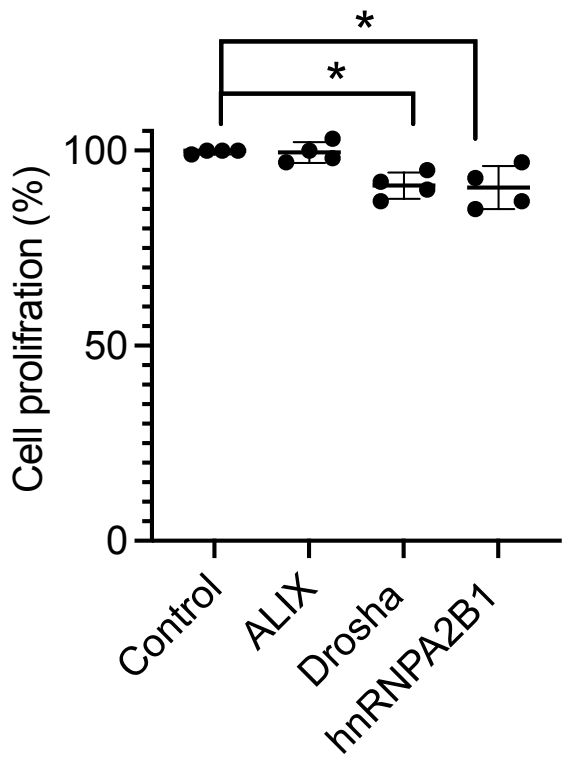

Figure S1- Dot plot showing the change in cell density following 48 hours of control siRNA, ALIX or Drosha or hnRNPA2B1 siRNAs. Scatter plots represent a mean ± standard deviation (SD). n = 4 per group. <0.0001, One-way ANOVA was use for comparison of multiple group and Student's T test was used for pairwise comparison. *$p < 0.05$.

