262 Macrophage Programming for Immunotherapy

Asset Overview

Product Type	Genetically modified macrophage (Cell Therapeutic)
Indication	Oncology
Current Stage	Lead Identification/optimization
Target (MoA)	Tumor antigen binding and phagocytosis via genetically reprogrammed macrophage
Brief Description	UC San Diego researchers have developed methods and processes for engineering macrophages to carry both response elements and effector modules that can provide directed immunotherapy. By modulating the cellular response profile, macrophages can now target cells that would otherwise evade detection and clearance. By relying on the natural phagocytic process, the therapeutic potential of this technology is enhanced and the off-target risks may be minimized.
Organization	University of California, San Diego

Differentiation

□ **Unmet Needs**

- One of the major impediment to successful cancer immunotherapy is high level of CD47 expression in cancer cells, which inhibits phagocytic uptake of tumor cells by immune cells
- Conventional monoclonal antibody strategy targeting CD47 can cause anemia and other side effects due to normal blood cells expressing CD47

□ **Innovations**

- The technology in development utilizes Shp2-and Spleen tyrosine kinase (Syk)-integrated sensing and actuating protein (iSNAP) (Shp2- and Syk-iSNAP) chimeric protein comprising: a bi-phosphorylatable peptide, optionally a bisphosphoryl tyrosine-based activation (BTAM) motif; a Fluorescent Protein (FP) Forster Resonance Energy Transfer (FRET) (or FP FRET) pair or pair of motifs to reprogram macrophage in innovative manner
- Genetically modified macrophages can induce phagocytosis when CD47 binds to SIRPa through FRET-based sensor genetic circuit that can override macrophages tendency to ignore cells expressing CD47 at a high level
- Potentially, the genetically modified circuit can be activated to override CD47-induced inhibition of phagocytosis by overriding the signaling via CD47- and tumor antigen-co-induced activation of macrophage. As tumor antigen binding is also required for circuit activity, it could potentially discriminate normal blood cells from tumor cells for phagocytic process

