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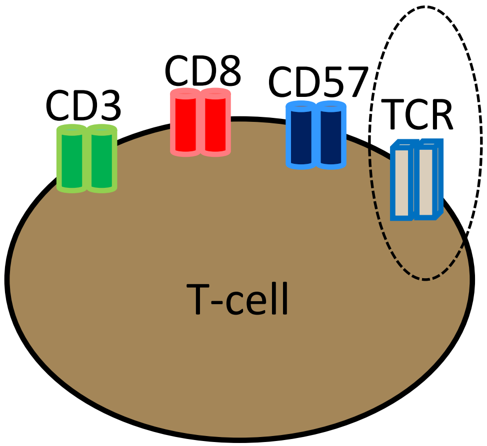
What is the T-cell receptor (TCR)? (unabridged version)

T-cell with CD3, CD8, CD57 markers and TCR.



Introduction:

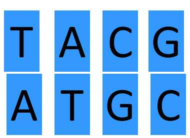
- LGLL is typically diagnosed by the presence of either a T-cell or NK-cell clone in the blood (rarely, both can be present).
- For T-cell LGLL, the presence of a clone is established by a test called **T-cell receptor** gene rearrangement test (or **TCR** test). The TCR is circled in this diagram. If the test cannot confirm that the cells are clones of each other then it may not be LGLL.
- The TCR is not expressed on an NK-cell, therefore clonality of NK-LGLL is more difficult to establish. However, chromosomal abnormalities or skewed expression of killer-cell immunoglobulin-like receptors (KIRs) may suggest clonality in NK-LGLL. Future content will discuss this topic in more depth.
- **The TCR is a protein that is a receptor.** Its job is to recognize a specific antigen. An antigen is a portion of a microbe or an allergen, basically something foreign to the body. Recognition of the antigen will cause an immune response.
- The TCR is created by several protein subunits. Different combinations are created to recognize a specific antigen.
- Since many combinations are possible, this provides a variety of TCRs, enabling production of T-cells that can recognize a variety of antigens.
- In LGLL, a large population of the T-cells have the exact same TCR subunits in the same arrangement/combination.

Overview for next pages:

- After T-cells are produced in the bone marrow, they go to the thymus to mature. This maturation process will include the TCR rearrangement. The next pages describe how the genes for the TCR express certain exons (a piece of DNA that will make a protein product). By mixing and matching exons, this will generate TCRs that have different sequences.

What is an exon?

Zoom in:
DNA nucleotide pairs



DNA sequence exists as pairs of nucleotides (*"What is some basic information about DNA?"* describes this in more detail).

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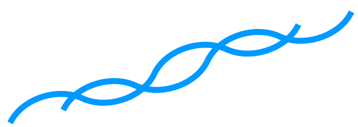
Zoom out:
double stranded DNA



DNA exists as double-stranded (paired), except when genes are being expressed. (*"How are protein products made from a gene?"* describes this in more detail).

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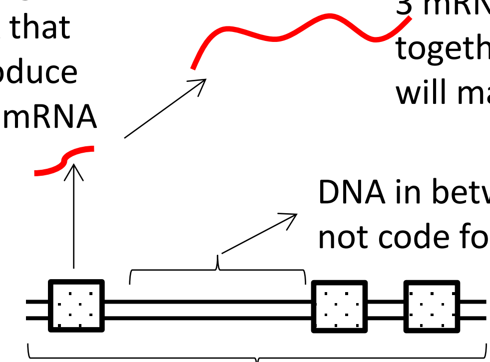
Zoom in:
gene structure



Each straight line is a strand of DNA. We are going to call this stretch of DNA a gene. In the gene, the patterned square is an exon. Where there is no square (just the lines) is non-coding DNA (DNA that will not make protein product). This non-coding DNA can make mRNA but it is not shown and will not be discussed here. An exon will produce messenger RNA (mRNA); it carries the message of the gene, which is the protein product. In this gene, there are 3 exons. The end result is that mRNA from the 3 exons will be joined to make one large mRNA. This will become an amino acid sequence that folds to make a protein (see *"How are protein products made from a gene?"* for more detail).

