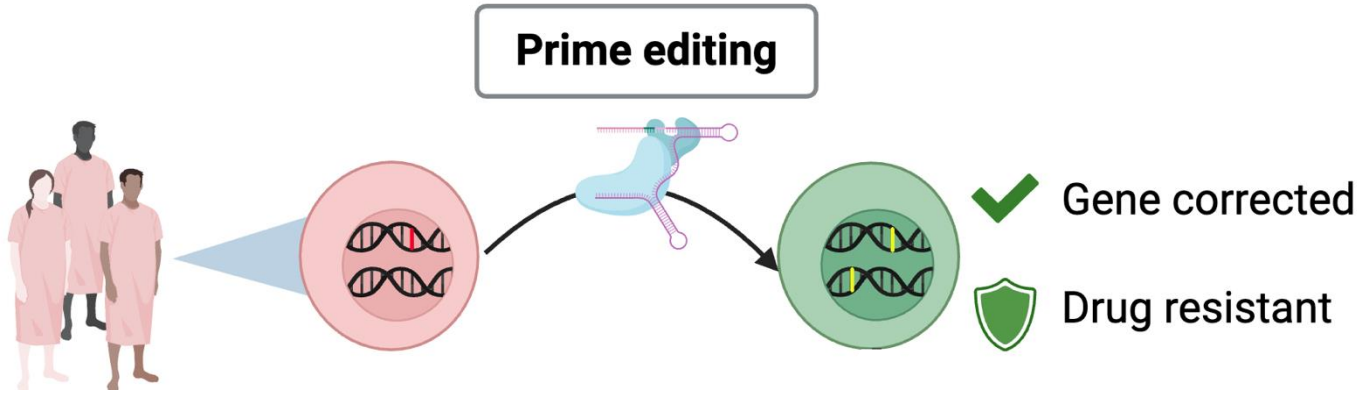
Multiplex prime editing enables safe, drug-controllable and immunosuppression-resistant T-cell therapies



Bandala-Sanchez E, Petley EV , Ramsay K, Hilton A, White C, Bediaga NG, Li Wai Suen CS, Naik SH, Davey AS, Call ME, Call MJ , van der Weyden C , Fox L, Ritchie D, Sutrave G, Micklethwaite K, Gottlieb D, Chan S , Roberts AW, Slade C**, Lew TE *, Horton MB***

ANZTCT ASM 2026

WEHI brighter together

Peter Mac Peter MacCallum Cancer Centre Victoria Australia

The Royal Melbourne Hospital

WESTMEAD HOSPITAL

Current immunosuppression is a blunt tool with major toxicity

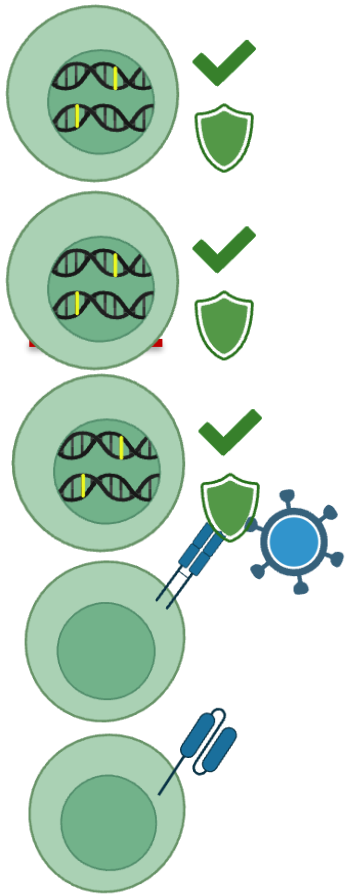
Suppress undesirable T cells

Inborn errors of immunity
with dysregulation (e.g. HLH)

Autoreactive T cells
(e.g. autoim

Alloreactive
(e.g. transpl

What if you could **correct** and **select?**



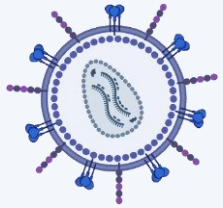
Gene corrected cells

Anti-infective cells

CAR-T cells

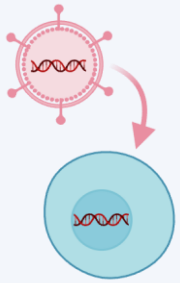
Safe, versatile T cell engineering

Lentivirus



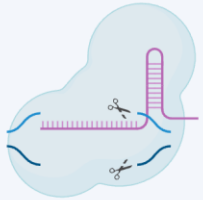
Viral integration

Insertional oncogenesis



Hacein-Bey-abina *Science* 2003
Eichler *NEJM* 2024

CRISPR/Cas9

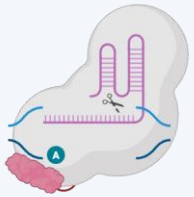


Homology directed repair

Error prone
Double stranded breaks
Chromosomal deletions

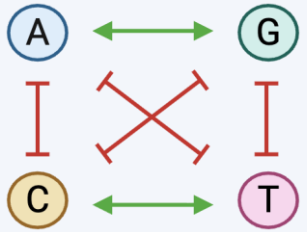
Wen *Genome Biol* 2021
Park *Sci Adv* 2022

