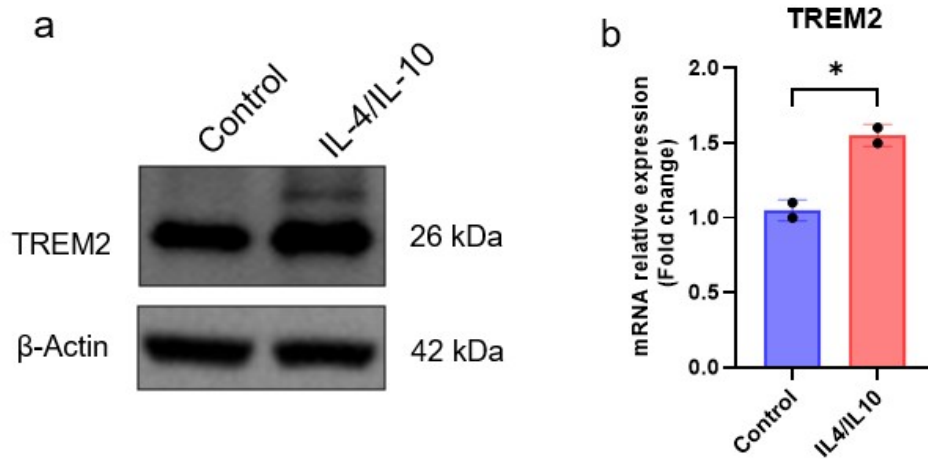


**Supplementary Fig.1** TREM2 expression in primary human macrophages following anti-inflammatory stimulation.

(a) Representative Western blot analysis of TREM2 protein expression in primary human macrophages treated with IL-4 and IL-10.  $\beta$ -actin was used as a loading control.

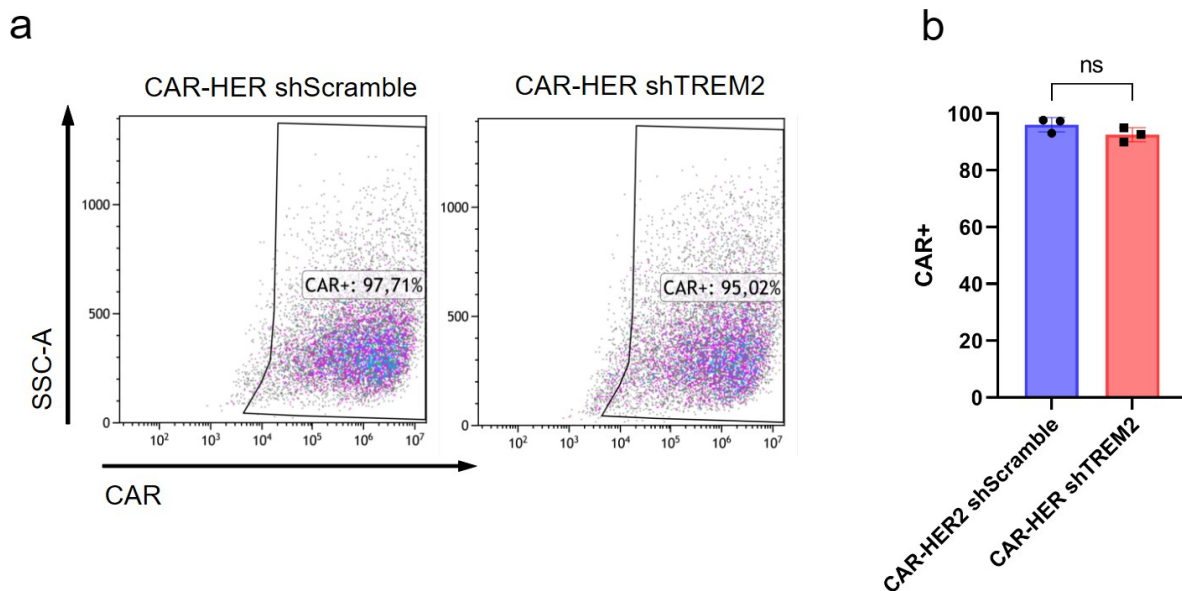
(b) RT-qPCR analysis of TREM2 mRNA expression in primary human macrophages treated with IL-4 and IL-10.