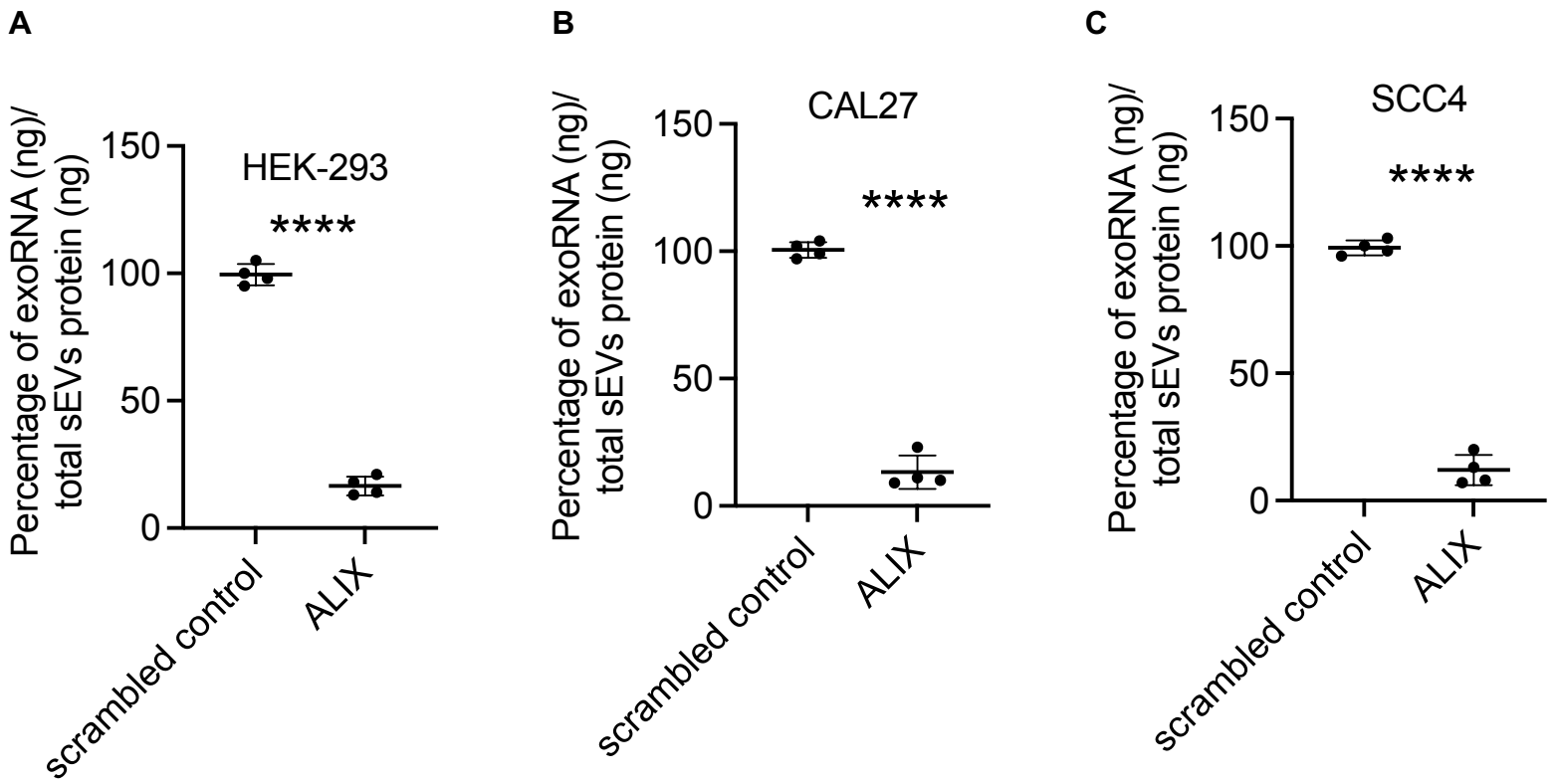

Figure S2- (a-c) Percentage change of total exo-RNA (ng) normalized based on the protein in sEVs, isolated from siRNA silenced ALIX HEK-293, CAL27 and SCC4 cells. Dot plots represent a mean ± standard deviation (SD). Student's T test was used for pairwise comparison. n = 4 per group. ****p < 0.0001.

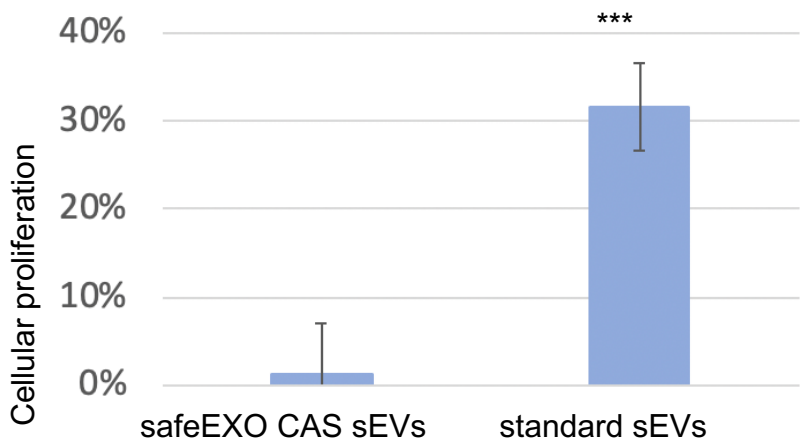

Figure S3- Bar plot showing the change in cellular proliferation following 72 hours of control administration of 25ug/ml safeEXO-CAS (derived from CAL27 after silencing Alix) and standard CAL27 sEVs. Bar graph represents mean ± standard deviation (SD). Student's T test was used for pairwise comparison. n = 4 per group. ***$p < 0.001$.