Base editing



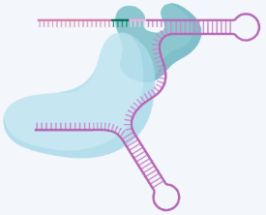
Deaminase

No double stranded breaks
Transition mutations only



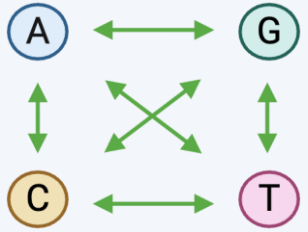
Komor *Nature* 2016
Gaudelli *Nature* 2017

Prime editing



Reverse transcriptase

No double stranded breaks
All mutations possible



Anzalone *Nature* 2019

The challenge of immune dysregulation syndromes

Subcutaneous panniculitis-like T cell lymphoma

HAVCR2

CD40L deficiency

CD40L

T cell gene therapy
Monogenic & severe
Exclusively T cell driven
Major role for immunosuppression
Curable by alloSCT

CTLA-4 haploinsufficiency

CTLA4

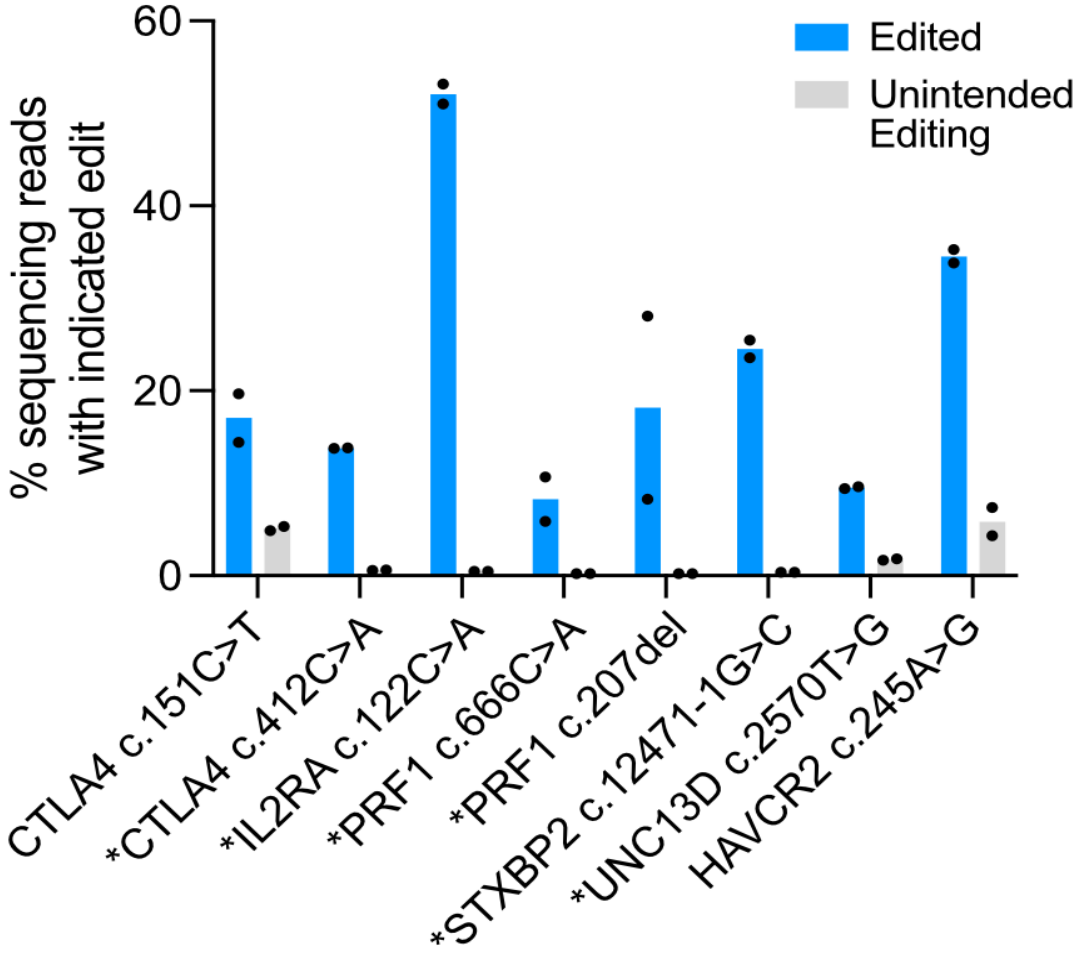
Familial HLH

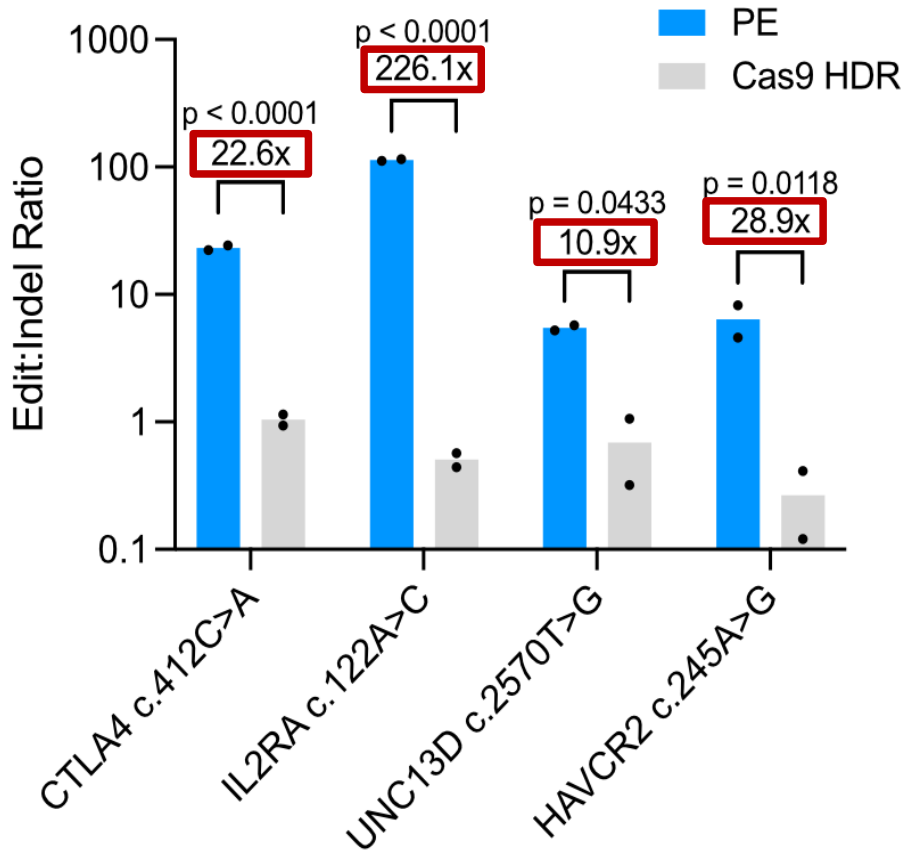
PRF1
STXBP2
UNC13D

CD25 deficiency

IL2RA

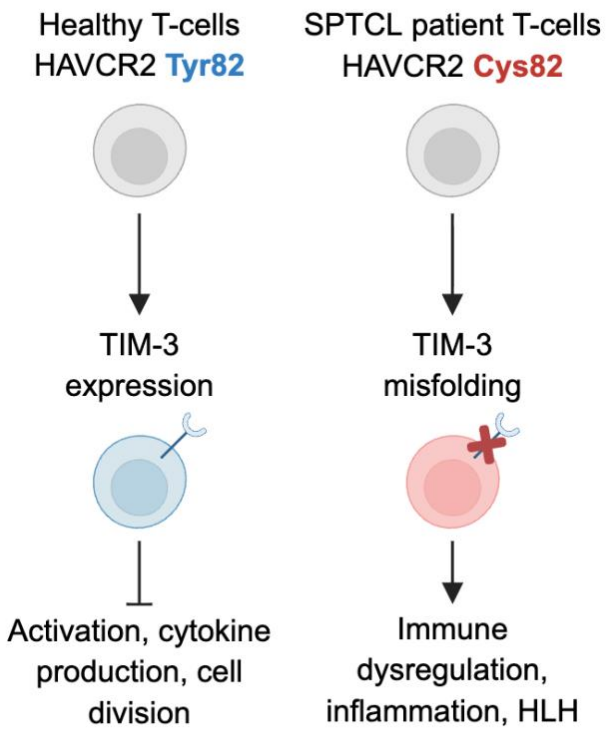
The challenge of immune dysregulation syndromes

