

A homing system targets therapeutic T cells to brain cancer

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Successful T cell immunotherapy for brain cancer requires that the T cells can access tumour tissues, but this has been difficult to achieve. Here we show that, in contrast to inflammatory brain diseases such as multiple sclerosis, where endothelial cells upregulate ICAM1 and VCAM1 to guide the extravasation of pro-inflammatory cells, cancer endothelium downregulates these molecules to evade immune recognition. By contrast, we found that cancer endothelium upregulates activated leukocyte cell adhesion molecule (ALCAM), which allowed us to overcome this immune-evasion mechanism by creating an ALCAM-restricted homing system (HS). We re-engineered the natural ligand of ALCAM, CD6, in a manner that triggers initial anchorage of T cells to ALCAM and conditionally mediates a secondary wave of adhesion by sensitizing T cells to low-level ICAM1 on the cancer endothelium, thereby creating the adhesion forces necessary to capture T cells from the bloodstream. Cytotoxic HS T cells robustly infiltrated brain cancers after intravenous injection and exhibited potent antitumour activity. We have therefore developed a molecule that targets the delivery of T cells to brain cancer.

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Figure 1i

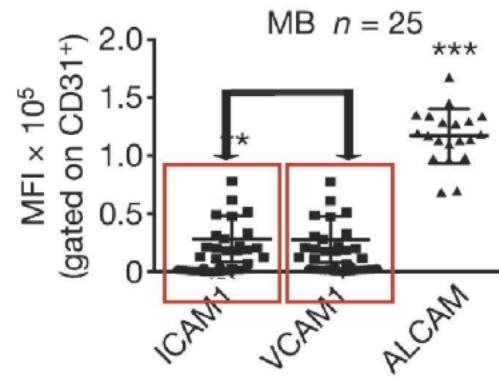


Figure 4g

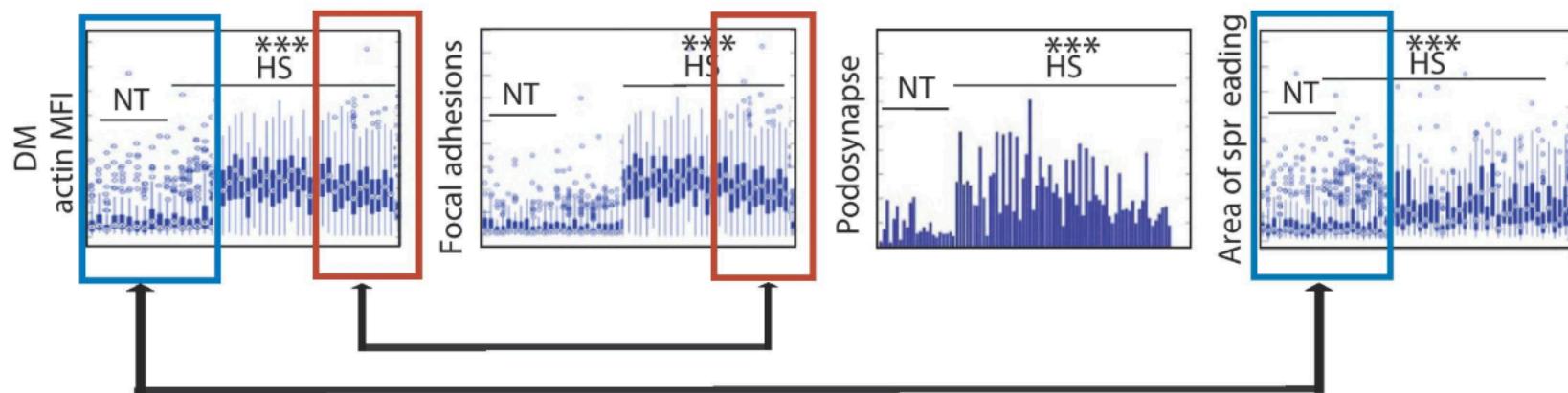


Figure 5c and 5e

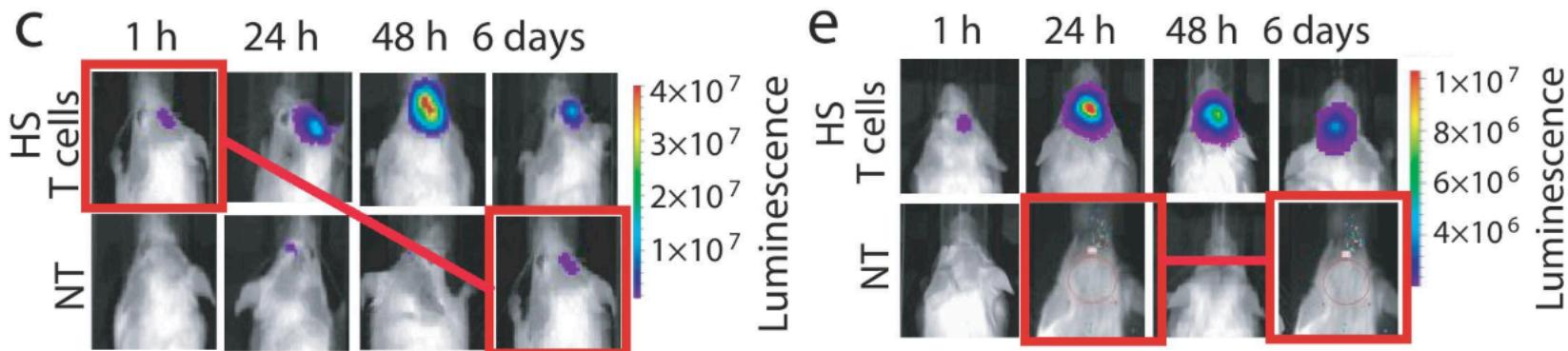
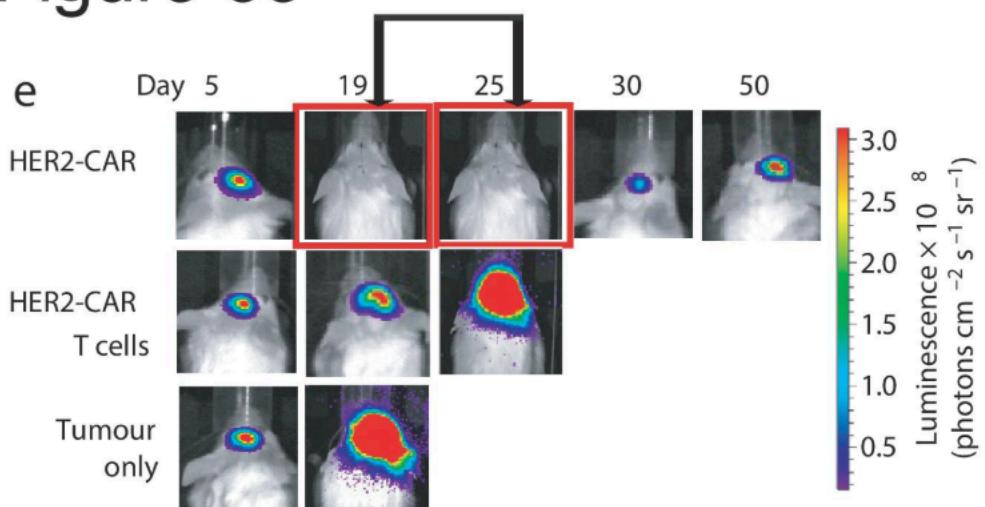
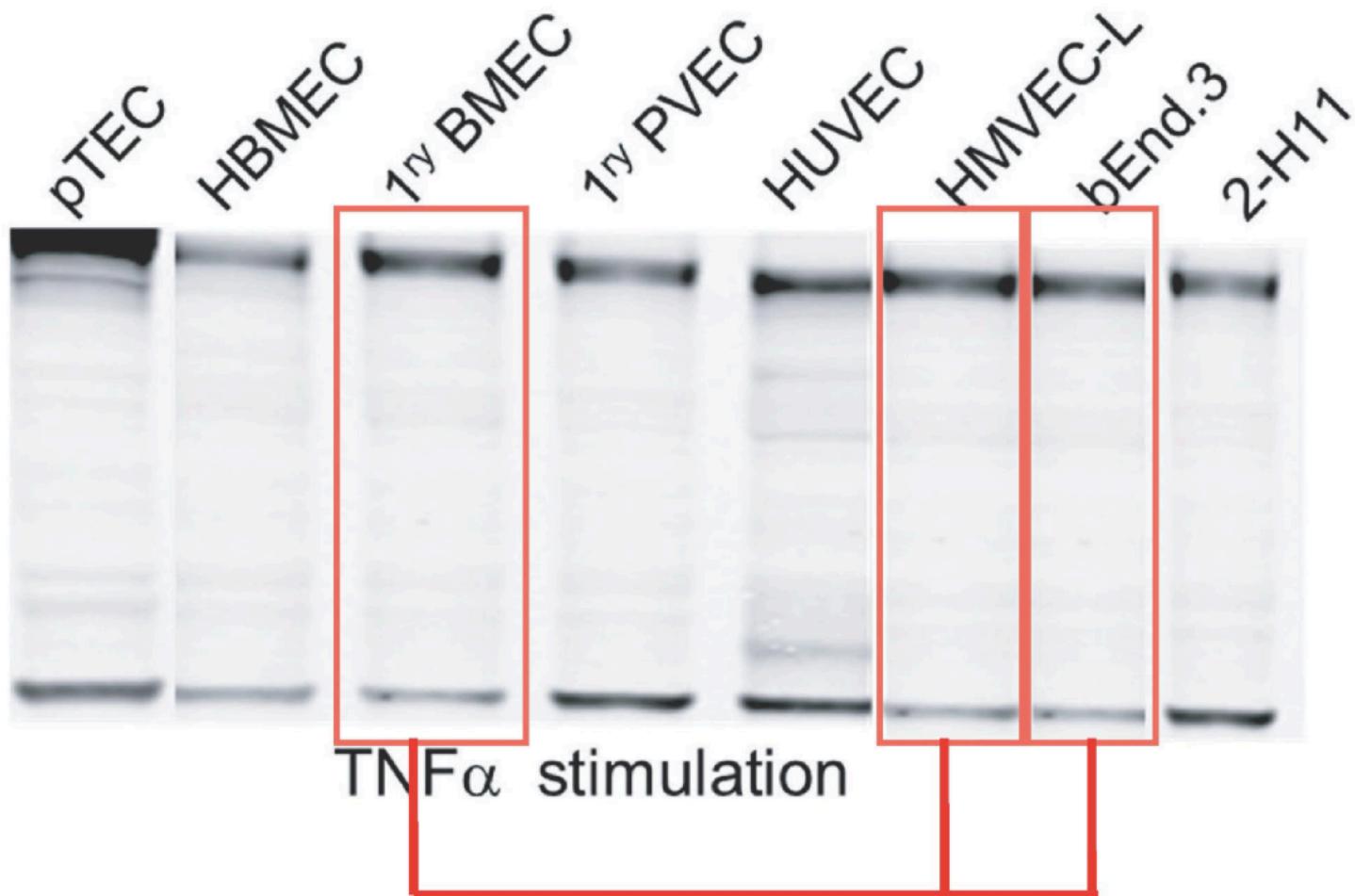