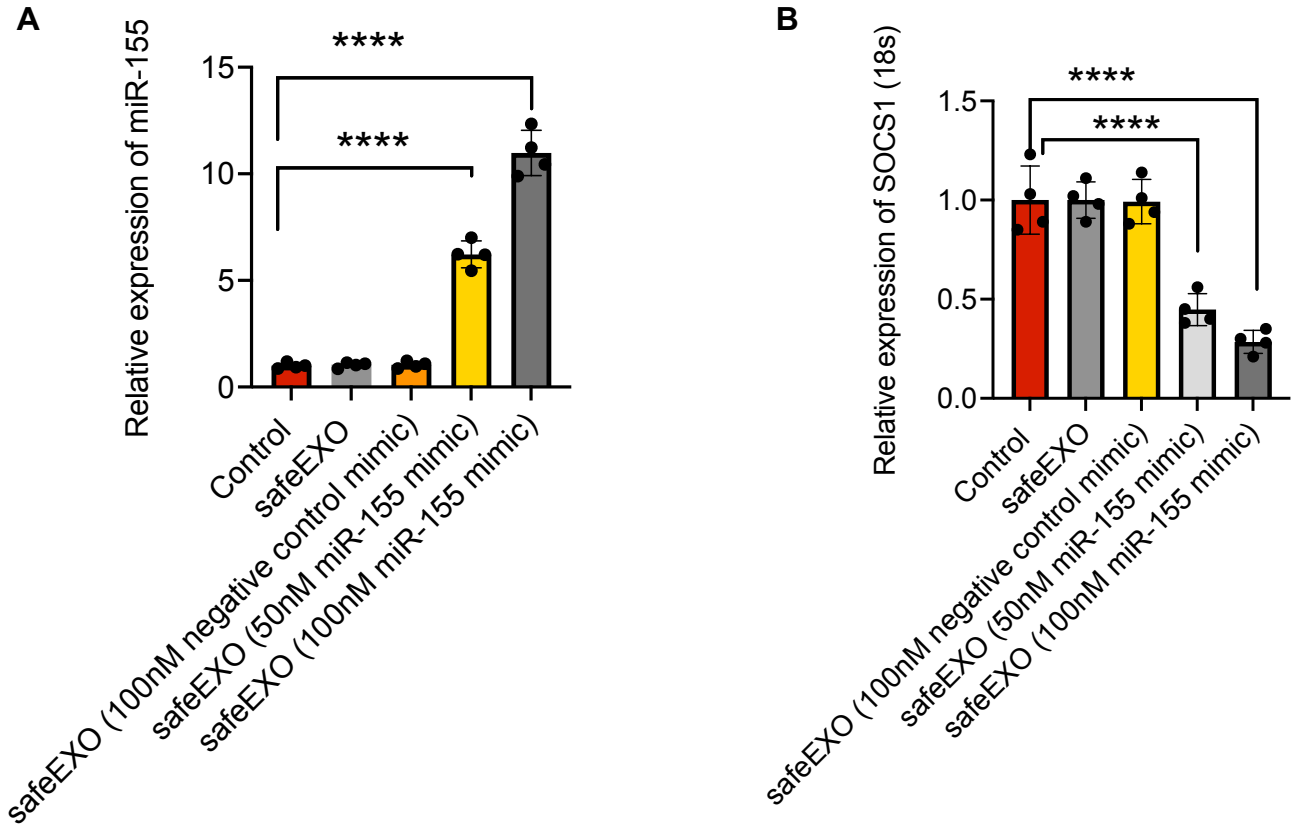

Figure S4- (a&b) Cells were seeded 1 day before treatment and different treatment conditions and controls were applied for 24 hours. Relative expression of miR-155 and miR-155 direct target (SOCS1) expression were measured by q-RTPCR. SOCS1 mRNA levels were significantly increased after exosome-mediated inhibition of miRNA-155. Cel-39 was used for normalizing miR-155. 18s was used as an internal normalizer for SOCS1. The data represents 4 independent experiments and presented as mean ± standard deviation (SD). One-way ANOVA was use for comparison of multiple group and Student's T test was used for pairwise comparison **** $p<0.0001$