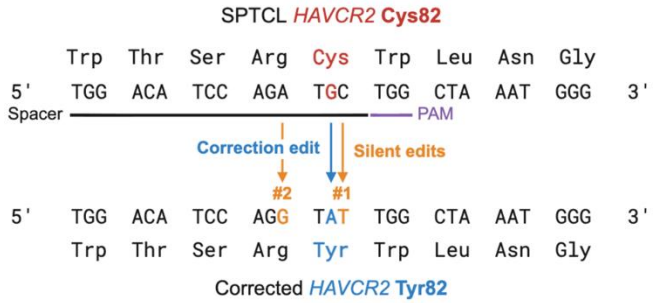


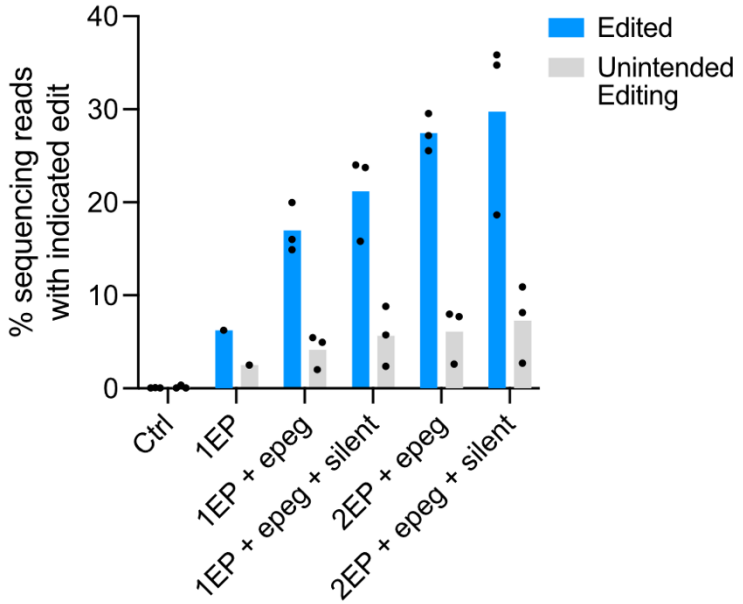


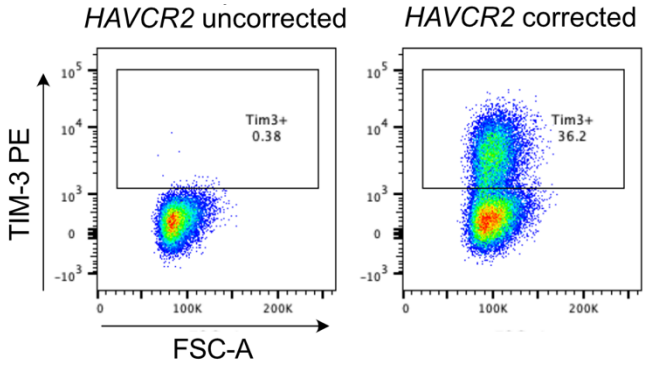
Anzalone *Nature* 2019

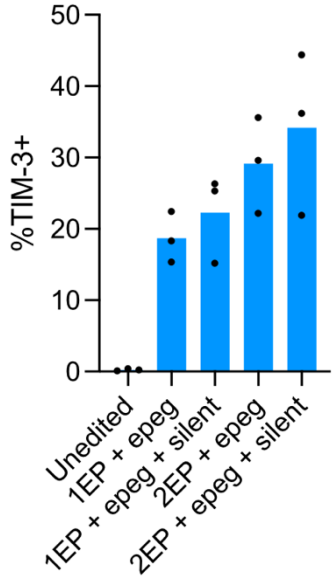
Efficient correction of patient T cells