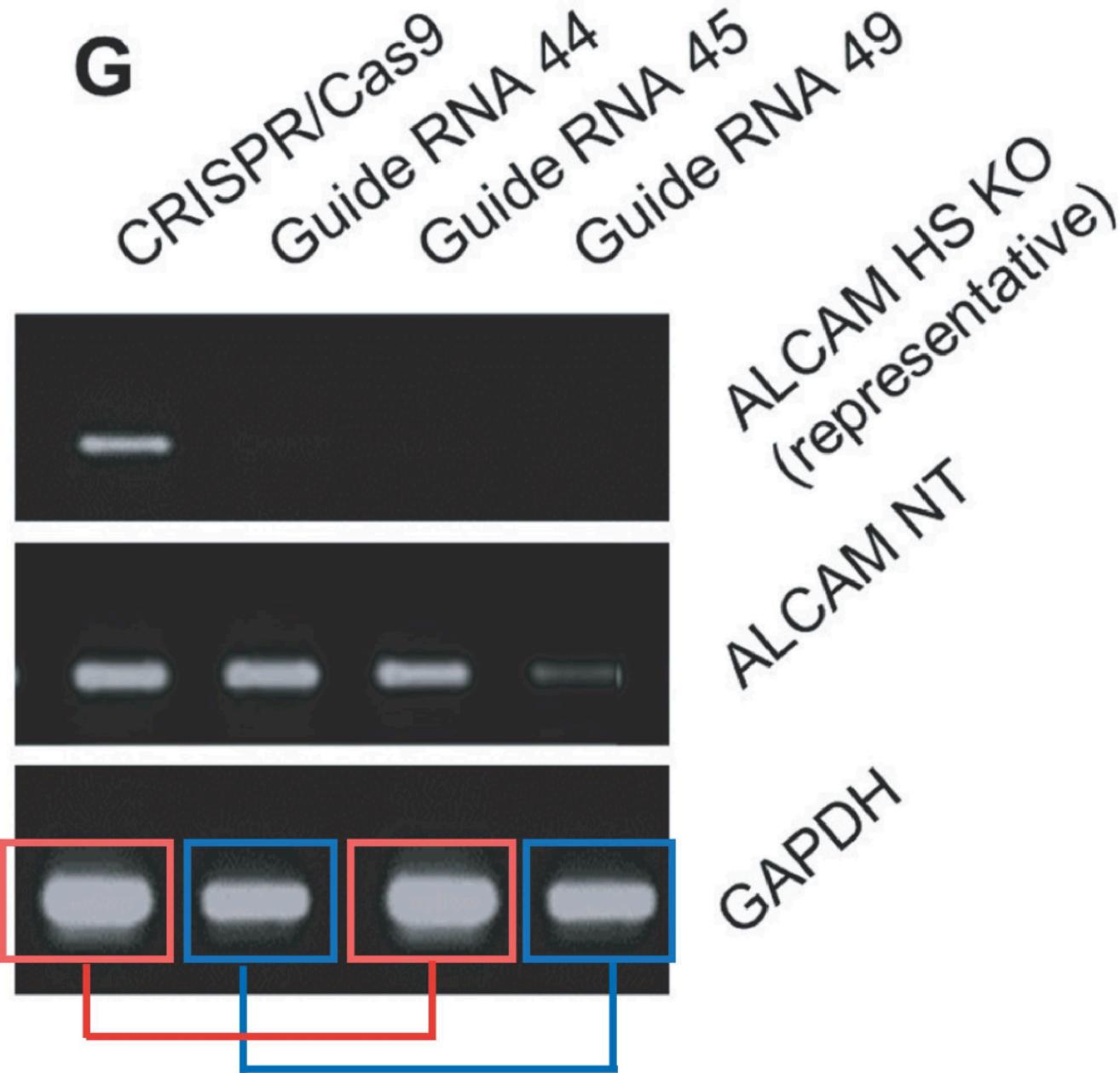
Figure 6e



Supplemental Figure 2A

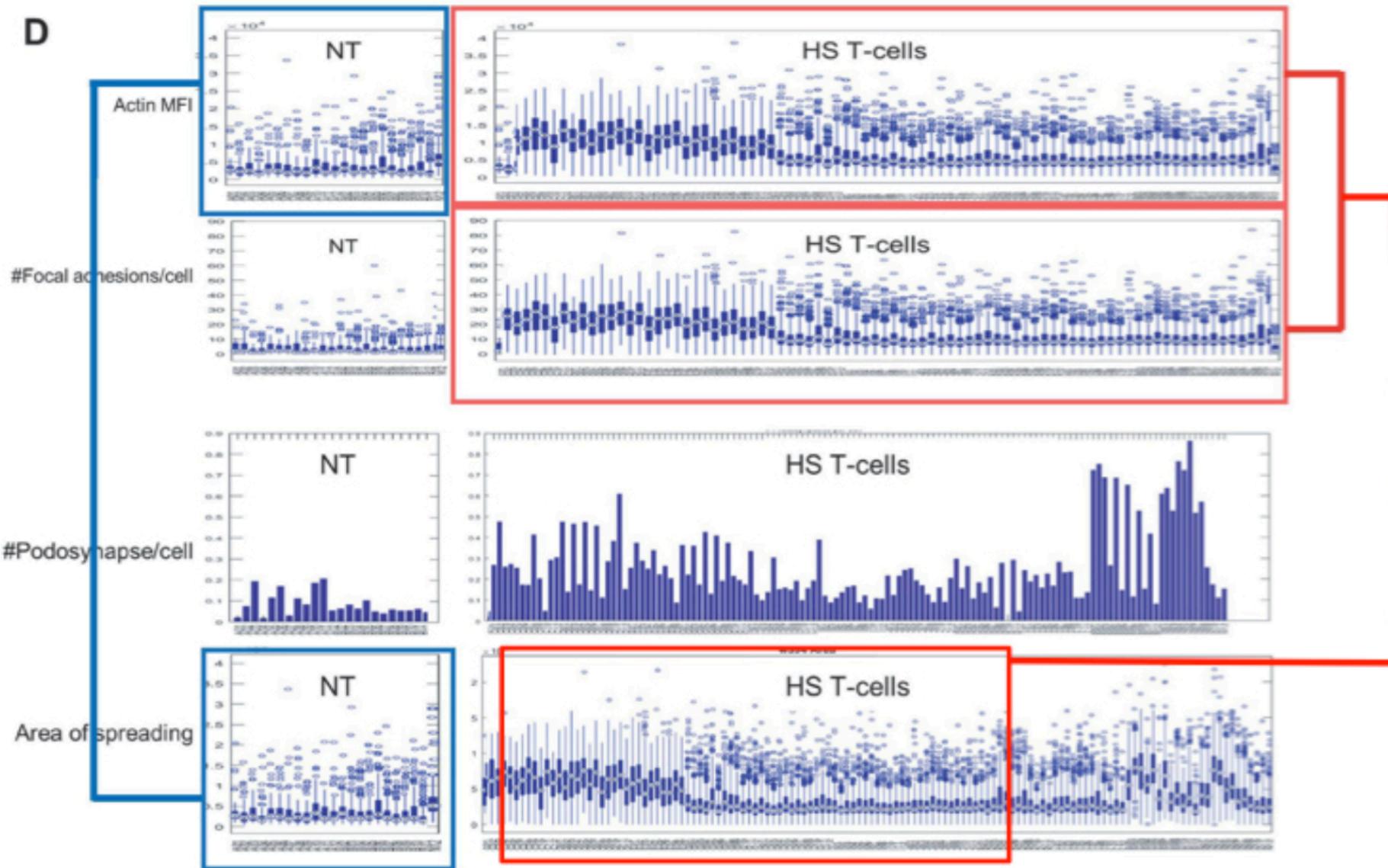


Supplemental Figure 4G



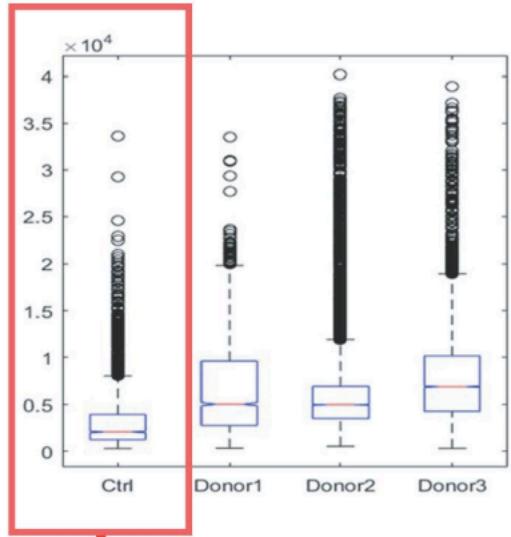
Supplemental Figure 5D and 5E

D

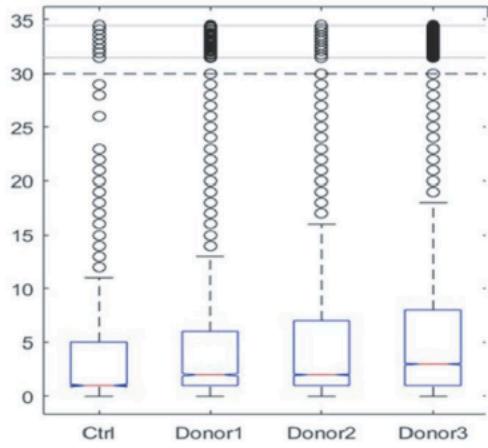


π

