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Abstract – Amino acid substitutions yield high levels of TCR expression and target-specific T-cell activation: The Dominant TCR technology

This work was performed in its entity in the laboratory of Prof Hans Stauss and the technology is exclusively licensed to Cell Medica

The concept of week and strong T-cell Receptor (TCR) has been known for almost a decade. Some TCRs are expressed at higher levels than others. Further, when a strong TCR is transduced into a T-cell with a weak TCR, the expression of the weak TCR is reduced. The strong TCR is therefore the dominant TCR in that cell. This is presumed to be the result of the limited and controlled amounts of CD3 in cells (most likely CD3 zeta).

Work in the laboratory of Prof Hans Stauss (UCL) focused on the sequencing of several hundred strong and weak TCRs, followed by bioinformatics analysis, that identified several amino acids that are more often associated with strong TCRs and others with weak TCRs. Subsequent substitutions of these amino acids in strong and weak TCRs have resulted in significant increases, in the cases when “strong” amino acids are used, or decreases, in the cases where “weak” amino acids were used, in the expression of the TCRs. Strong TCRs can be expressed at higher amounts and in more cells, while weak TCRs can be rendered strong.

Sufficient levels of TCR expression are vital for T-cell activation. When the levels are below a certain threshold, as in the case of many weak TCRs, T-cells fail to activate, or activate very poorly, in the presence of their target antigen. TCR expression is therefore a considerable hurdle for the development of efficacious TCR-transduced T-cell products and many such products suffer from poor levels of expression. The Dominant TCR modifications presented here are able to enhance the levels of expression, as well as the number of transduced cells expressing TCRs in all instances where they have been applied. This resulted in much higher levels of T-cell activation, measured by the expression of IFN-gamma and IL-1 beta, or full activation, in cases where the wild type TCR was unable to lead to activation.

The importance of this technology in TCR-modified T-cell immunotherapy is considerable, as it reproducibly yields optimal T-cell products demonstrating sensitivity and target-specific activation of the highest physiological level.