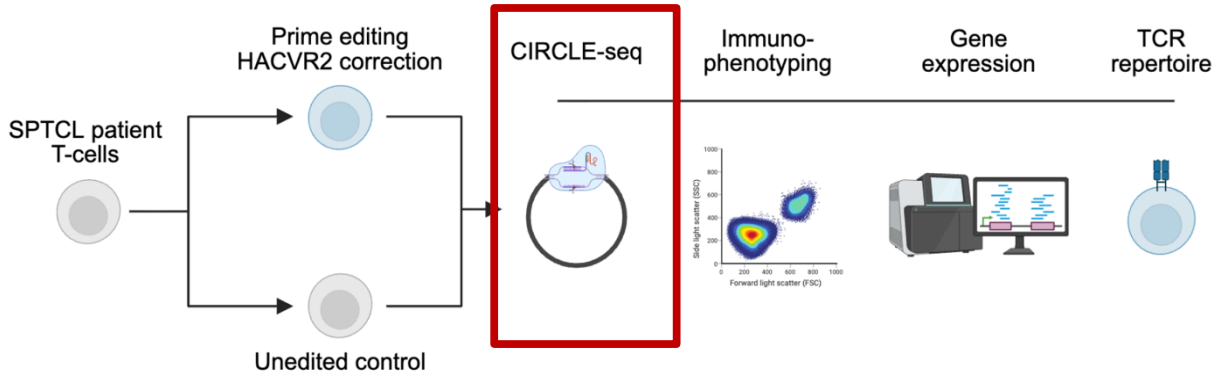


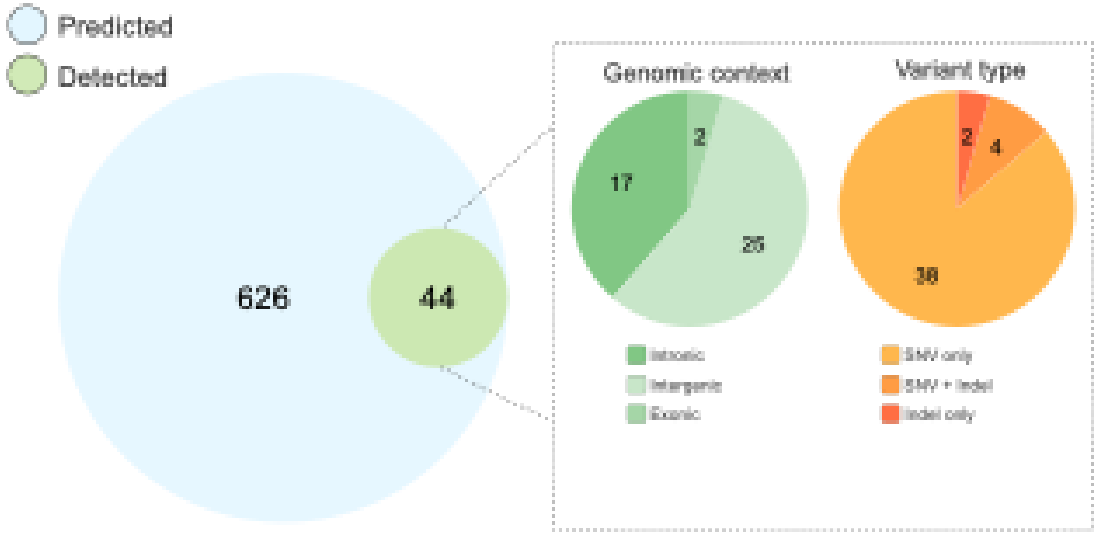


Gayden *Nat Genetics* 2018
Watson, Lew *Leuk Lymp* 2022

ANZTCT ASM 2026

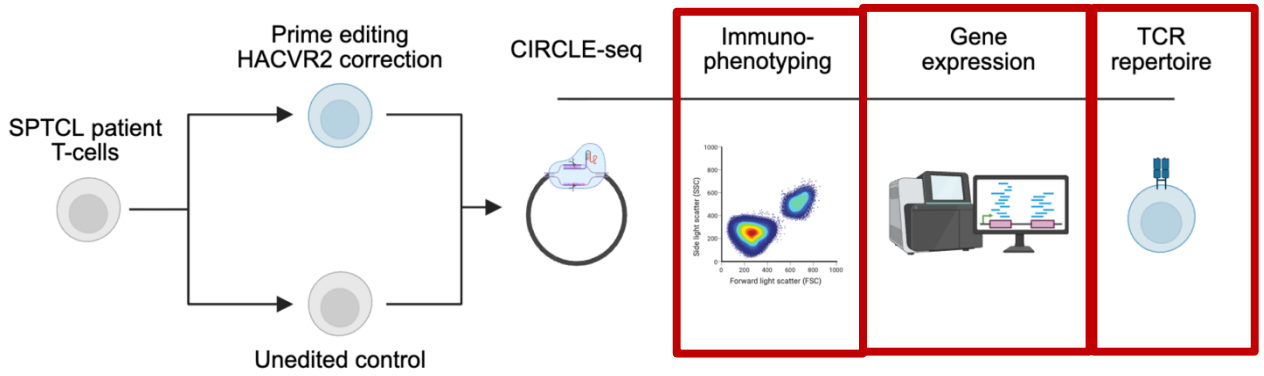
Prime editing of primary patient T cells is highly precise & safe

