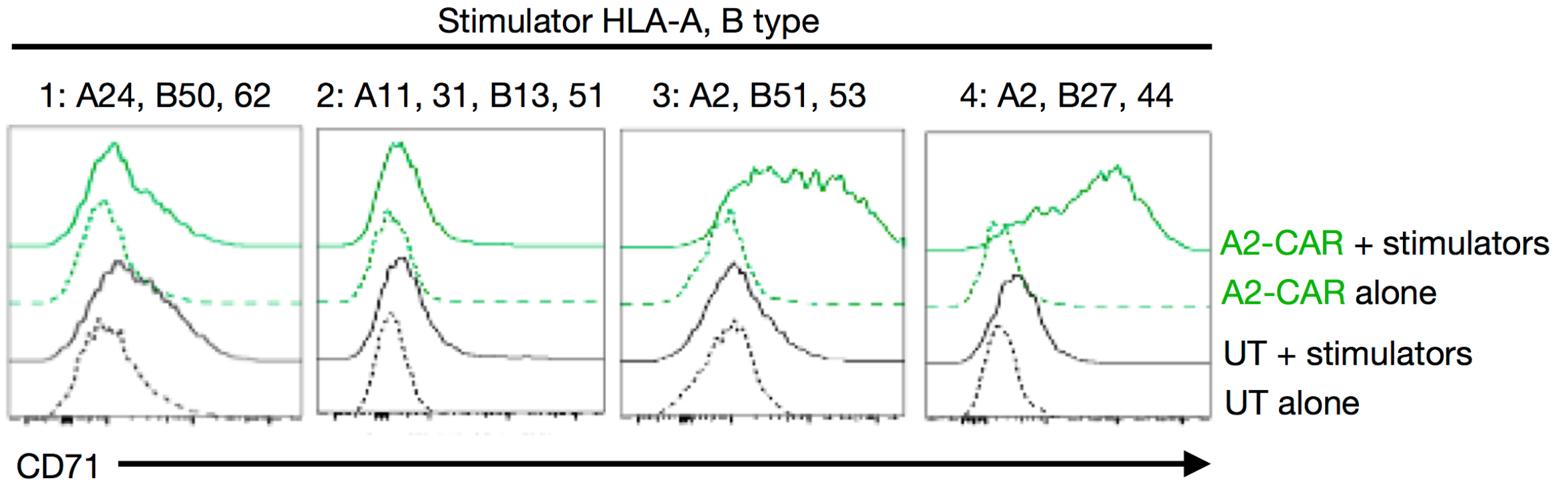
Treg activation



Immunogenic eplets in HLA-A2



A2-CAR Tregs recognize the 144TKH eplet, not 44RME, 105S or 127K



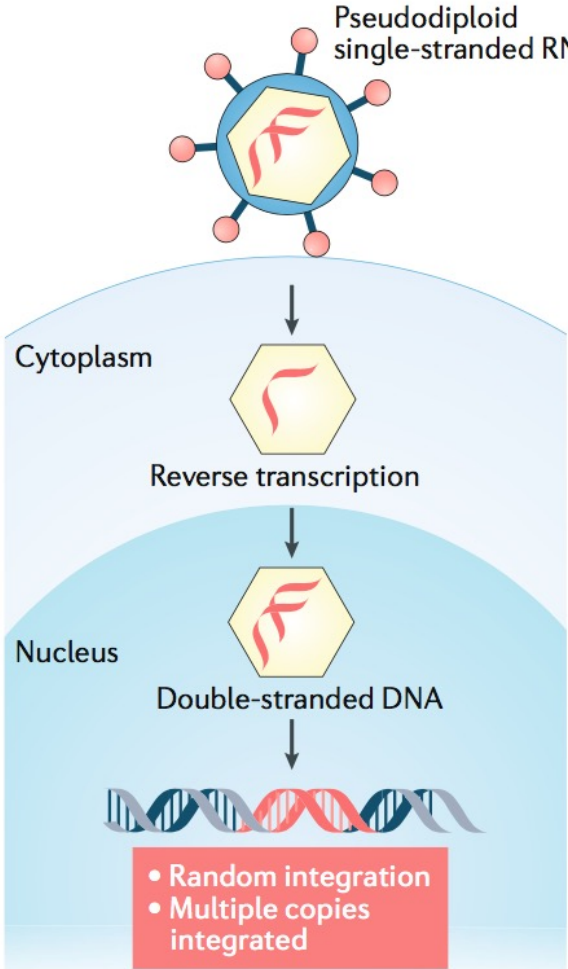
44RME: A11, A24, A31
105S: A24, A31
127K: A24

