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ON THE COVER Resistance to CAR-T cells can result from low expression of target antigens on cancer cells. In B-cell cancers, Majzner and colleagues found a high degree of intra- and interpatient heterogeneity in the expression of CAR-T cell target antigens. Importantly, though, the sensitivity of CAR-T cells to target-antigen level was tunable: CAR-T cells could be made more or less sensitive by altering their costimulatory and hinge–transmembrane (H/T) domains. Specifically, CD28 costimulatory and H/T domains (both as in axicabtagene ciloleucel) conferred more sensitivity than 4-1BB costimulatory domains and CDB H/T domains (both as in tisagenlecleucel). For details, please see the article by Majzner and colleagues on page 702.

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