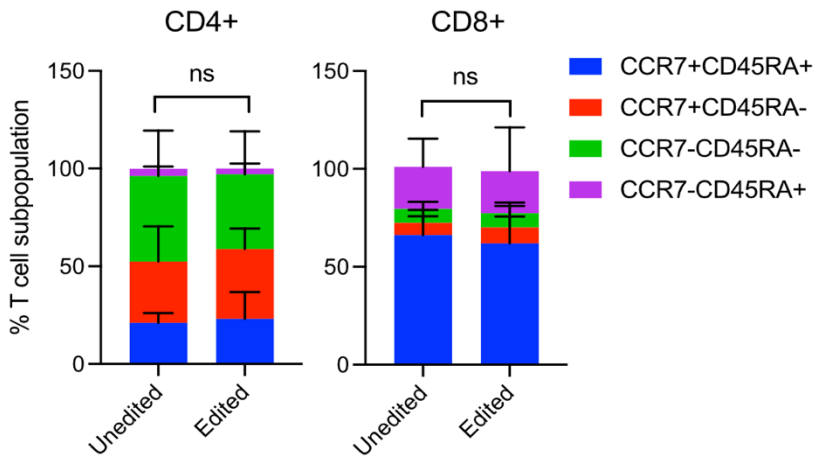


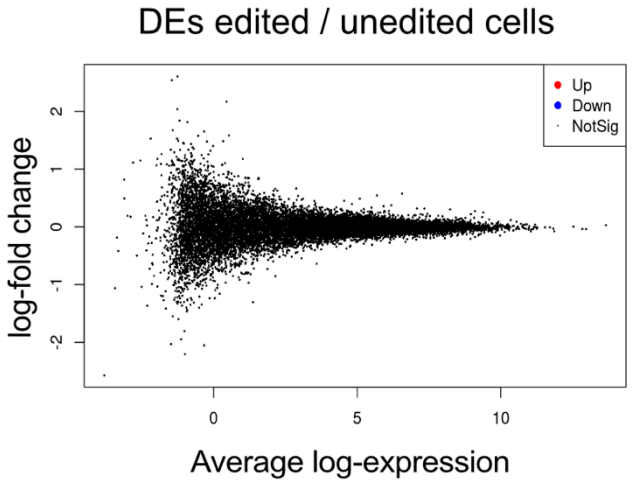


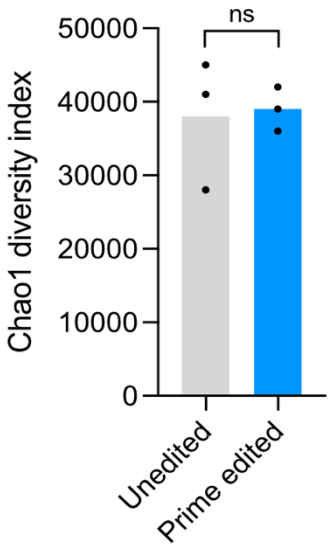
5/44 detected variants were statistically significant compared to unedited cells
0/5 variants reproduced across donors
0/5 variants in exons or oncogenes

Prime editing of primary patient T cells is highly precise & safe







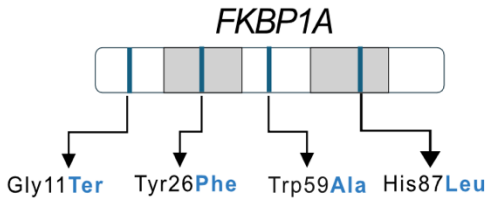


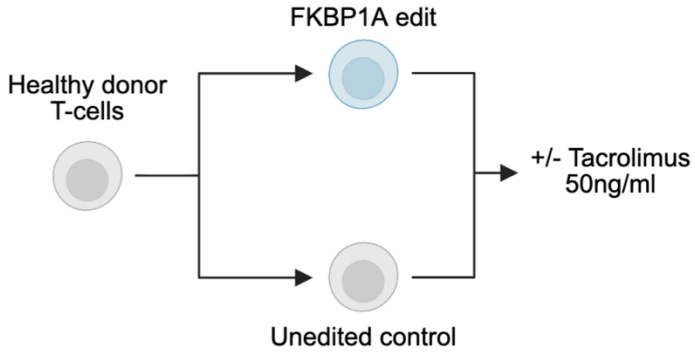
ANZTCT
ASM 2026

Prime editing can safely correct pathogenic variants in primary human T cells

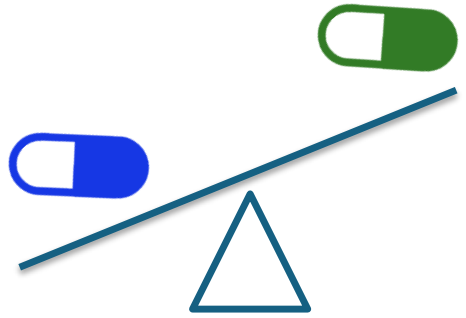
Prime editing to induce TAC resistance

TAC





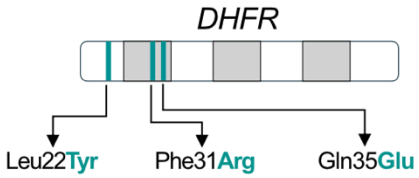
No cross resistance
Select with one
Suppress with another