A2-CAR Tregs co-incubated with allogeneic human islets

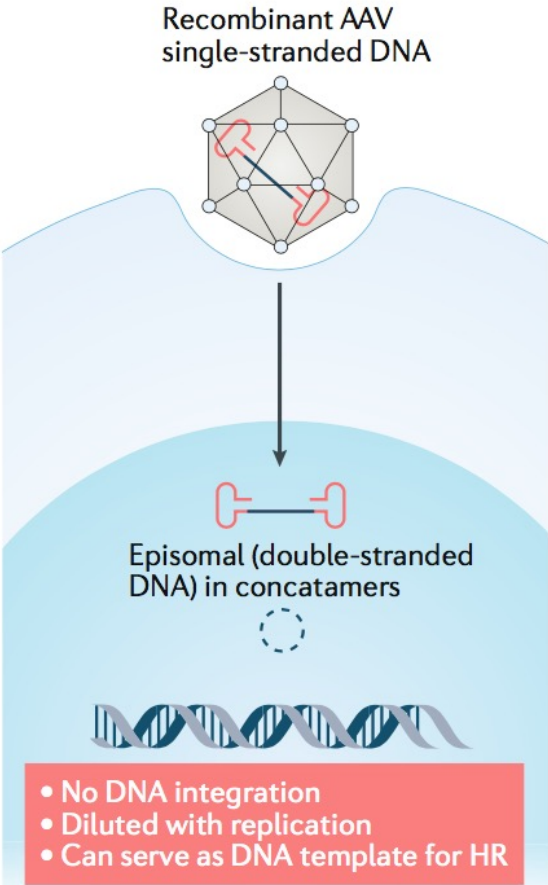
How to best genetically modify human Tregs?

a FDA approved (costly and time-consuming to produce)