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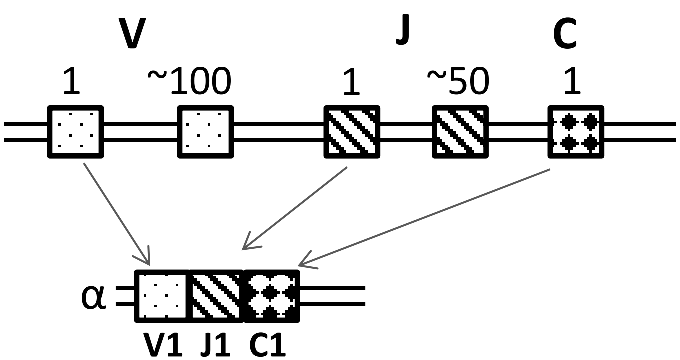
The TCR Genes

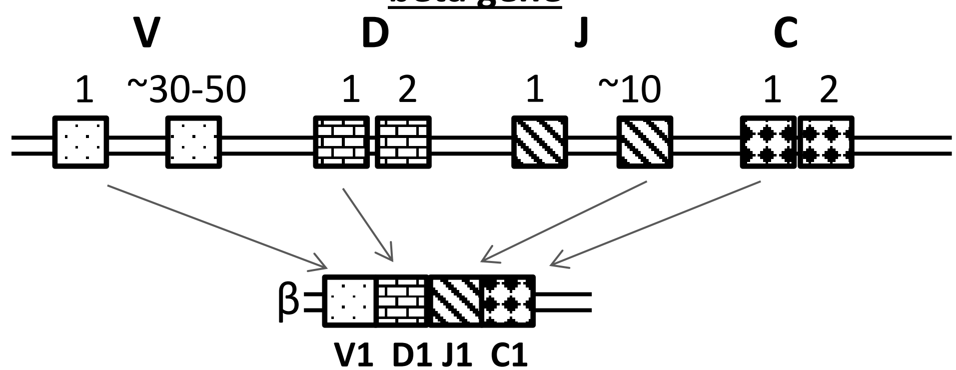
The T-cell receptor (TCR) protein product is made up of two genes (alpha and beta OR gamma and delta). We will focus on alpha and beta, but know that gamma and delta follow the same workflow.

alpha gene



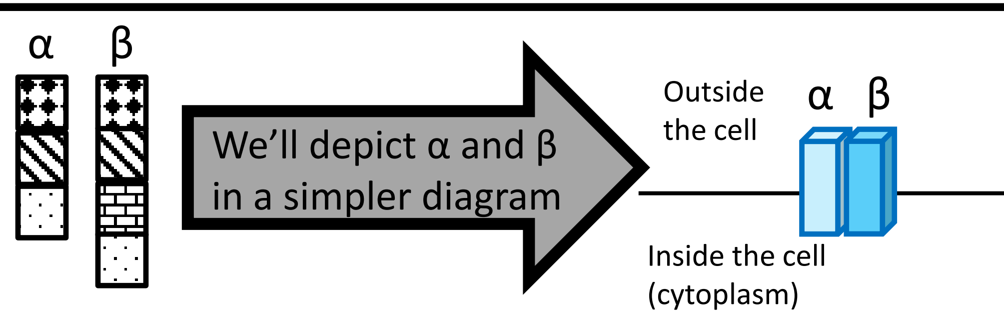
- In the alpha (α) gene, there are about 100 V exons, 50 J exons, and 1 C exon.
- In this example, exons V1, J1, and C1 made an α protein product.
- There are many possible combinations of all the different VJC exons, thus many different α protein products. For example, V2 J1 C1 could be another combination.

beta gene



- In the beta (β) gene, there are about 30-50 V exons, 2 D exons, 10 J exons, and 2 C exons.
- In this example, exons V1, D1, J10, and C1 made a β protein product.
- There are many possible combinations of all the different VDJC exons, thus many different β protein products. For example, V2 D1 J1 C1 could be another combination.