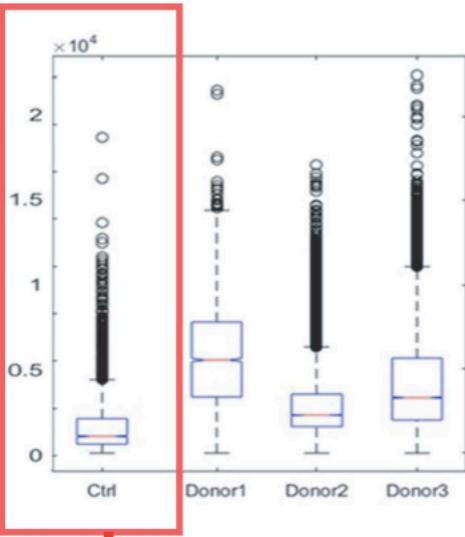
Actin MFI



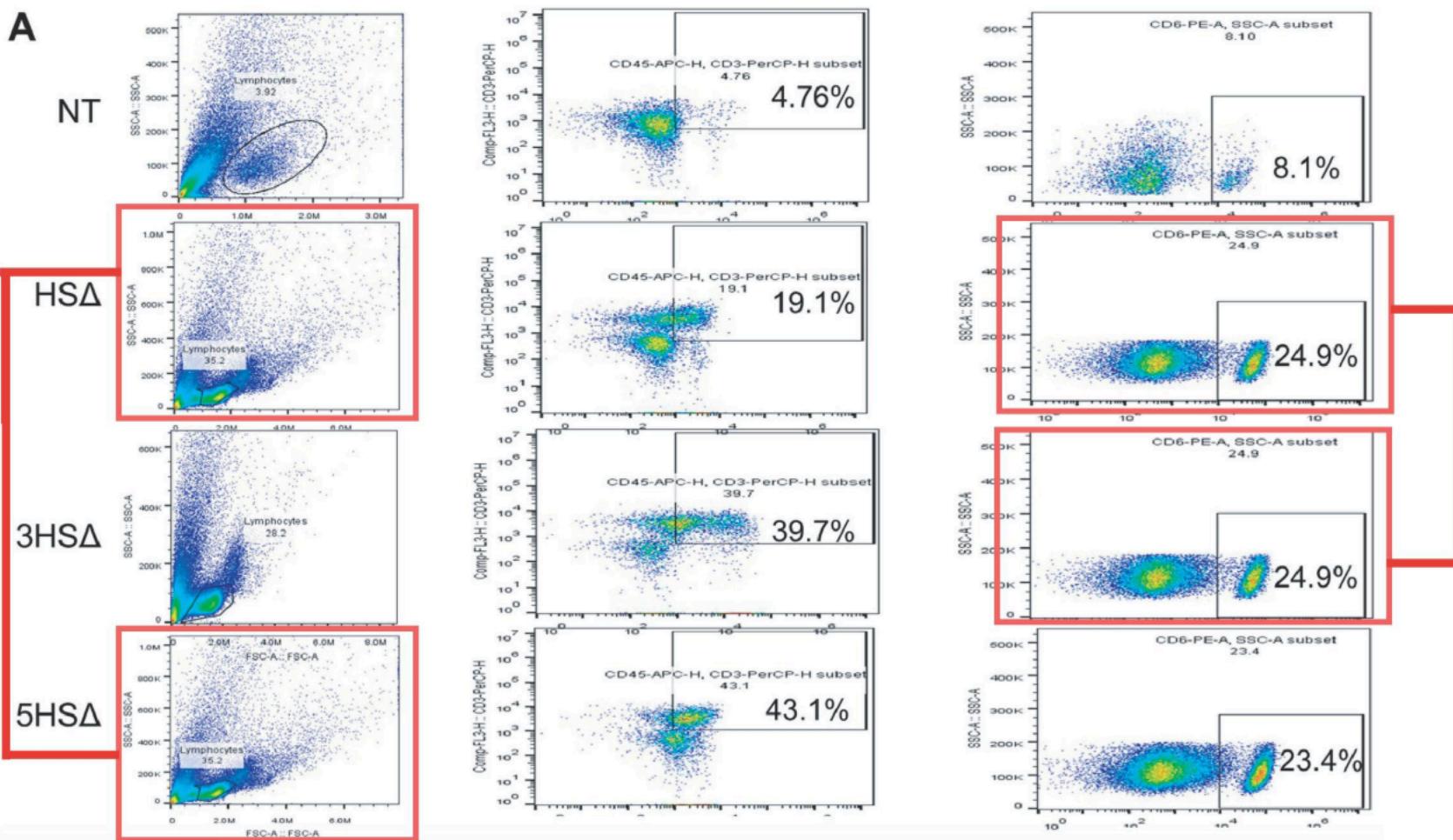
#focal adhesions/cell



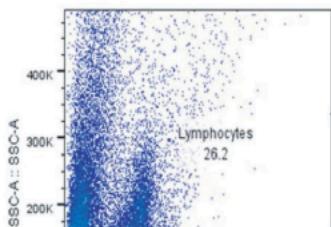
area of spreading



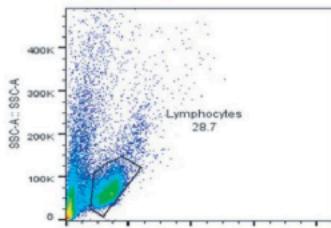
Supplemental Figure 6A



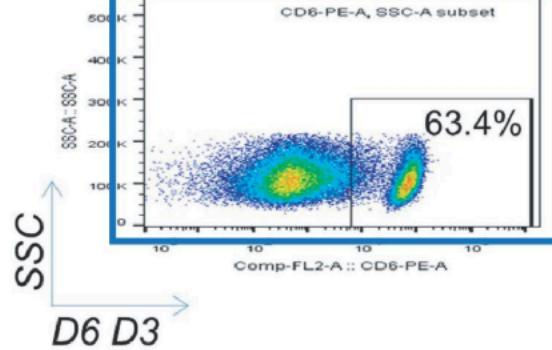