**Supplementary Fig.2** CAR expression in HER2 CAR macrophages following transduction with shRNA constructs.

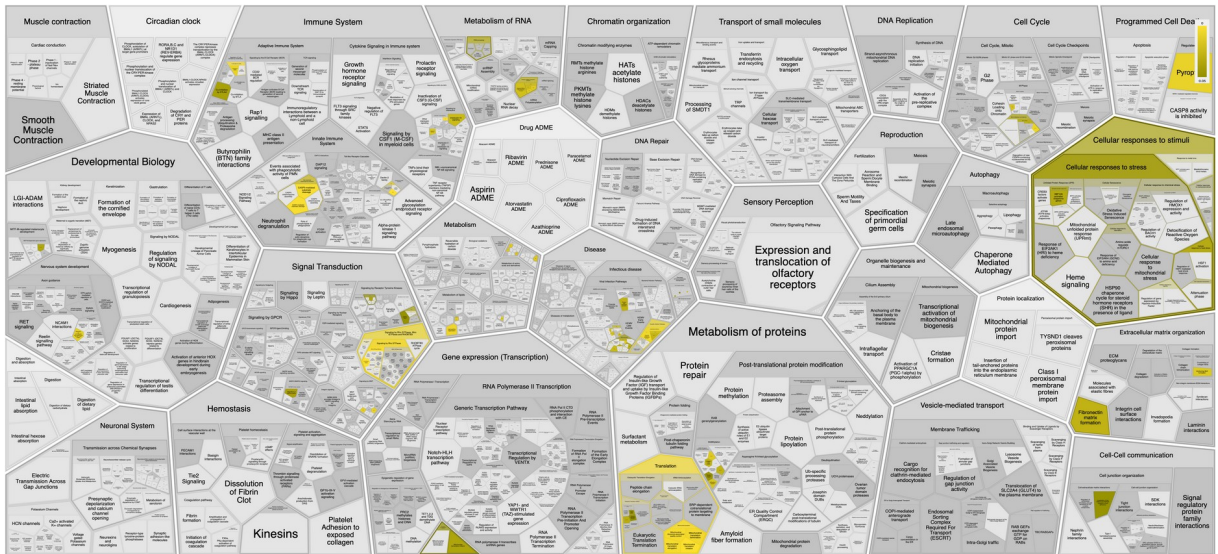
(a) CAR expression in HER2 CAR-M expressing shScramble or shTREM2 after transduction.

(b) Quantification of flow cytometry data from (a).

