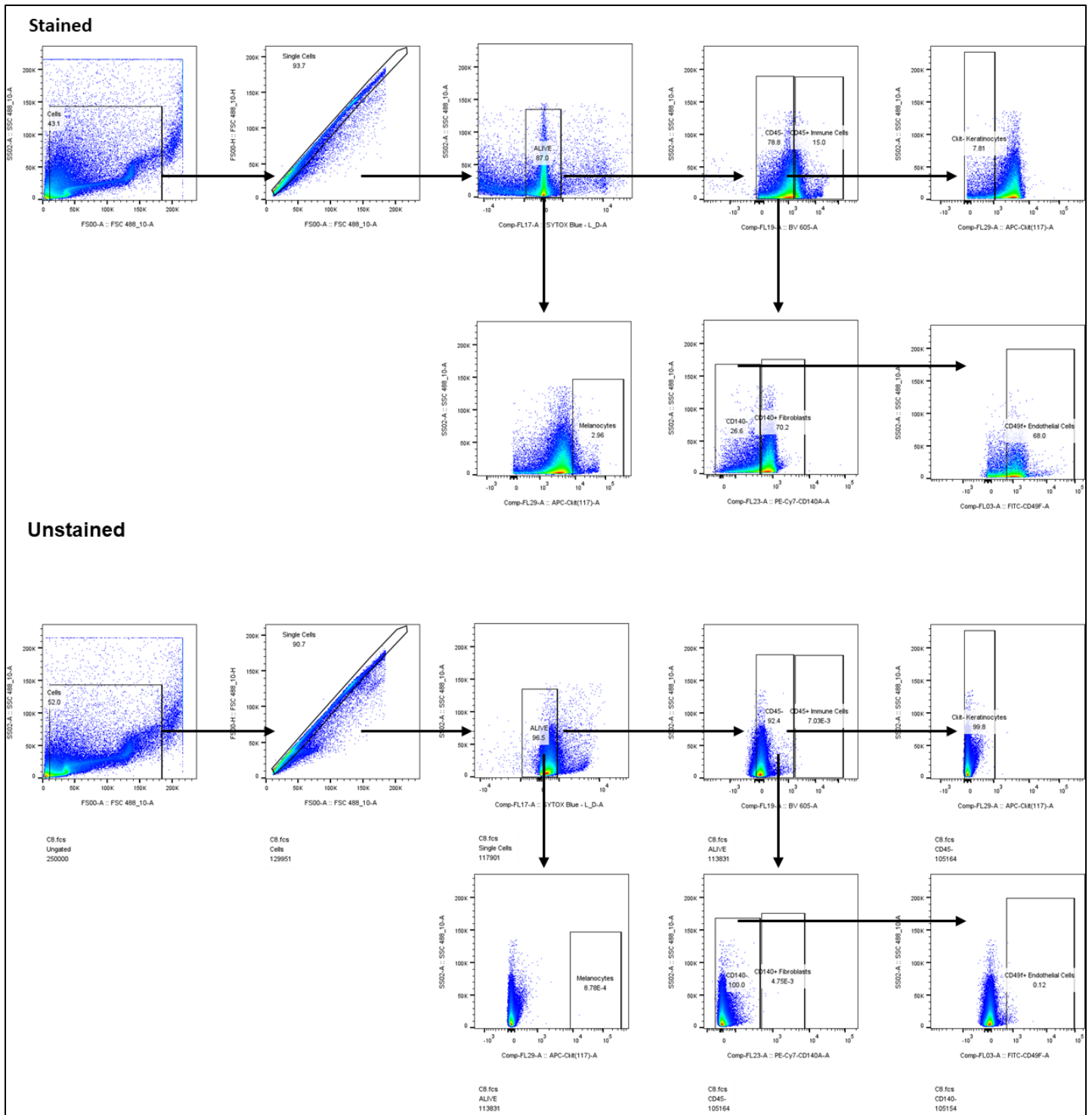
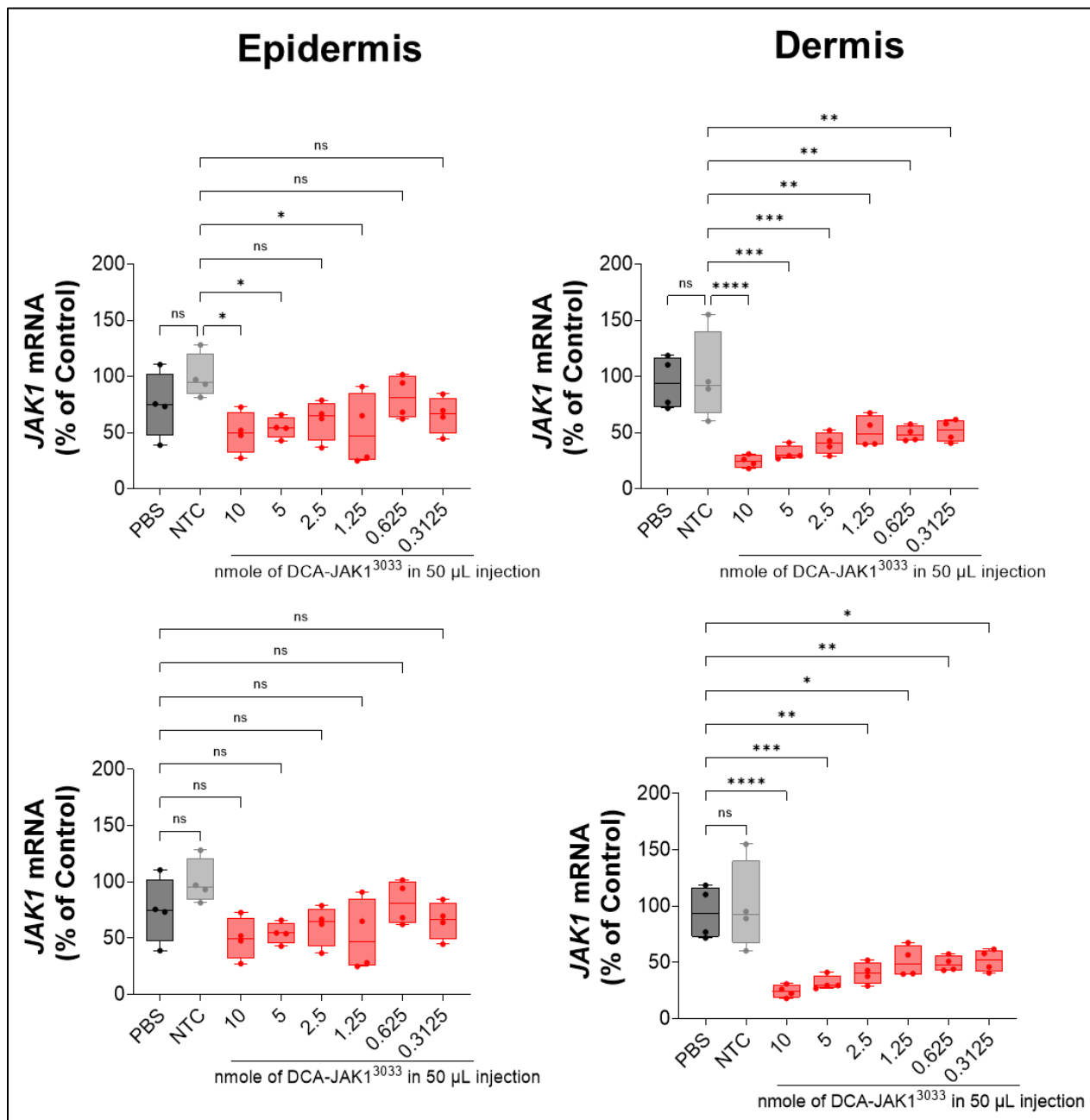


Supplementary Information:

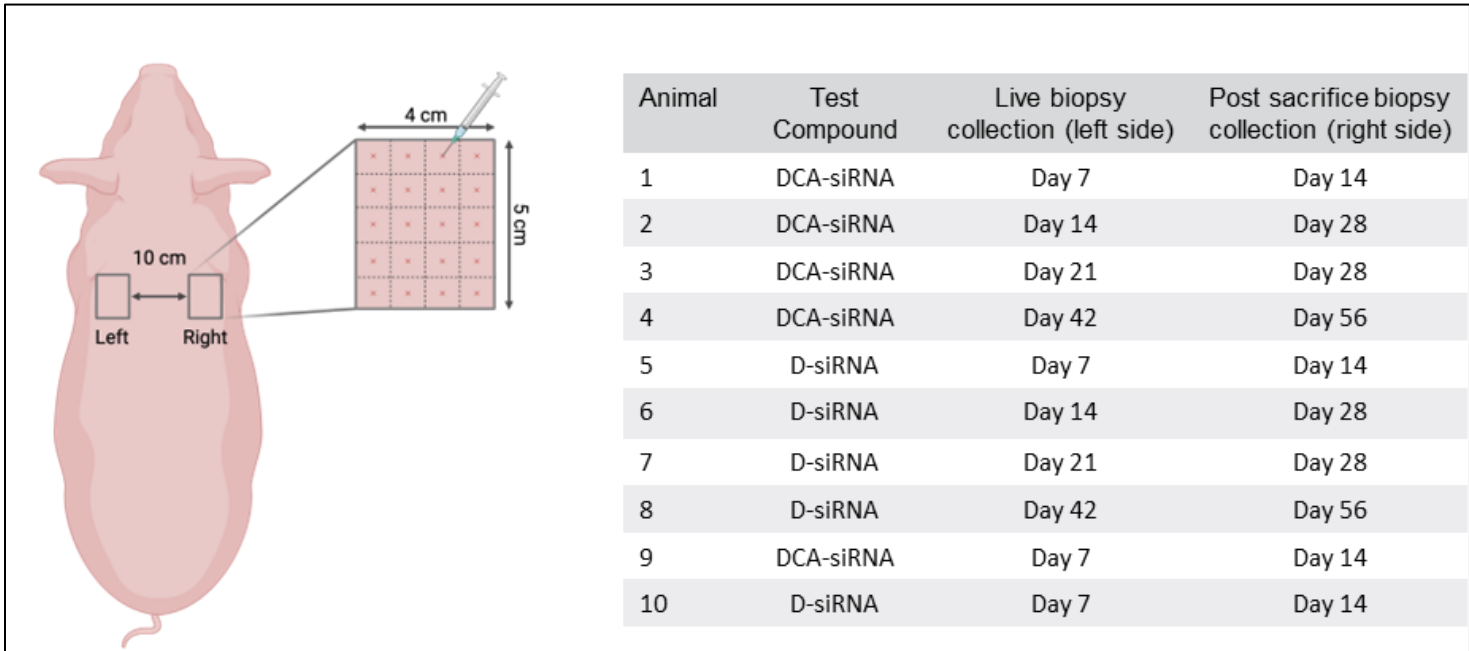


Supplementary Figure 1 Flow cytometry gating strategy used to distinguish major cell types in human skin. Detailed methodology and antibody information is provided in the methods section.

