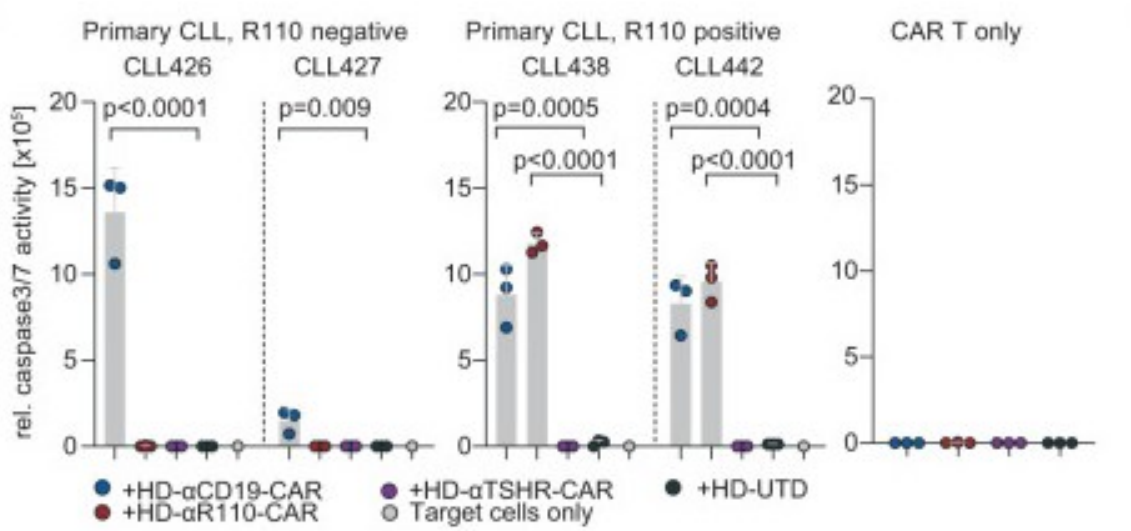
Paper of the month:

Florian Märkl et al, **Mutation-specific CAR T cells as precision therapy for IGLV3-21^{R110} expressing high-risk chronic lymphocytic leukemia** published in ***Nat Commun***, 2024 Feb 2;15(1):993.

The new immunomodulating strategies, such as chimeric antigen receptor (CAR)-modified T cells, are gaining substantial interest in the CLL field. However, although CAR T cells against CD19, a component of the BCR complex, provide a significant response in patients with high-risk and refractory CLL, the rate of complete remissions and long-term responses is not as good as in other lymphoma types. The reasons for these suboptimal outcomes include CD19 antigen loss, CAR T cell loss or dysfunction, as well as severe toxicity associated with complete eradication of the B cell lineage.

To respond to these challenges, Märkl and colleagues engineered selective CAR T constructs that target a recurrent oncogenic point mutation in the BCR light chain of malignant CLL cells. In this original study, they provide proof-of-concept for the activity of tumour-specific CAR T cells for high-risk CLL patients that express the IGLV3-21^{R110} BCR light chain. The IGLV3-21^{R110} CLL subset is typically associated with an aggressive CLL disease. It is observed in 10–15% of unselected CLL patients and in a higher percentage of CLL patients that require treatment. It was previously shown that the G-to-R exchange at position 110 of the IGLV3-21 light chain confers autonomous signalling capacity to the BCR. The IGLV3-21^{R110} BCR is, therefore, a CLL-specific tumour driver, and the assumption was that targeting this receptor would spare normal B cells and therefore reduce treatment toxicity.

Indeed, the authors showed that humanised CAR constructs expressed in T cells from healthy donors and CLL patients eradicate IGLV3-21^{R110}-expressing cell lines and primary CLL cells but do not target cells expressing the non-pathogenic IGLV3-21^{G110} light chain or polyclonal healthy B cells. Furthermore, in vivo experiments confirmed epitope-selective cytolysis in xenograft models in female mice using engrafted IGLV3-21^{R110}-expressing cell lines or primary CLL cells. These data suggest potential clinical applications of IGLV3-21^{R110}-targeting CAR T cells in the treatment of relapsed or refractory disease after a suboptimal response to standard first-line CLL treatment. The curative potential of this approach, however, will require further evaluation in clinical trials.



Cytolysis of freshly isolated primary CLL cells from IGLV3-21R110-positive and IGLV3-21R110-negative CLL cases in vitro.