Retroviruses or lentiviruses

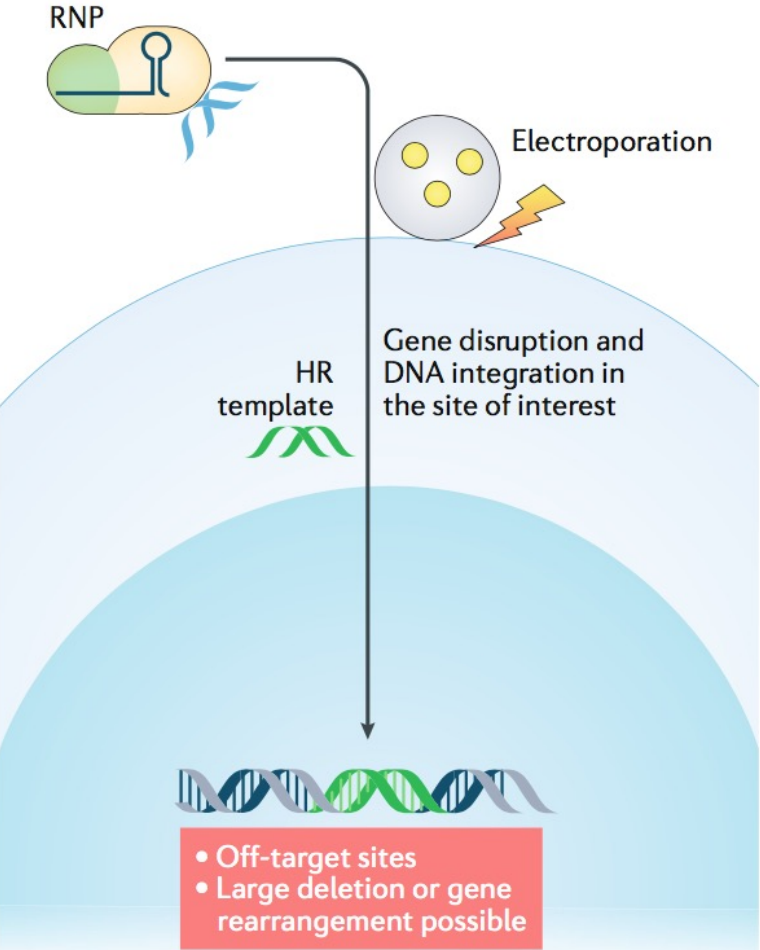


Adeno-associated viruses