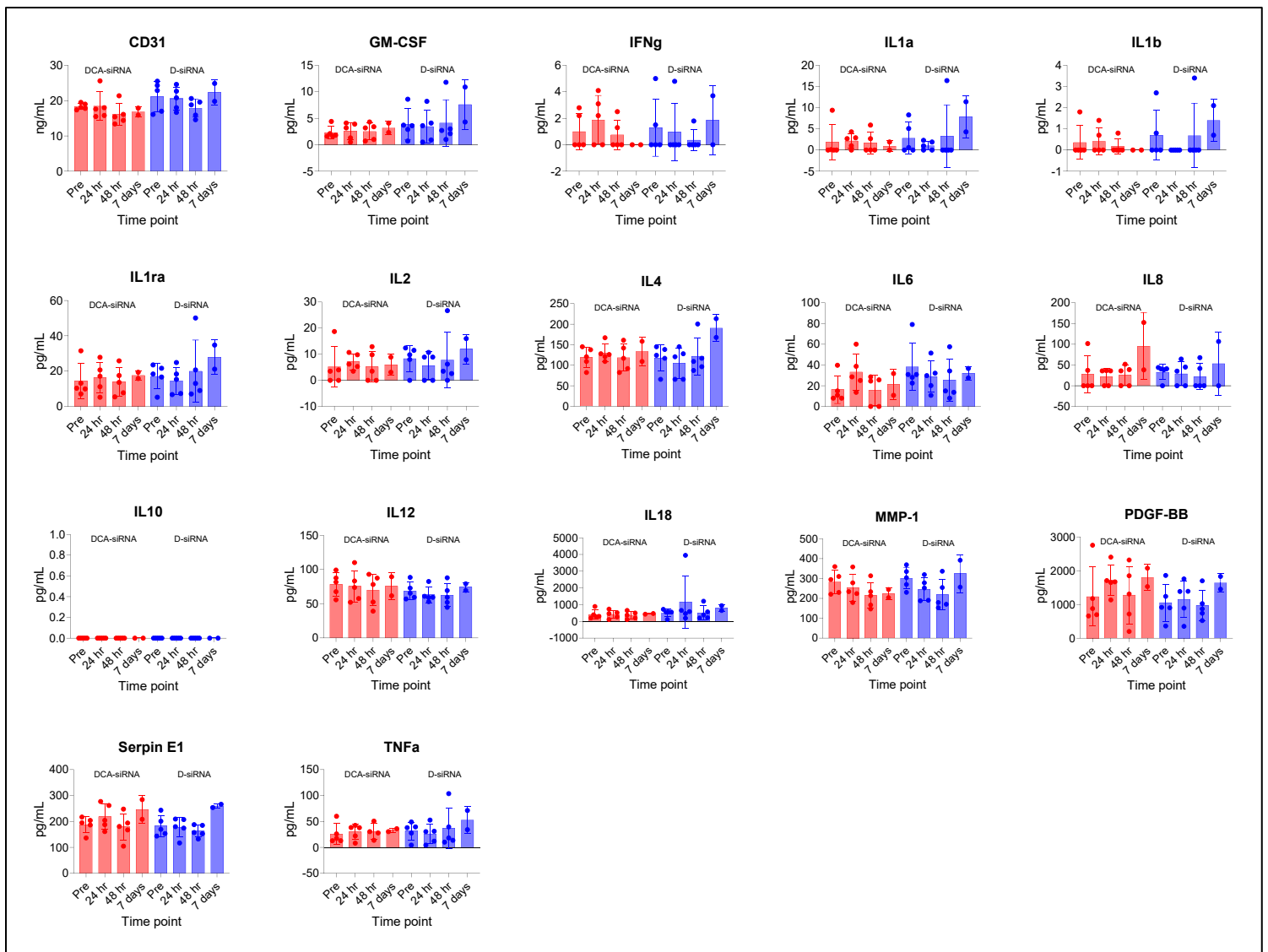


Supplementary Figure 2 Dose-dependent silencing of JAK1 mRNA in human skin biopsies. Following four days of incubation, skin punch biopsies (n=4) were separated, and JAK1 mRNA expression was quantified using a Quantigene bDNA assay. Statistical analysis showed in comparison to NTC and PBS. Data were normalized to the housekeeping gene (ACTB) and displayed as a percentage of non-targeting control siRNA (NTC).