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A SST14 based T-cell engager for the treatment of neuroendocrine tumors

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BACKGROUND

Somatostatin receptor 2 (SSTR2) is overexpressed and currently used as a therapeutic target in well-differentiated neuroendocrine tumors (NETs). We designed a novel bispecific T-cell engager targeting SSTR2 via Somatostatin-14 (SST-14), linked with a scFV-based anti-CD3.

METHODS

293T cells expressing SSTR2-GFP or mock-GFP as control, the pancreatic NET cell line BON1, and patient-derived tumoroids from pancreatic NETs were used as target cells, while T cells enriched from PBMCs of healthy donors were used as effector cells. As an alternative, autologous tumor-infiltrating lymphocytes (TILs) and peripheral blood T cells from patients were used. Flow cytometry and ImageStream were used to assess the molecule's interaction with CD3 and SSTR2, and immune synapse formation. T-cell activation and cytotoxicity induced by the engager were measured using ELISA and real-time live-cell imaging. The effect of the molecule alone on tumoroids was quantified by bioluminescence and octreotide was used as control. Cibacron blue–agarose beads coated with 100 µg of albumin were used to detect the interaction between the engager and albumin, and a scrambled SS14 engager was used as a control.

RESULTS

The T-cell engager interacts with the CD3 on T-cells and the SSTR2 on target cells between 100nM and 20nM, inducing the formation of immunological synapses upon interaction. The molecule significantly increases IFN-γ, TNF-α, and Granzyme-B secretion when T cells are co-cultured with $SSTR2^+$ 293T cells or BON1cell line. A similar effect is observed when patient-derived tumoroids are cocultured with autologous T cells or TILs. Moreover, at 20 and 100 nM, the engager shows dose-dependent cytotoxicity against $SSTR2^+$ 293T cells in the presence of T cells, which is specific for the presence of the SSTR2. The molecule showed an intrinsic antiproliferative effect on patients derived tumoroids, which was comparable to octreotide. It also exhibited specific binding to albumin, in contrast to the control.

CONCLUSIONS

This engager elicits a dose-dependent T cell response against several SSTR2-expressing cells, including NET cell lines and patient derived organoids. In the absence of T cells, the molecule retains its SST14-derived antiproliferative activity, which resembles that of octreotide.

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