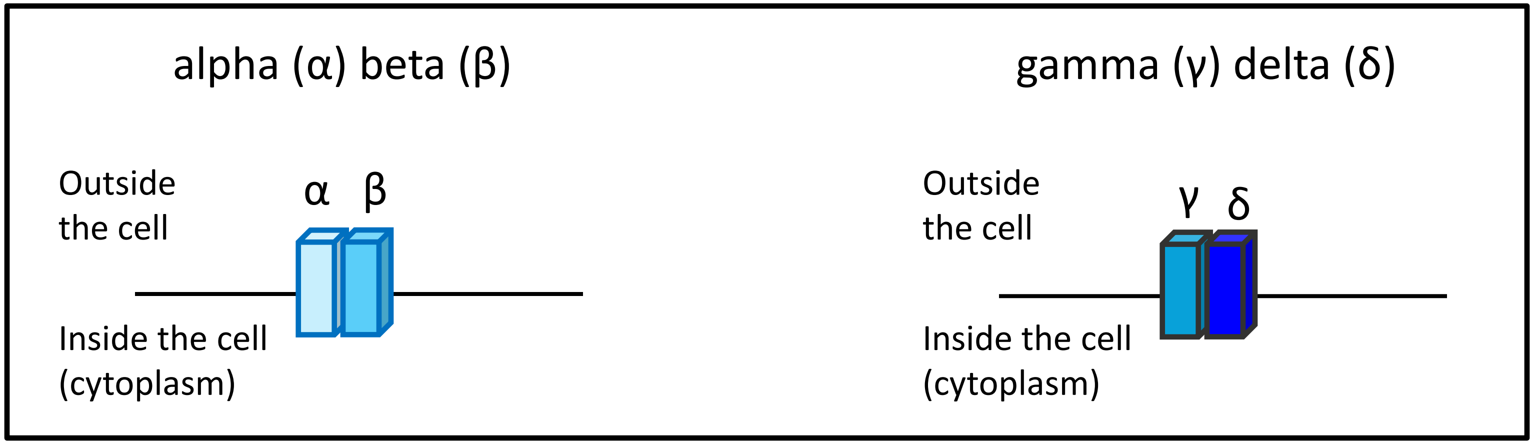
The TCR's different combination of exons enable generation of a diverse set of T-cells to recognize a variety of foreign things (microbes, allergens, etc). Refer to *"What does clonality look like in LGL leukemia?"* to see how lots of different TCRs are produced.



If every T-cell has the same TCR exon sequence, this tells you that T-cell copied itself over and over due to an immune response to a specific antigen.

The TCR: αβ vs. γδ

- The αβ version of the TCR was described on the previous page. The αβ type is more common, however another TCR type called γδ can also exist. This type of receptor is made up of gamma (γ) and delta (δ) proteins. These are also composed of subunits, but are different from αβ. The type of TCR that is found in a patient's diagnostic test is not known to affect prognosis (likely outcome of the disease). It just means some patients create a different TCR type.
- Below, you can see the TCR now depicted as either an αβ or γδ type.



- To visually see how TCR clonality in T-cells differs between LGLL and a healthy individual, you can refer to *"What does clonality look like in LGL leukemia?"*

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Linking together the TCR, T-cells, bone marrow, and thymus:

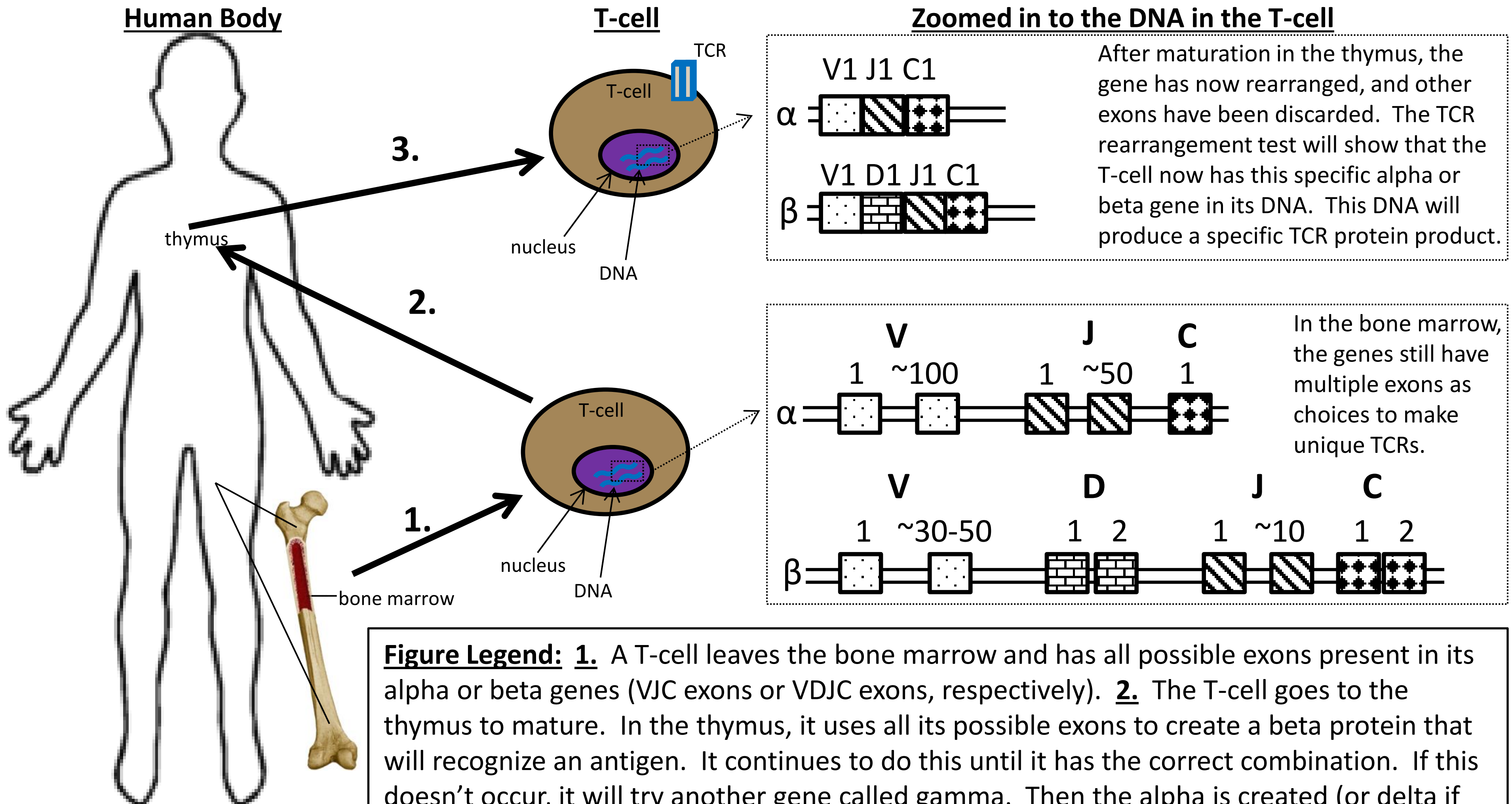

Figure Legend: **1.** A T-cell leaves the bone marrow and has all possible exons present in its alpha or beta genes (VJC exons or VDJC exons, respectively). **2.** The T-cell goes to the thymus to mature. In the thymus, it uses all its possible exons to create a beta protein that will recognize an antigen. It continues to do this until it has the correct combination. If this doesn't occur, it will try another gene called gamma. Then the alpha is created (or delta if gamma is used). **3.** The T-cell has now changed its DNA so that only specific exons are present, and these exons will create the specific TCR to recognize a specific antigen.