260 INVESTIGATING CANCER CELL AUTONOMOUS CAR T CELL THERAPY RESISTANCE IN DLBCL *IN VITRO*

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Background CD19 CAR T cell therapy has greatly improved the outcome of r/r DLBCL patients, but durable responses are achieved in only 40% of cases. Relapses can be due to declining T cell fitness and/or cancer cells becoming inherently refractory. However, besides antigen loss, cancer cell autonomous resistance mechanisms are poorly understood.

Methods We generated DLBCL cell lines that are refractory to CD19 targeting CAR T cells by longterm co-culture *in vitro*. We assessed response to alternative CAR T cells targeting other antigens and performed RNAseq of resistant cancer cell lines to identify yet unknown resistance mechanisms.

Results Our *in vitro* longterm co-cultures recapitulate common resistance mechanisms observed in the clinics including CD19 loss. Interestingly, we do observe CD19 positive resistance and multiple of our CD19 CAR T cell resistant cell lines had become less sensitive also to alternative CAR T cells. Moreover, our RNAseq data indicate that the majority of transcriptional changes are associated with a common resistant phenotype rather than a specific resistance mechanism (e.g., antigen loss).

Conclusions Our results suggest that besides CD19 loss, DLBCL cells evolve mechanisms to overcome T cell killing which may render them cross-resistant to CAR T cells targeting other antigens. Analysis of our RNAseq data will allow us to characterize these mechanisms.

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