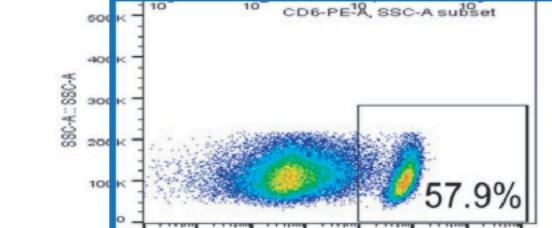
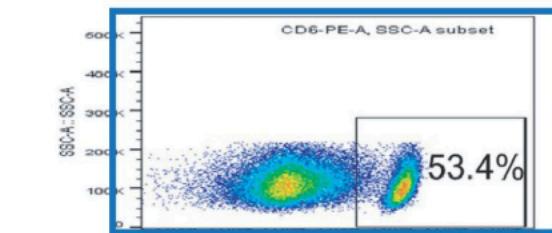
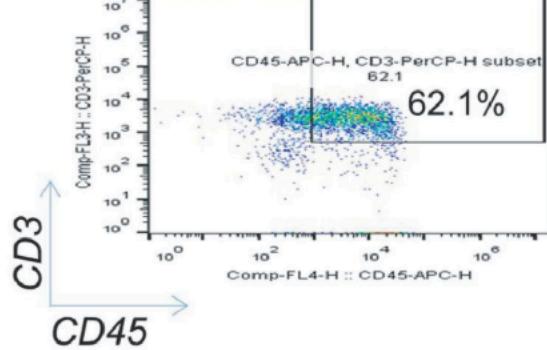
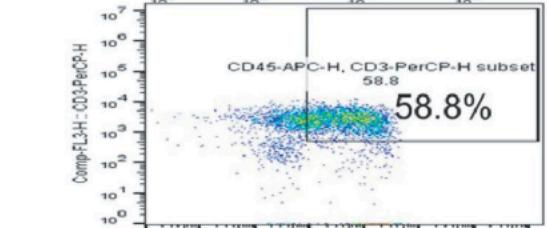
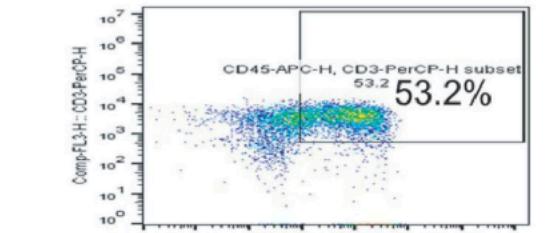
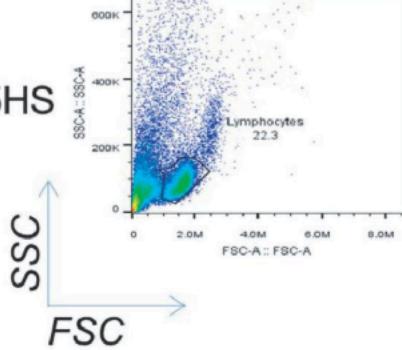
HS



