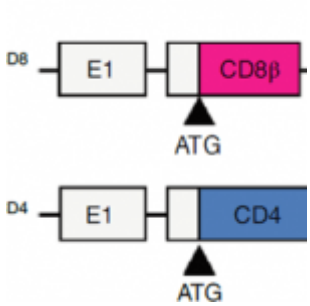
T cell lineage fate is driven by CD4 and CD8 co-receptor gene loci



The thymus is the site responsible for the development of mature and functional T-cells. During selection in the thymus , the specificity and function of T-cells are taken to be linked since MHC-II-specific TCR signals generate CD4 helper T cells and MHC-I-specific TCR signals generate CD8 cytotoxic T cells. The exact molecular basis of this linkage, however, continues to be a matter of contention and this is where Shinzawa and colleagues step in, to identify whether the fate of thymocyte lineage is determined by coreceptor gene loci that regulate TCR signal duration, or by coreceptor proteins, which determine TCR signal strength.

The authors proceeded to assess this in FlipFlop mice that they developed, as highlighted in Figure 1 below. These mice had Cd4 and Cd8 genes encode opposite coreceptor proteins of what is present in wild-type (WT) mice.

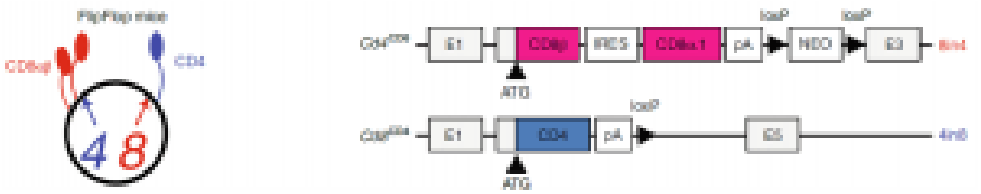


Figure 1: "Schematic of altered Cd4 and Cd8α gene loci in FlipFlop mice. *Cd8a gene loci in FlipFlop mice were altered to encode CD4*

> *proteins (Cd8CD4)25, and Cd4 gene loci were altered to encode CD8αβ.1 proteins (Cd4CD8), which are distinct from CD8αβ.2 proteins in WT B6 mice. Left, surface proteins encoded by altered Cd4CD8 (4) and Cd8CD4 (8) gene loci in FlipFlop DP thymocytes. Right, schematic of the altered Cd4CD8 and Cd8CD4 gene loci in FlipFlop mice: E, exons; IRES, internal ribosome entry site; pA, polyadenylation signals; NEO, neomycin-resistance cassette. The altered Cd4CD8 gene locus was obtained from 8in4 mice, which were constructed for this study"(Shinzawa, et al., 2022).*

Swapping the coreceptor proteins that Cd4 and Cd8 gene loci functionally encode reversed the lineage fate of CD4- and CD8-expressing T cells such that the immune system of the FlipFlop mice now consisted of CD4 cytotoxic-lineage T cells and CD8 helper-lineage T cells. From this the authors concluded that; "regardless of which coreceptor proteins they encode, Cd4 gene loci regulate expression of helper-lineage genes and Cd8 gene loci regulate expression of cytotoxic-lineage genes".

The authors demonstrated that the fate of T-cell lineage is indeed driven by Cd4 and Cd8 coreceptor gene loci, which govern the kinetics and duration of TCR signalling during positive selection in the thymus. In the authors words, "this would invalidate coreceptor signal-strength as the basis of T lineage determination." This came as a result of the fact that Cd4-encoded coreceptors promoted long-duration TCR signalling to induce helper-lineage fate and Cd8-encoded coreceptors promoted a short-duration TCR signalling, thereby inducing cytotoxic-lineage fate.

Lastly, a reversal of T-cells function in these mice did fail to promote the generation of protective immunity, which shows that *in vivo* protective immunity strictly requires that Cd4

genes encode an MHC-II-specific coreceptor protein and Cd8 genes encode an MHC-I-specific coreceptor protein. The authors stated that; “This explains why evolution fixed the particular coreceptor proteins that Cd4 and Cd8 gene loci encode in all surviving species”.

Journal article: Shinzawa, M., et al., 2022. Reversal of the T cell immune system reveals the molecular basis for T cell lineage fate determination in the thymus. *Nature Immunology.*

Summary by Vanessa Muwanga