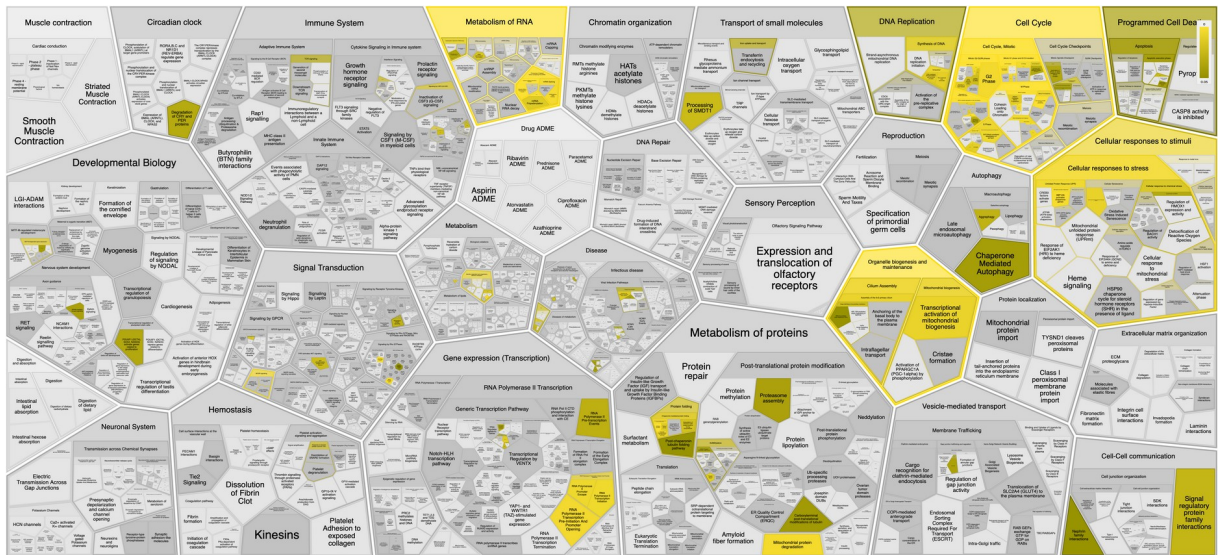




# CAR-HER2



# CAR-HER2 iTREM2

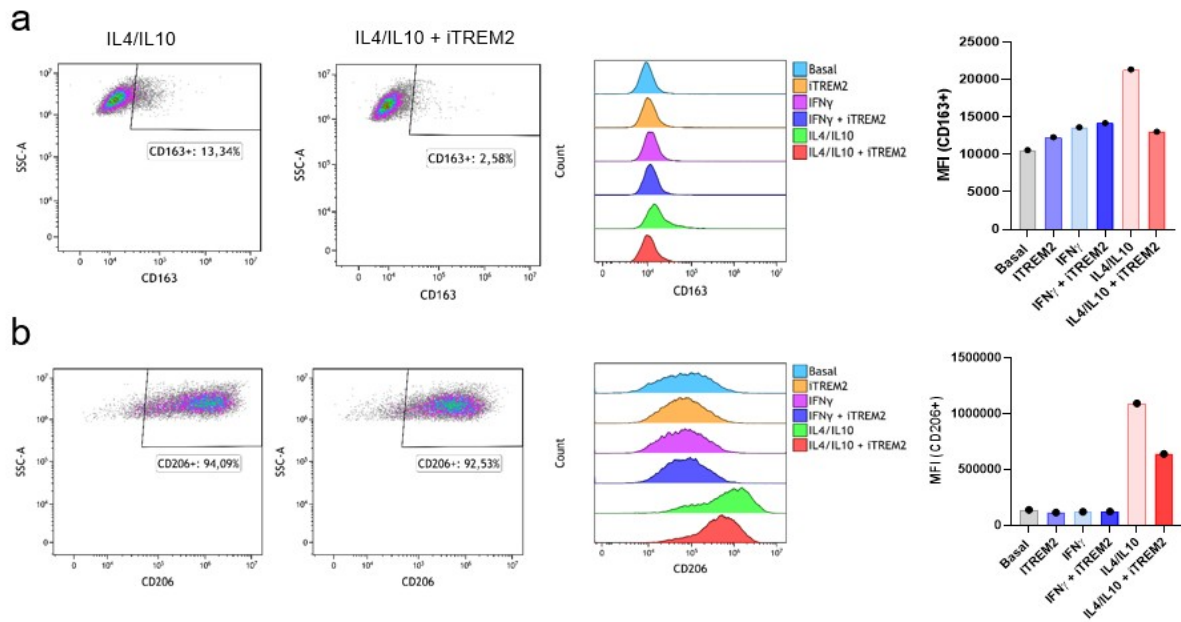


**Supplementary Fig.4: Flow cytometry analysis of anti-inflammatory markers in primary human macrophages.**

(a) CD163 expression under IL-4/IL-10 polarization in the presence or absence of iTREM2.

(b) CD206 expression under IL-4/IL-10 polarization in the presence or absence of iTREM2.

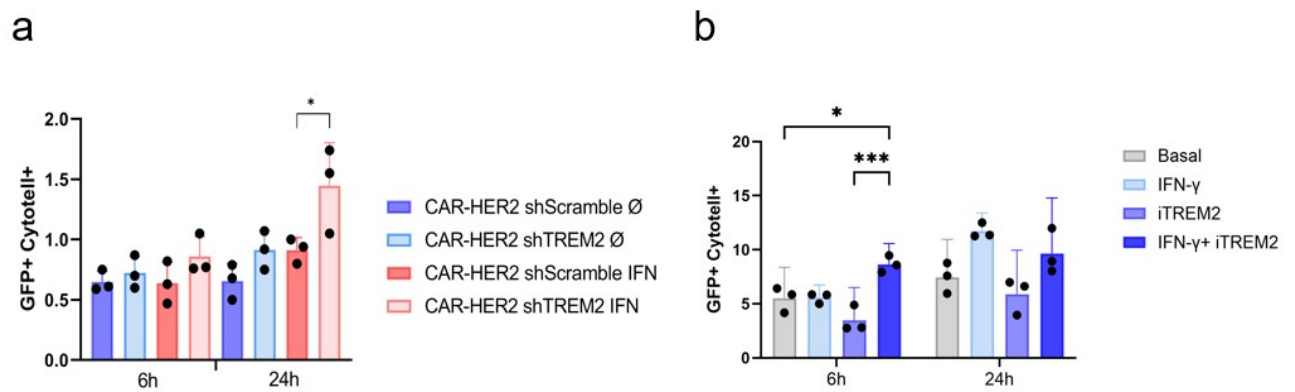
Representative dot plots, histograms, and quantification of MFI are shown.



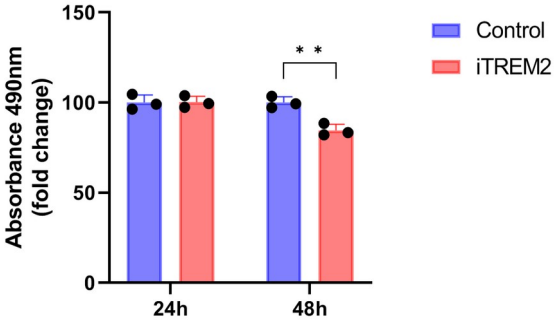
**Supplementary Fig.5 Phagocytosis of HER2 negative breast cancer cells by CAR-M**

(a) Phagocytosis of MDA-MB-231 cells by HER2 CAR-M expressing shTREM2 or shScramble after 6 and 24 h of coculture at a 3:1 effector-to-target (macrophage/cancer cell) ratio. Phagocytosis was quantified as the percentage of CytotellBlue+/GFP+ cells.

(b) Phagocytosis of MDA-MB-231 cells by HER2 CAR-M treated with or without iTREM2 after 6 and 24 h of coculture at a 3:1 effector-to-target ratio. Phagocytosis was quantified as the percentage of CytotellBlue+/GFP+ cells.



**Supplementary Fig.6** Viability of AU565 after treatment with the TREM2 inhibitor for 24h and 48h.



**Supplementary Fig.7** HER2 expression of HER positive breast cancer tumoroids

(a) Flow cytometry analysis of HER2 expression in HCl032 cells using isotype-PE (left) or anti-HER2-PE (right)

(b) Representative flow cytometry histograms of HER2 expression in different tumoroid lines