(n=4 8mm biopsies/sample; various volumes depending on the dose from a stock of 200 μ M siRNA/biopsy;; one-way

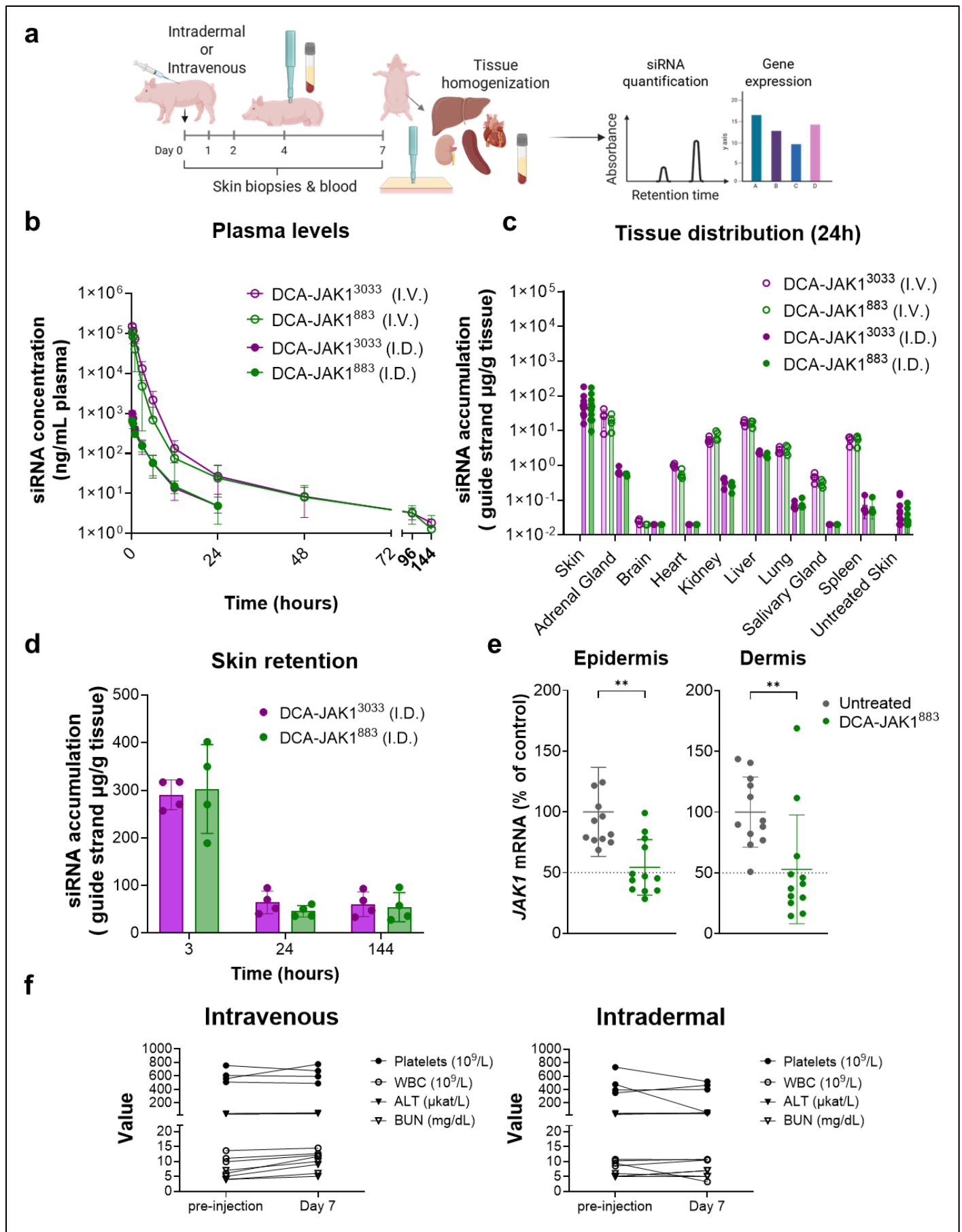
ANOVA, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; ns, not significant; all data are presented as mean value +/- standard deviation) (mRNA quantification was via Quantigene 2.0 assay). Source data are provided as in Source Data file.