3HS



5HS



CD3
CD45

D6 D3

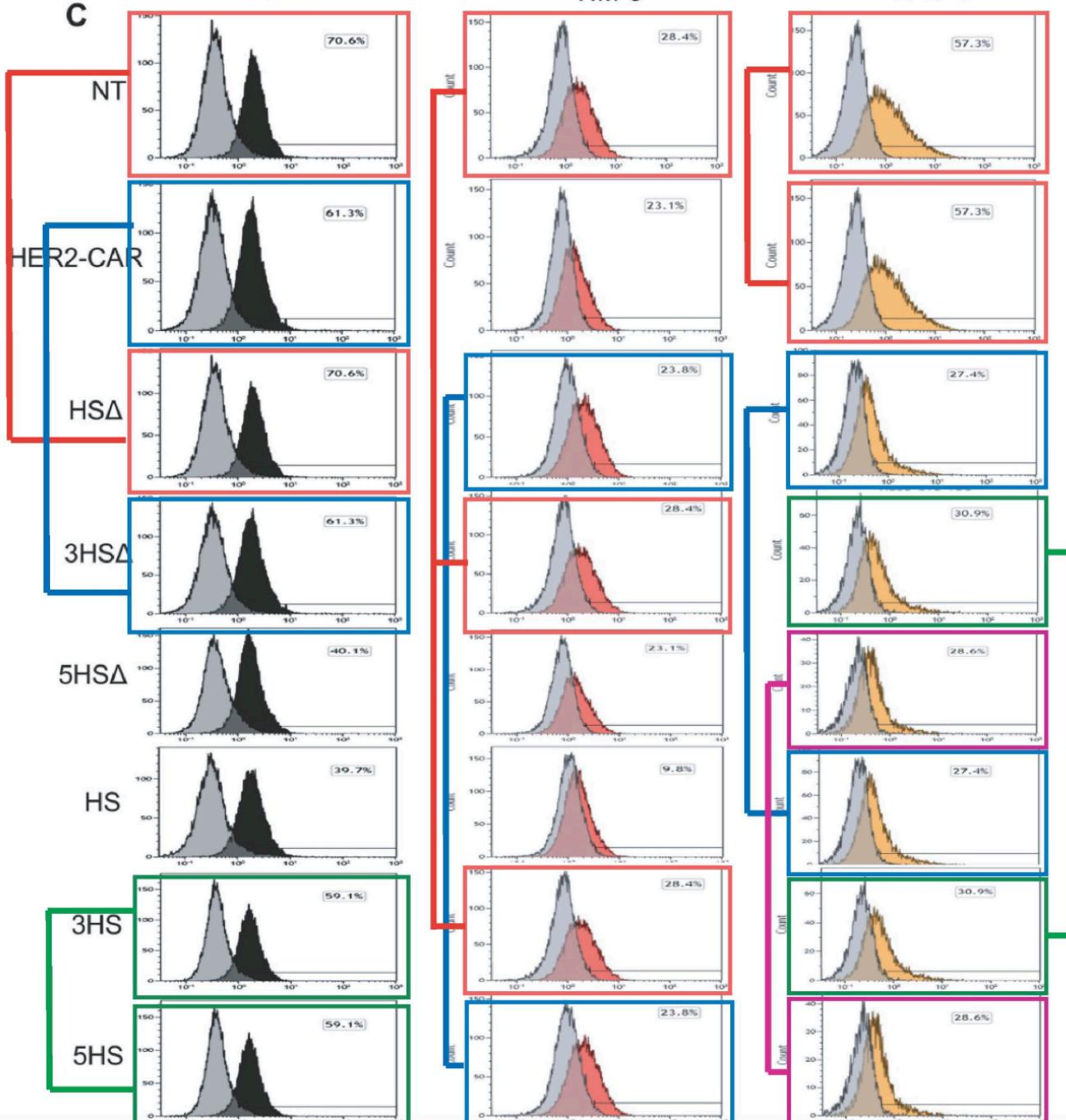
Supplemental Figure 8C