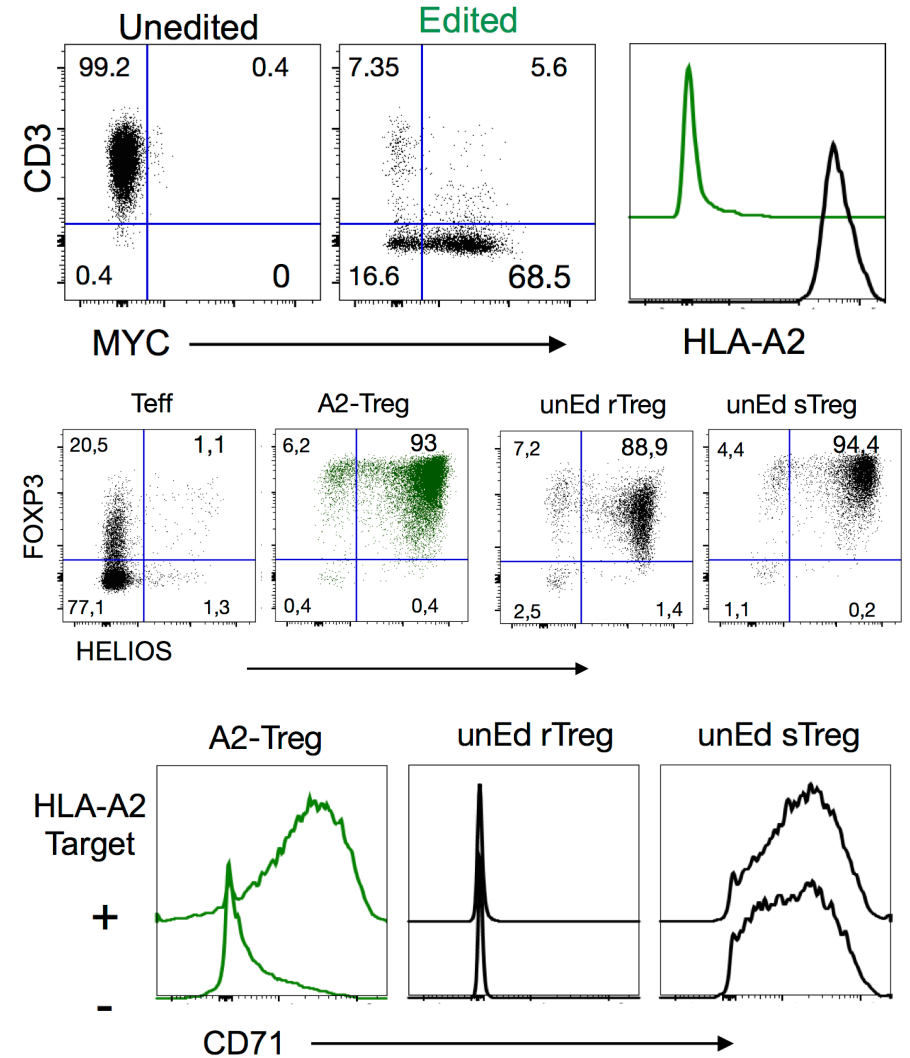
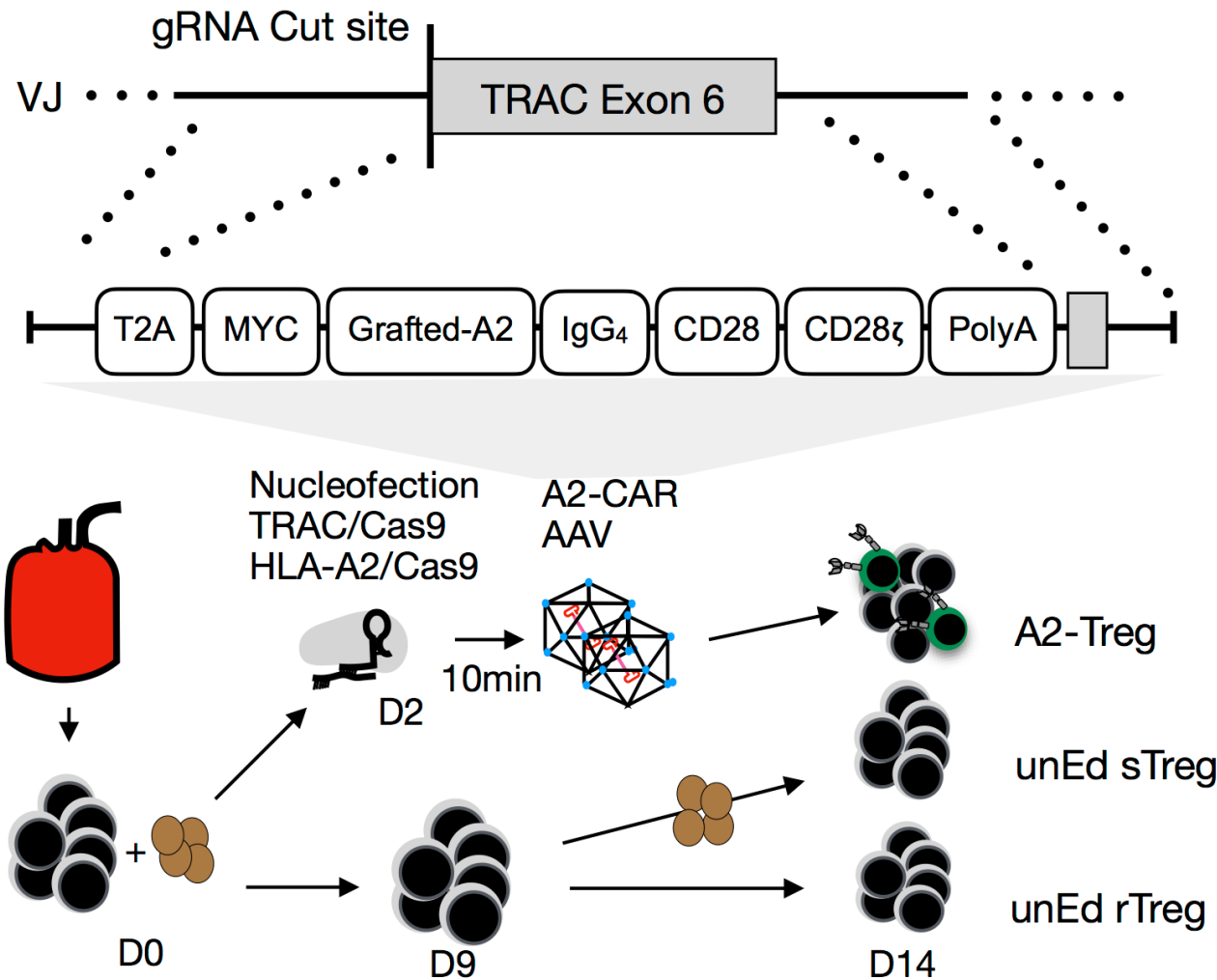