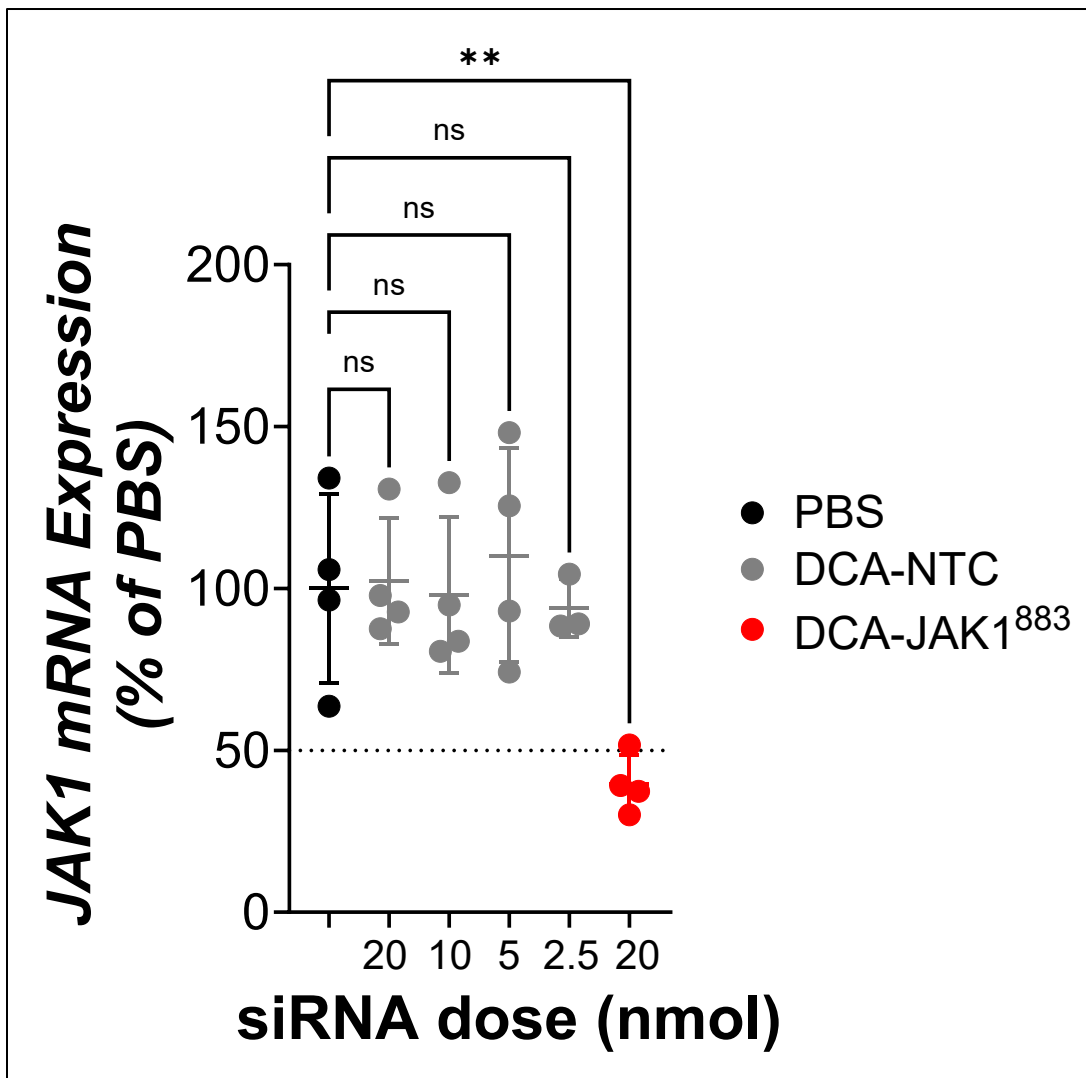
Supplementary Figure 3. Detailed study design for pharmacokinetics and accumulation of D-siRNA and DCA-siRNA following intradermal injection in pig. Two 20 cm² (5 × 4 cm) zones were marked on the backs of 10 animals, creating 40 injection sites per animal. Each site was intradermally injected with 50 µL of 200 µM DCA-JAK13033 or D-JAK13033 as shown in the table above. Skin punch biopsies (0.5 cm diameter, ~0.5 cm deep) were collected from the left side of anaesthetized animals on days 7, 14, 21, or 42. Animals were euthanized on days 14, 28, or 56 for the collection of right-sided skin punch biopsies, as well as heart, spleen, liver, and kidney samples. Elements of this figure were created in Created in BioRender. FakiH, H. (2025) <https://BioRender.com/pl0rnzu>.