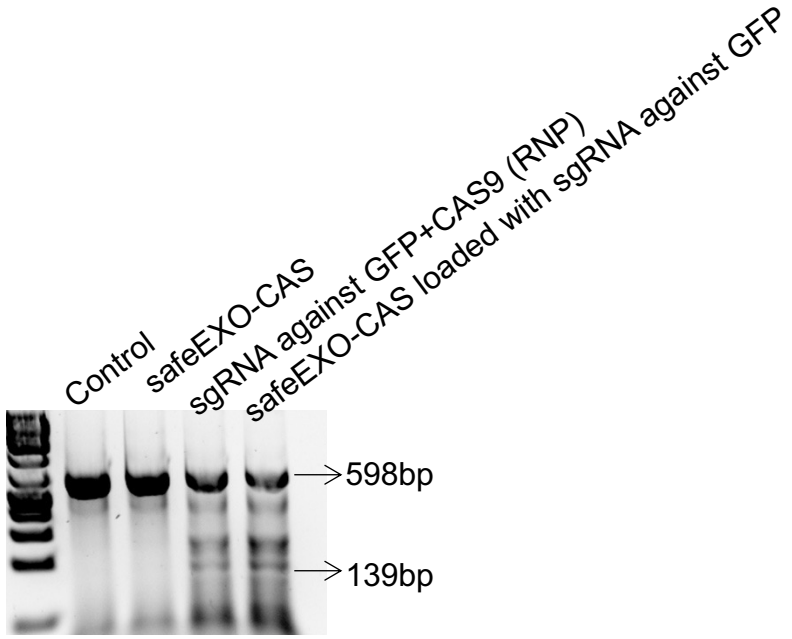

Figure S5- SafeEXO-CAS-mediated non-homologous end joining (NHEJ) genome editing. T7 endonuclease assay against the GFP in HEK-293 cells. Cells were treated with different safeEXO or safeEXO-CAS.

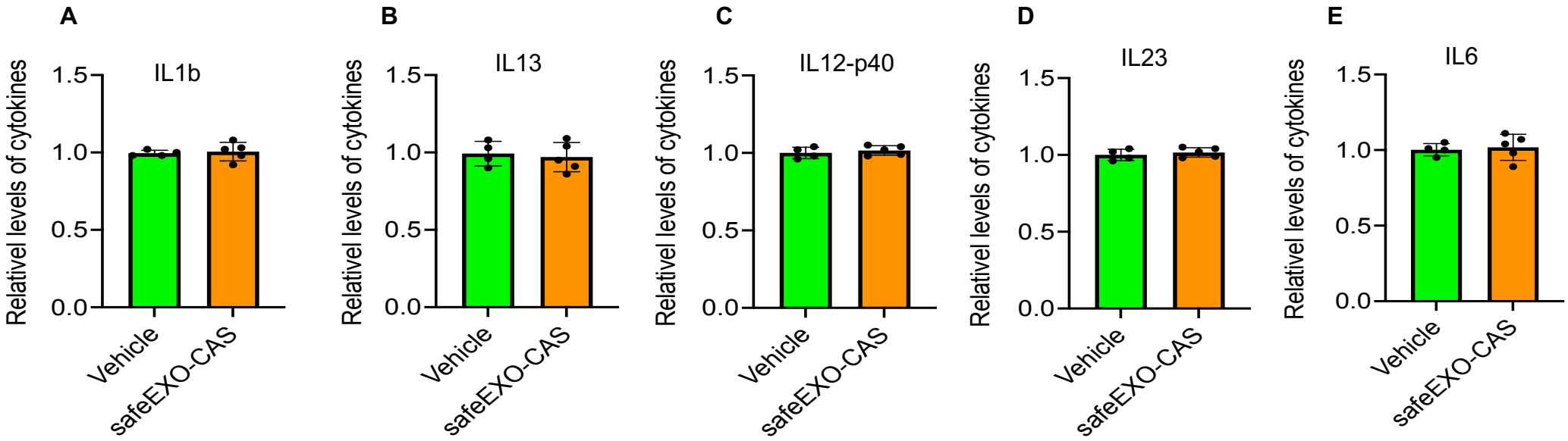

Figure S6- (a-e) The level of cytokines was identified in the mouse plasma using a LEGENDplex assay (BioLegend). The cytokine levels were normalized and presented based on the mean of the vehicle group. Data presented as mean ± standard deviation (SD). Student's T-test was used for pairwise comparison. n = 4-5 per group.