b Not yet FDA approved (faster and cheaper to produce)

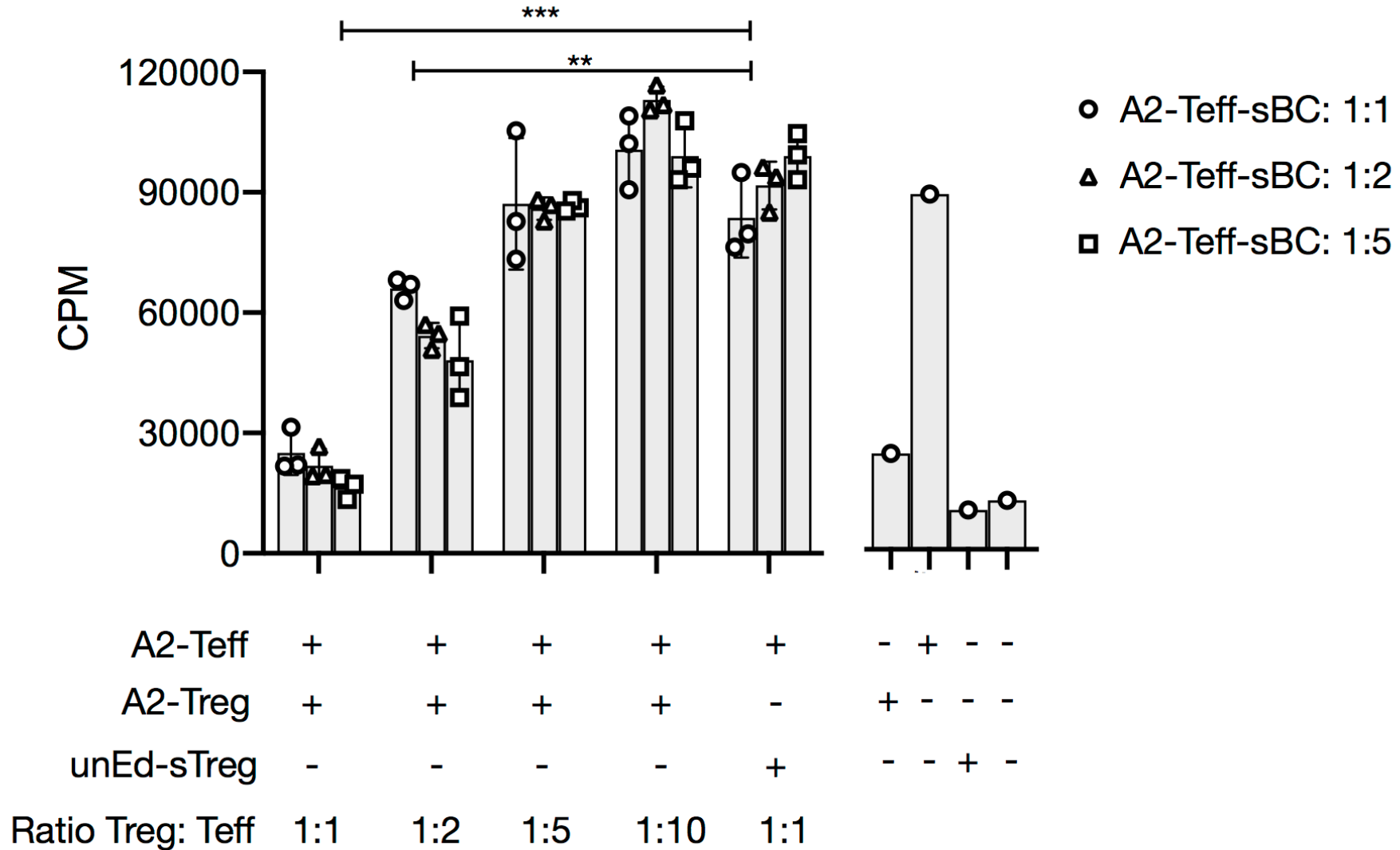
Non-viral approaches



Reprogramming Treg specificity



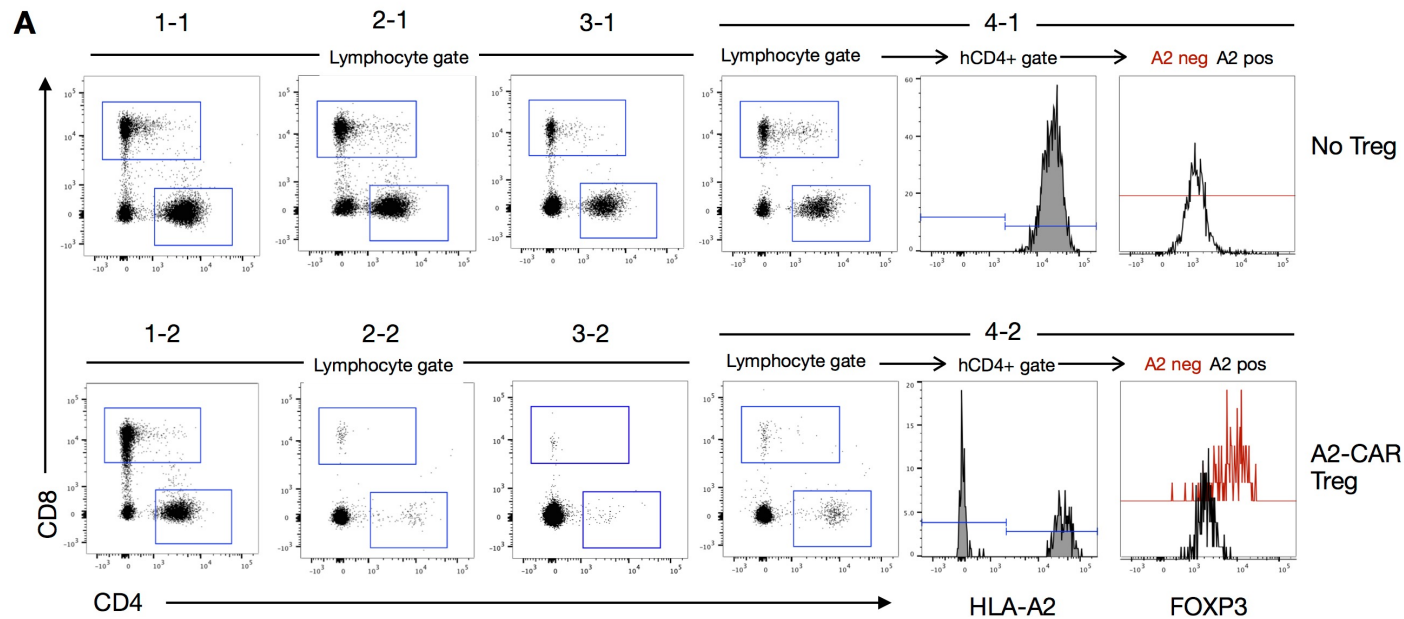