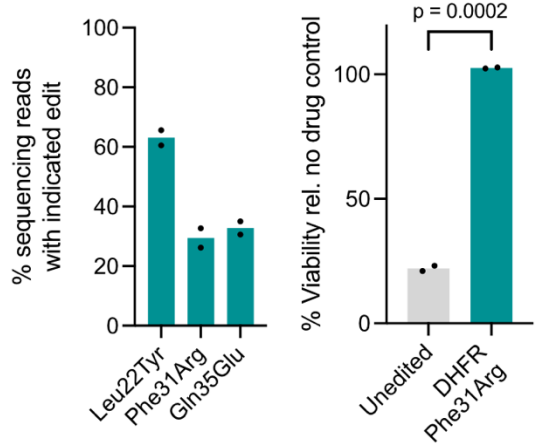


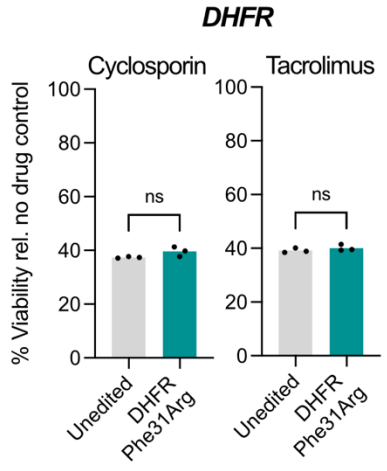
Siekierka *Nature* 1989
Futer *J Biol Chem* 1995