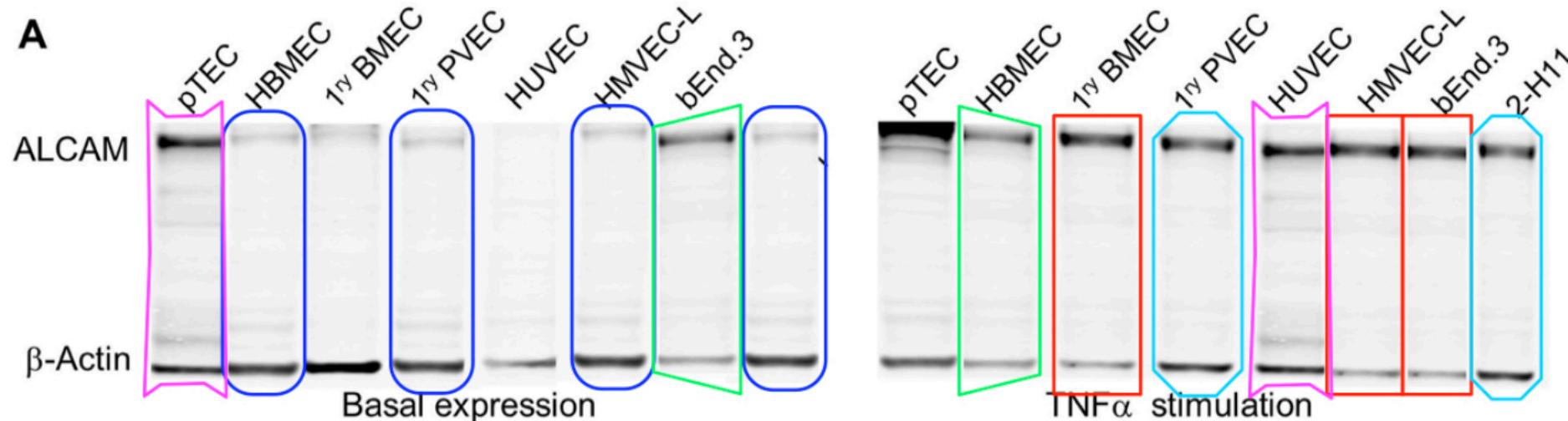
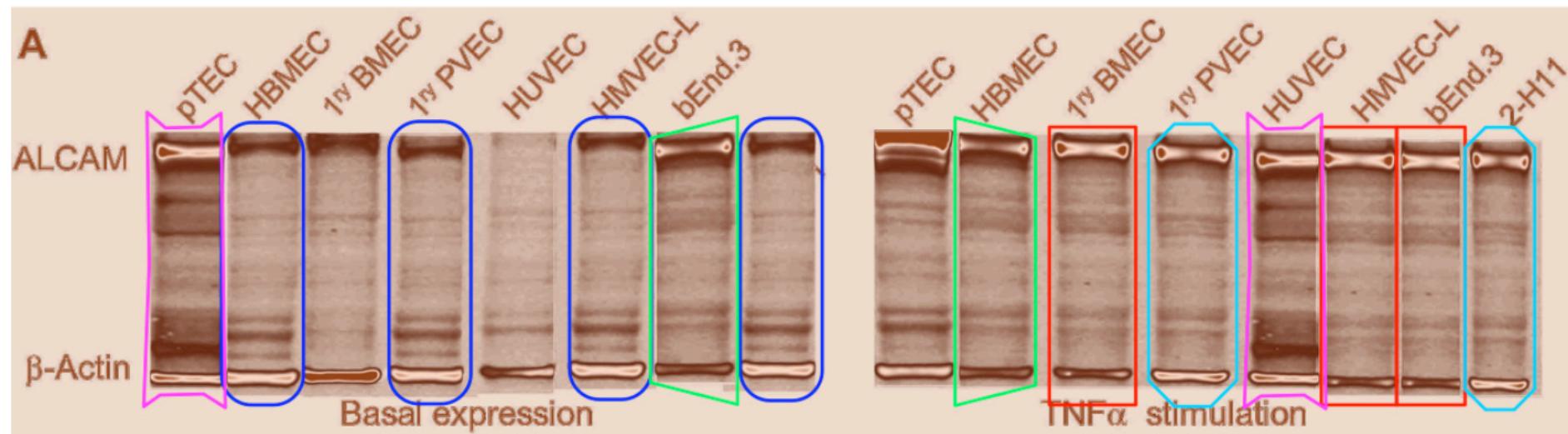
PD-1