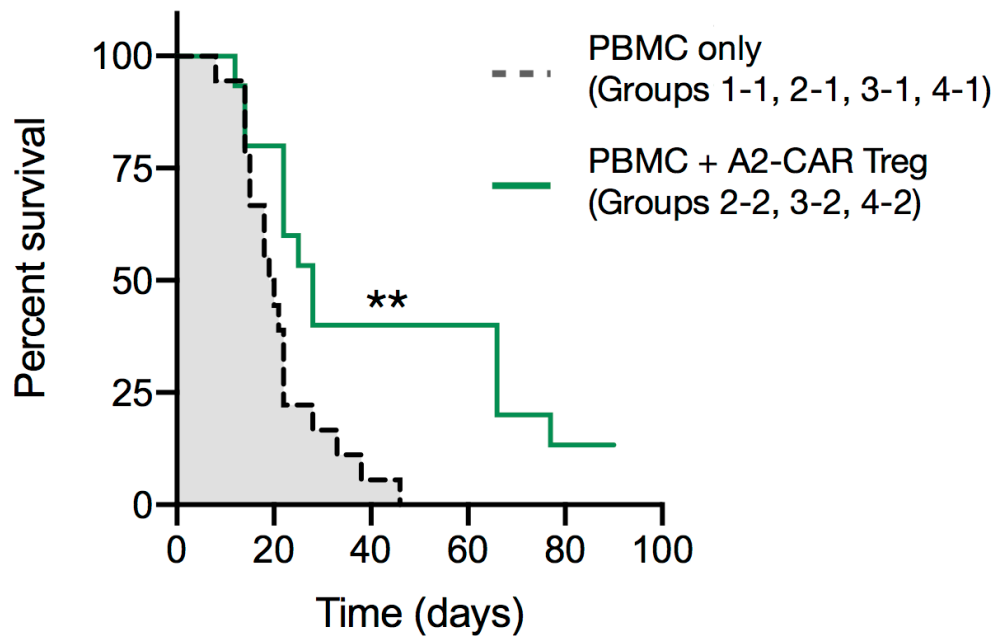
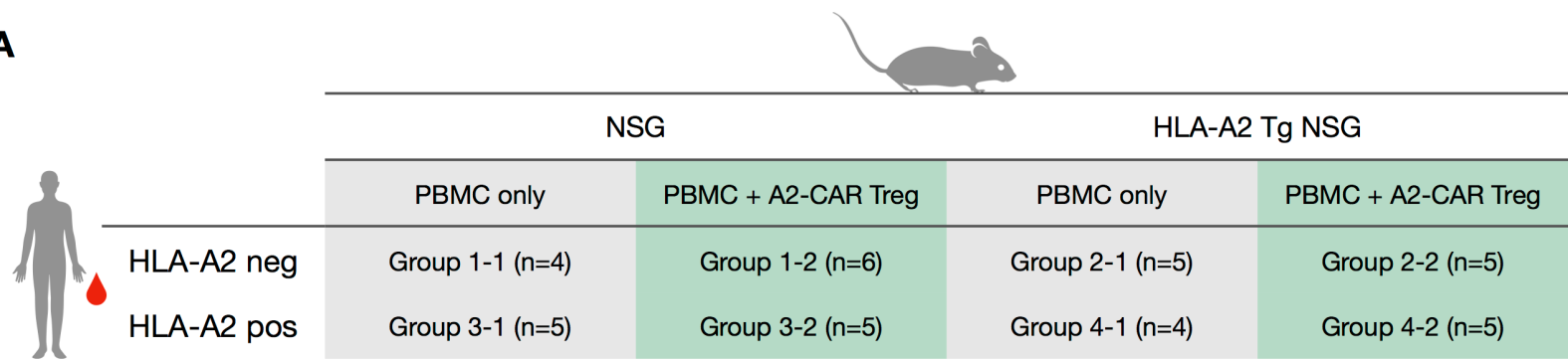
A2-CAR Tregs suppress Teff cell proliferation





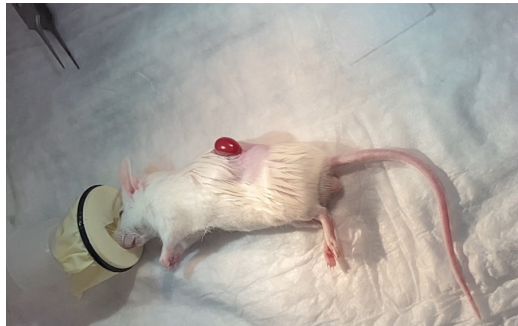
A2-CAR Tregs prevent graft-vs-host disease