Multiple immunosuppressants are amenable

MTX

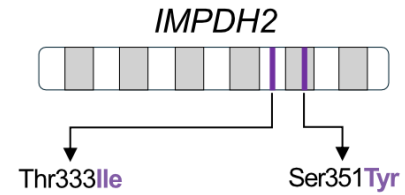


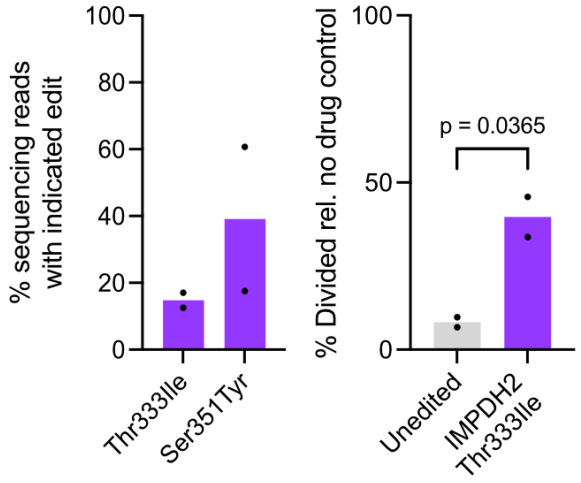


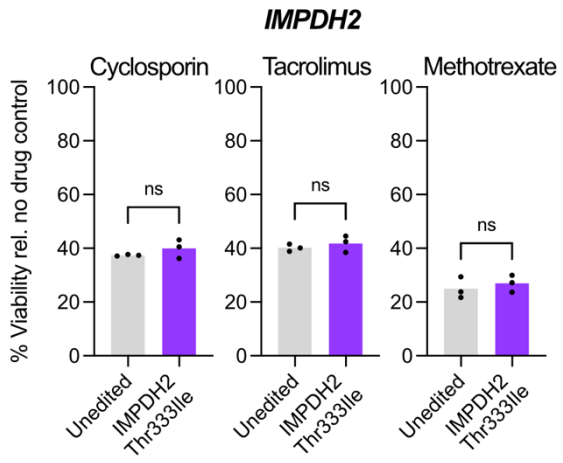


No cross resistance
Select with one
Suppress with another

MMF

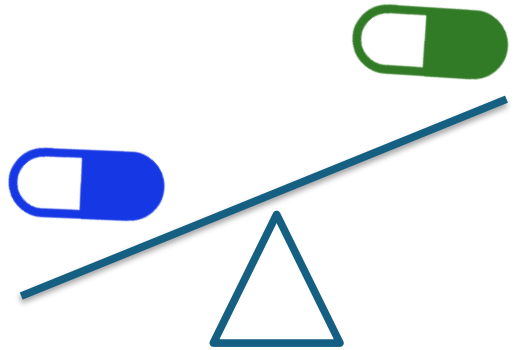




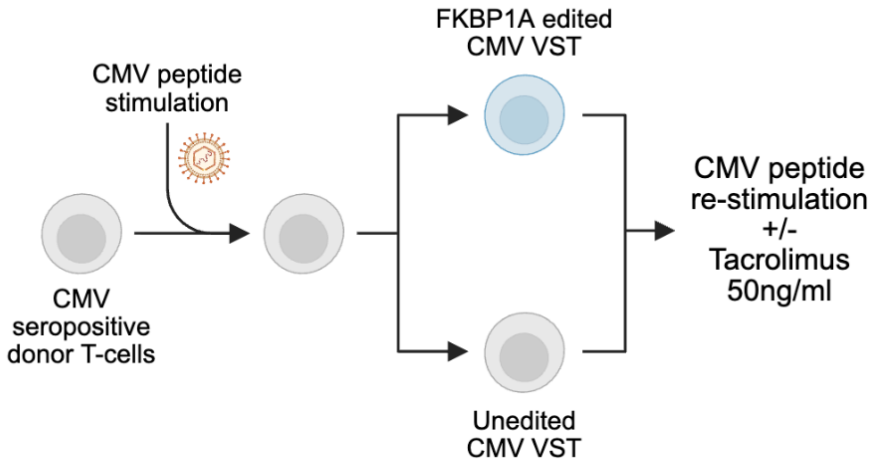


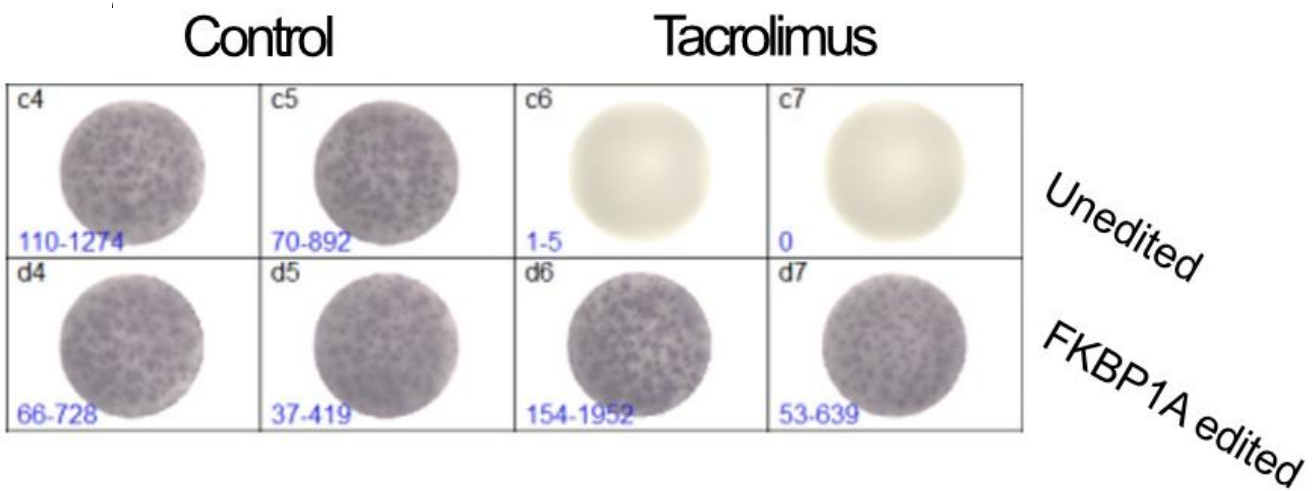
Volpato *J Mol Biol* 2007
Jonnalagadda *PLoS One* 2013

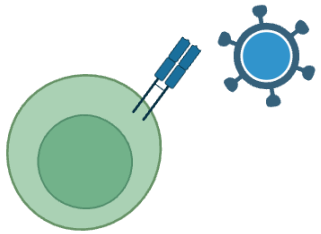
In vivo drug control of T cell gene therapy



Drug controllable cell therapies with prime editing



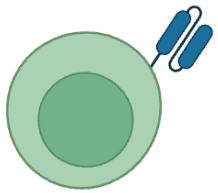




Anti-infective cells

Application