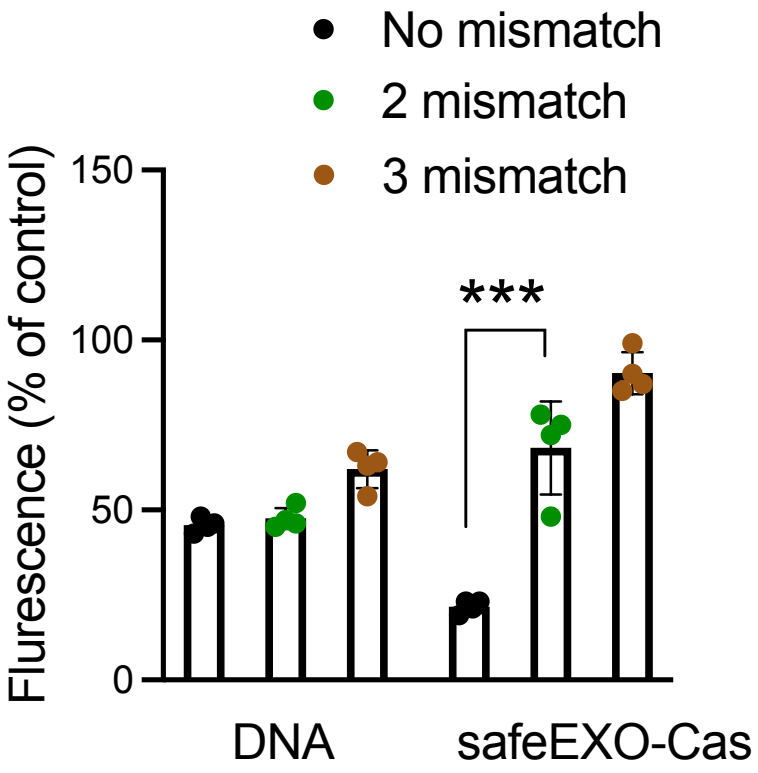

Figure S7- The off-target effect was identified in GFP reporter cell lines and gRNAs with 1-3 mismatch. Data presented as mean ± standard deviation (SD). Student's T test was used for pairwise comparison. n = 4 per group. ***p < 0.001.