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Key Data

Genetic modification schematics

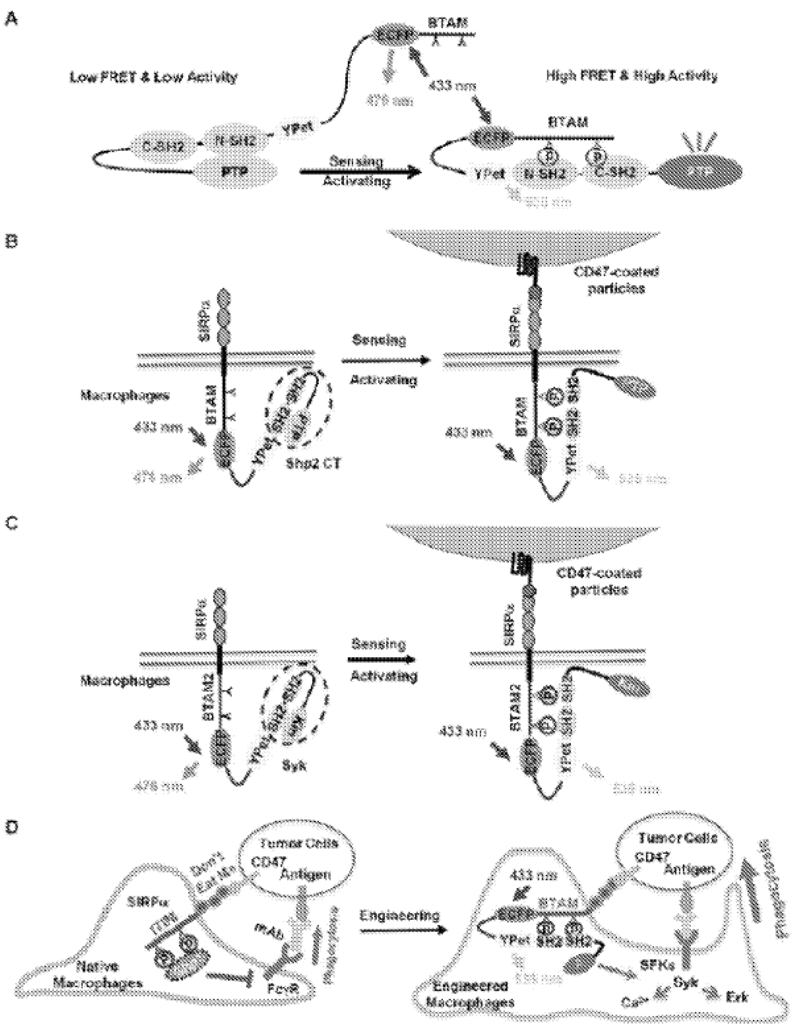
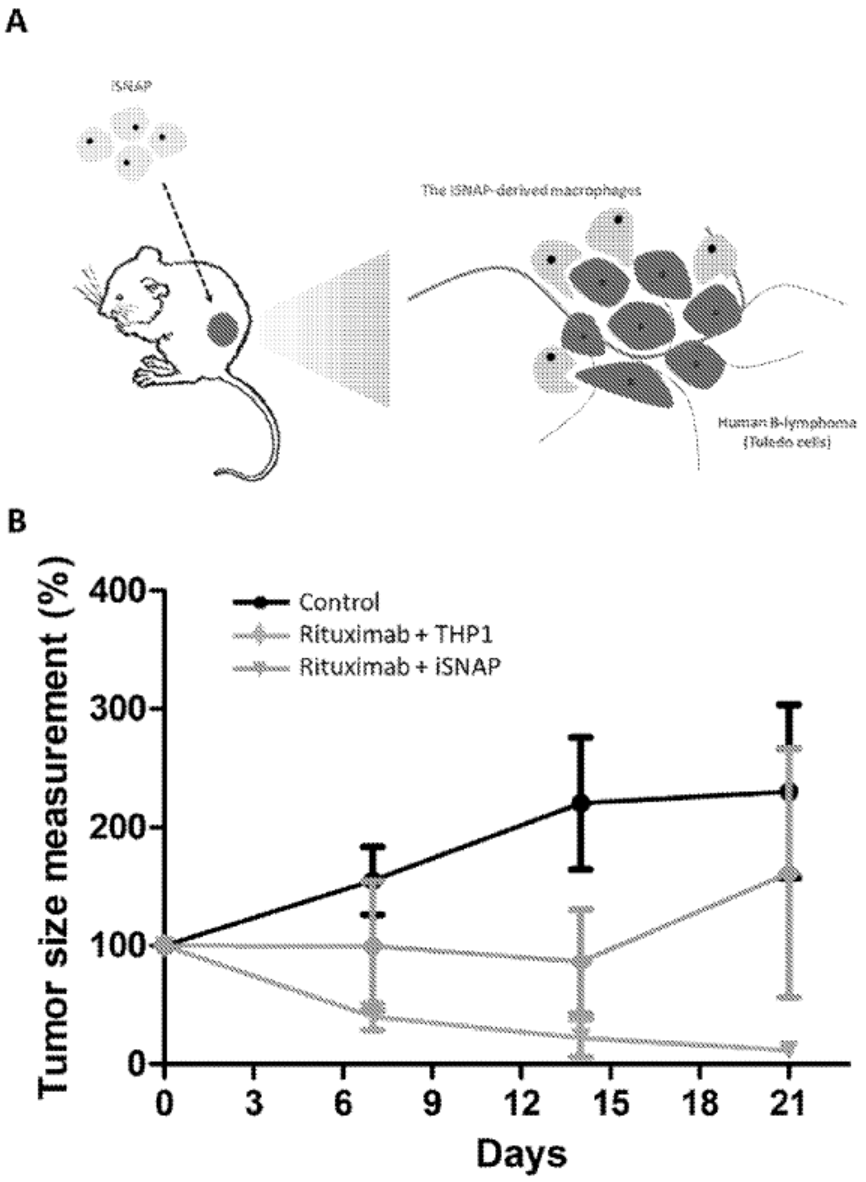


Figure 1 (A) Schematic drawing of the Shp2-iSNAP and its putative activation mechanism. Shp2-iSNAP consists of a phosphorylatable peptide, a FP FRET pair, a truncated Shp2 consisting of two SH2 domains (N-SH2 and C-SH2) and a PTP domain. Two sensing tyrosine sites are indicated as Y (without phosphorylation), P indicates phosphorylation, activated PTP domain is colored in red. (B) Schematic drawing of the SIRPa Shp2-iSNAP and its putative activation mechanism upon engagement of CD47. Structurally, SIRPa Shp2-iSNAP contains a human SIRPa without its PTM-containing C-tail, fused to the Shp2-iSNAP. At rest, PTP domain is quenched by its SH2 domains. Upon CD47 stimulation, tyrosines in BTAM motif will be phosphorylated to bind SH2 domains and result in the release and activation of the PTP domain. (C) SIRPa Syk-iSNAP has similar design with BTAM2 instead of BTAM, Syk instead of Shp2. Activated kinase domain is colored in red. (D) Engineering macrophage for mAbs-guided cancer cell eradication. In native macrophages, pro-phagocytic activities mediated by the antigen-recognizing antibody and FcγR is inhibited by CD47-SIRPa signal pathway via the recruitment of negative regulator Shpl. In engineered macrophages, the anti-phagocytic signals of CD47-SIRPa axis are rewired by SIRPa iSNAPs to promote phagocytic activities for the tumor cell eradication.

Antitumor activity of reprogrammed macrophages



Human B-lymphoma tumor model was established by subcutaneous injection of Toledo cells in nude mice (Fig. 8A). The tumors were then treated by local injection of parental control and iSNAP-engineered TFIP cells, guided by rituximab, an anti-CD20 monoclonal antibody, in recognizing the tumor antigen CD20. The tumor sizes were followed and measured weekly (Fig. 8B).

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Intellectual Property

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