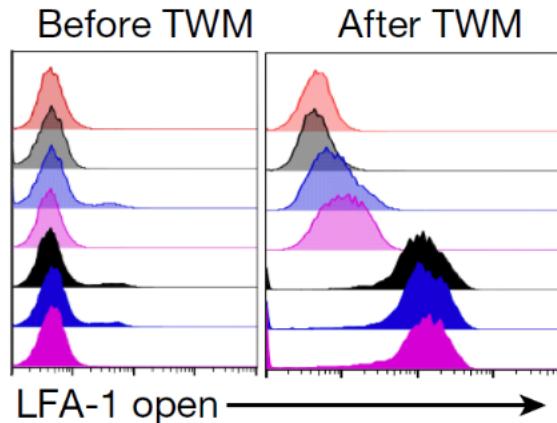
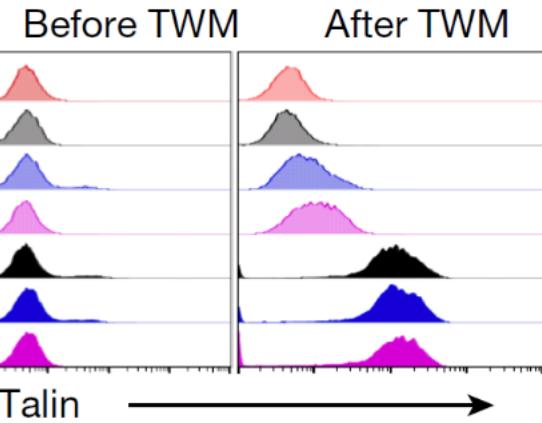
TIM-3

LAG-3

C



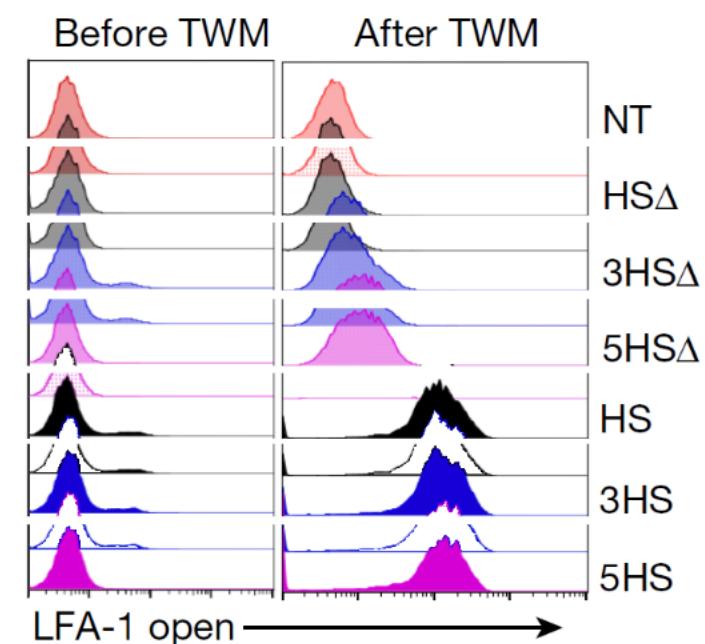
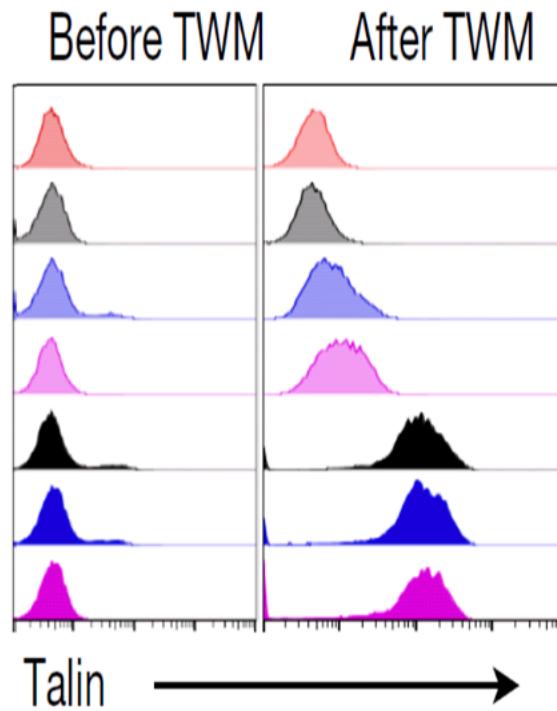
A**A**



NT
HS Δ
3HS Δ
5HS Δ
HS
3HS
5HS



170% stretch vertically



NT
HS Δ
3HS Δ
5HS Δ
HS
3HS
5HS