A

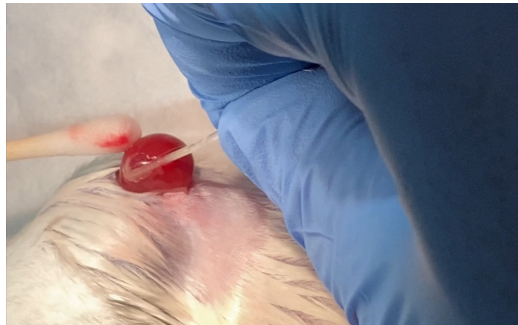


A2-CAR Tregs traffic to A2⁺ human islet grafts

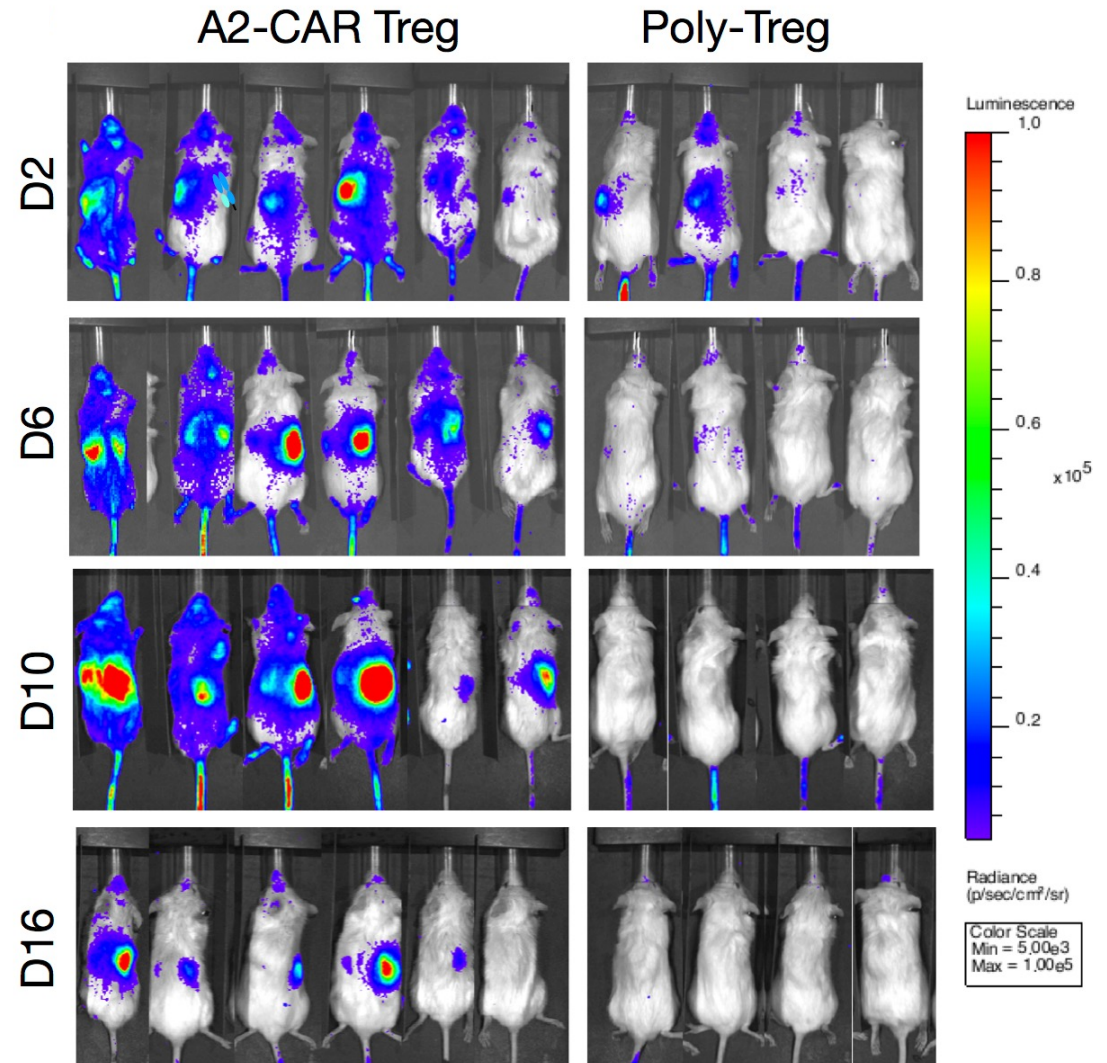
Kidney capsule exposure



Human A2⁺ islet transplant

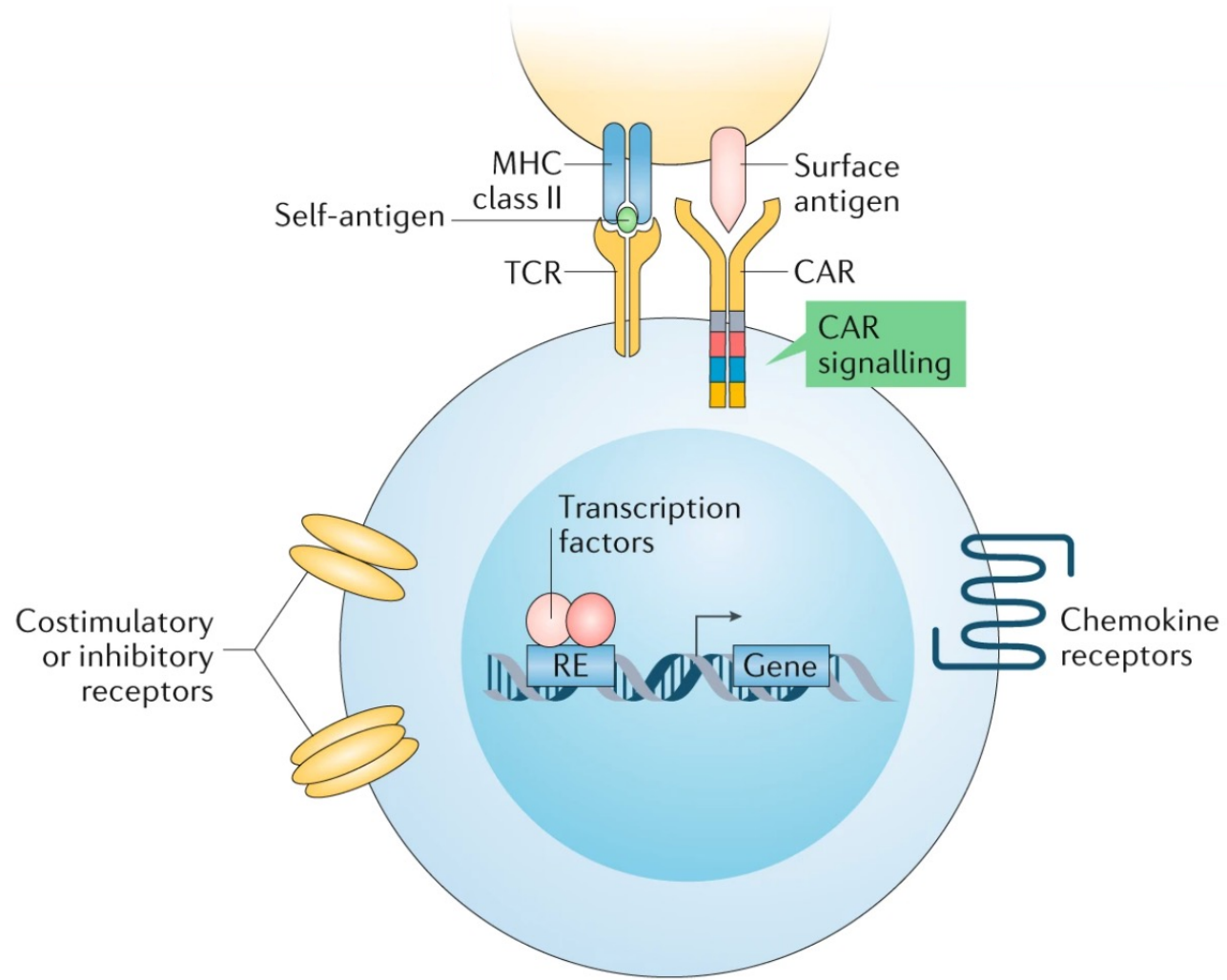


Luciferase⁺ A2-CAR Treg i.v. injection



Outstanding questions and future directions

- Does CAR Treg survival and/or function suffer with TCR ablation?
- What unique challenges do CAR Tregs face in pancreatic islets? Inflammation? Insulin? IL-2 deprivation?
- Can CAR Tregs prevent T1D in humans? Reverse it?
- What are the best targets and CAR designs for T1D CAR Tregs?
- What is the best source for T1D CAR Tregs?



Designer immunology



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