Preserved immunity in organ transplants

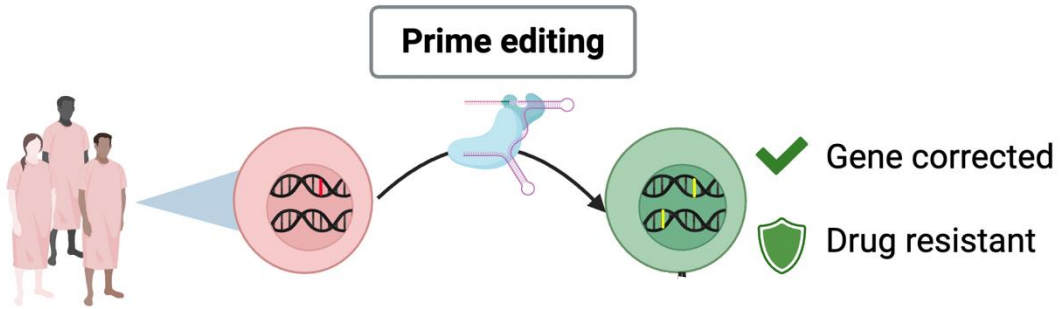
Drug controllable cell therapies with prime editing



CAR-T cells

Application
CAR-T for immunosuppressed patients (PTLD)
Prevent rejection of alloCAR-T

Prime editing enables drug-controllable T cell therapies



What next?

Acknowledgements

Lab members
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Collaborators
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David Gottleib
Samantha Chan
Theresa Cole

WEHI consumers
Maddie Riedwolt's vision
Our patients & their families

NHMRC
MRFF
Watt Mirisklavos
Foundation
Jack Brockhoff Foundation
Ramacciotti Foundation