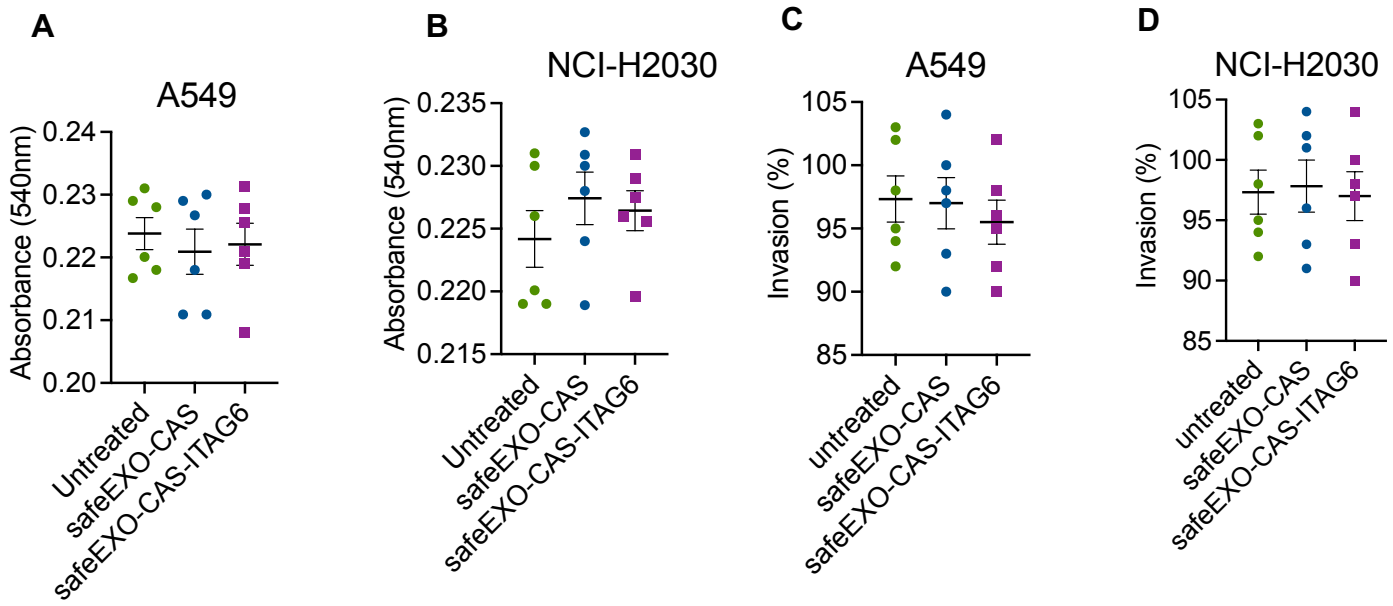

Figure S8- MTT assay (a,b) and transwell invasion assay (b,c). Detection of cell proliferation and cell migration 72h after incubation of lung cancer cell lines (A549 and NCI-H2030) with 25ug of safeEXO-CAS or safeEXO-CAS-ITGA6 in culture media. For the invasion assay, the percentage of cells was normalized based on the untreated condition. Data presented as mean ± standard error of the mean (SEM). The results are obtained from 2 independent experiments with 3 replicates each. Data were analyzed using one-way ANOVA.

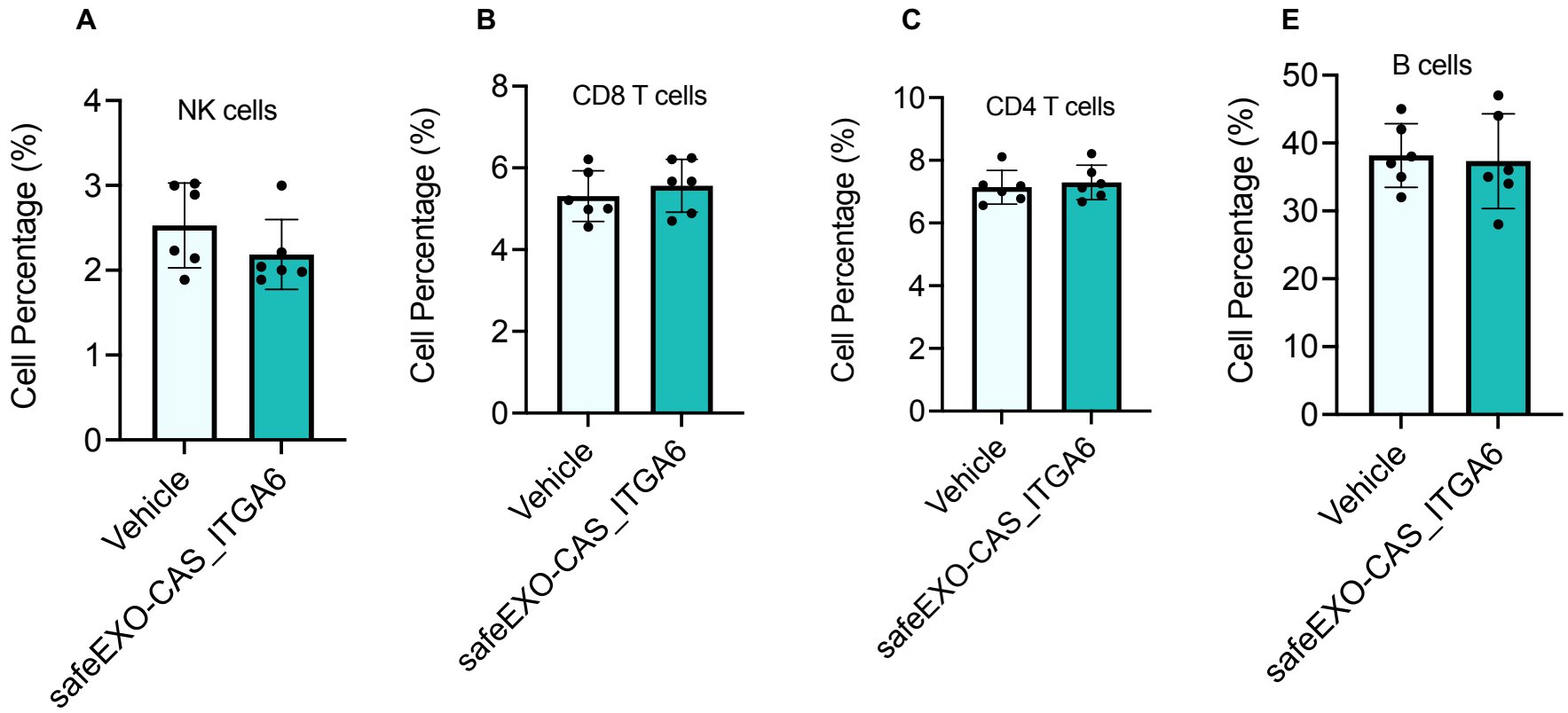

Figure S9- (a-e) Percentage of immune subtypes frequency in $CD8^{+}$T cells, B cells, monocytes, NK cells, neutrophils, and $CD^{+}4$ T cells in bone marrow (n=6 per group). Data are represented as mean ± standard deviation (SD).

