DNA-scaffolded biomaterials enable modular and tunable control of cell-based cancer immunotherapies

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Advanced biomaterials provide versatile ways to spatially and temporally control immune cell activity, potentially enhancing their therapeutic potency and safety. Precise cell modulation demands multi-modal display of functional proteins with controlled densities on biomaterials. Adoptive cell therapy using chimeric antigen receptor (CAR) engineered T cells has shown success and clinical approval for the treatment of B cell cancers. However, for CAR T cells to fulfill their promising potential, particularly for targeting solid tumors, important challenges must be overcome to improve both efficacy and safety. For engineered anti-tumor T cells to achieve durable tumor remission in patients, a demanding manufacturing process is required to ensure the quantity and quality of the cell product for therapeutic use. To increase the tumor targeting specificity and avoid "on-target, off-tumor" toxicity in bystander healthy tissues, CAR-T cells have been engineered with combinatorial antigen AND-gate activation control that requires sensing two antigens on a target cell to initiate killing. Here, we develop an artificial immune cell engager (AICE) platform – biodegradable particles onto which multiple proteins are densely loaded with ratiometric control via short nucleic acid tethers. We demonstrate the impact of AICE with varying ratios of anti-CD3 and anti-CD28 antibodies on *ex vivo* expansion of human primary T cells. We also show that AICE can be used to control the activity of engineered T cells *in vivo*. AICE injected intratumorally can provide a local priming signal for systemically administered AND-gate chimeric antigen receptor T cells, driving local tumor clearance while sparing uninjected tumors that model potentially cross-reactive healthy tissues. This modularly functionalized biomaterial thus provides a flexible platform to achieve sophisticated control over cell-based immunotherapies.
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