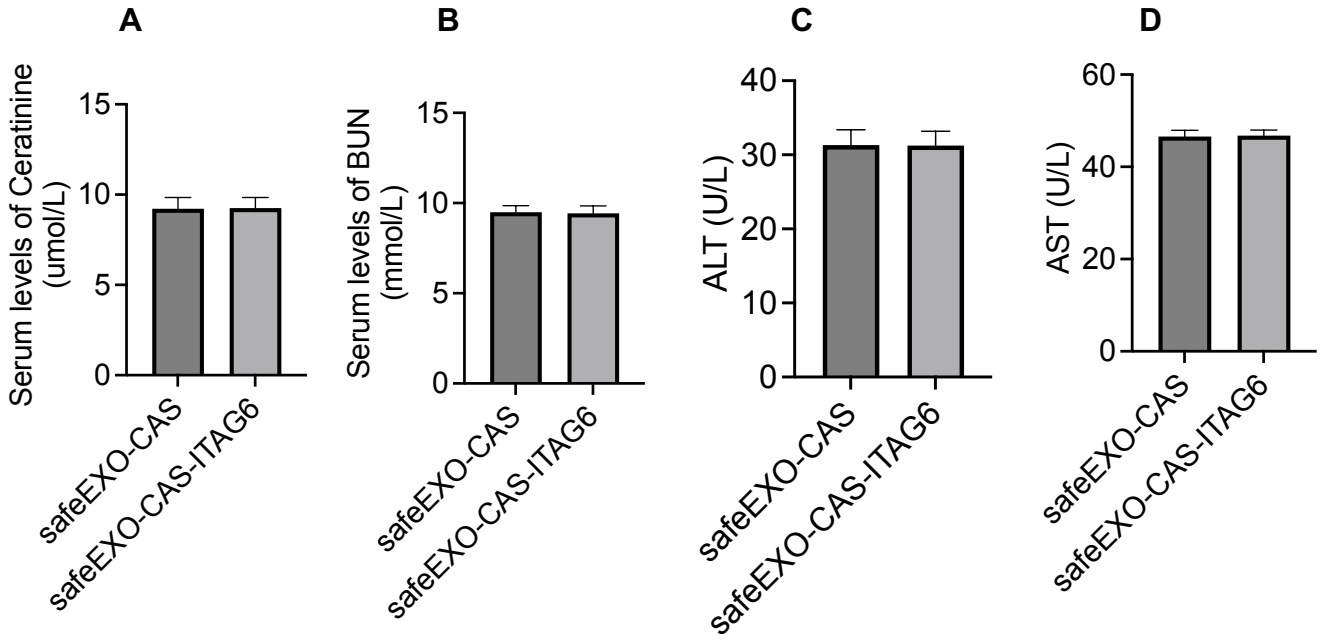

Figure S10- (a-d) Mice serum levels of Creatinine, blood urea nitrogen (BUN), ALT, and AST in safeEXO-CAS injected and safeEXO-CAS-ITGA6 treated mice. (N=4 per group)

Table S1- Mice toxicology panel (3 mice included in every comparison)

	Vehicle mice	Vehicle mice	Vehicle mice	safeEXO-CAS injected mice	safeEXO-CAS injected mice	safeEXO-CAS injected mice	P-value
Phosphorus	7.2	7.6	7.4	7.6	7.7	7.6	ns
Uric Acid	1.9	1.9	1.8	1.9	1.9	1.9	ns
Calcium	6	6.1	5.9	5.8	6	5.9	ns
Glucose	99	98	98	99	98	97	ns
Total Protein	3.2	3.2	3.1	3.1	3.2	3.2	ns
Albumin	1.6	1.6	1.7	1.7	1.7	1.7	ns
ALP	146	145	155	149	147	147	ns

ns: non-significant