Supplementary Figure 4. Cytokines and Interleukins measured following intradermal injection of D- and DCA-JAK1³⁰³³ siRNAs in pigs. Blood samples were collected pre injection and on days 1, 2, and 7 (post injection), followed by serum separation and analysis on Porcine 17-plex Discovery Panel. Specific study design is detailed in Figure 3 and Supplementary Figure 3. N=2 or n=5 per timepoint (due to euthanasia of some animals at various timepoints)



Supplementary Figure 5. Pharmacokinetics and pharmacodynamics of DCA-conjugated siRNA in pigs, showing no difference between human targeting JAK1³⁰³³ and pig targeting JAK1⁸⁸³. **a** Scheme of intradermal (I.D.) or intravenous (I.V.) injection of human- targeting JAK³⁰³³ or pig-targeting JAK1⁸⁸³ DCA-siRNAs into pigs with biopsies (plasma, skin, organs) collected over time to quantify siRNA in circulation, skin retention, tissue distribution and gene silencing. **b** siRNA plasma levels over time following intradermal or intravenous injection up to 7 days post injection (n=4 pigs/group). **c** siRNA distribution to tissues following I.D. or I.V. injection (n=4 pigs/group, with n=12 skin biopsies/group – 3 biopsies/pig, no siRNA was detected in skin in the I.V. group). **d** siRNA retention in skin following intradermal injection (n=4 pigs/group, 1 biopsy/pig). **e** mRNA silencing of JAK1 in pig skin 7 days post I.D. injection of only JAK1⁸⁸³ siRNA (n=3 biopsies/pig, n=4 pigs, total of n=12 skin biopsies/group). **f** Platelets, white blood cell count (WBC), ALT and BUN levels in pigs over time following IV and ID injections of DCA-JAK1. (all skin biopsies are 8mm; 50 µl of 400 µM siRNA/1cm² site; 20nmol final dose/biopsy; one-way ANOVA analysis for E., *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; ns, not significant; all data are presented as mean value +/- standard deviation). (siRNA accumulation in plasma, tissue and skin was quantified via LC-MS/MS; mRNA quantification was quantified via Quantigene 2.0 assay). Source data are provided as a Source Data file). Elements of this figure are created in BioRender. Fakhri, H. (2026) <https://BioRender.com/iu0wv7a>.



Supplementary Figure 6 NTC-DCA-siRNA and PBS do not impact expression of JAK1 in ex vivo pig skin.

Intradermal injection of PBS, multiple DCA-NTC doses and DCA-JAK⁸⁸³ into ex vivo pig skin with mRNA silencing of JAK1 measured 4 days post (n=4 biopsies/group). (all skin biopsies are 8mm; 50 µl of 400 µM siRNA/1cm² site; 20nmol final dose/biopsy at highest dose, with decreasing amounts for NTC; one-way ANOVA analysis for E., *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; ns, not significant; all data are presented as mean value +/- standard deviation). (mRNA quantification was quantified via Quantigene 2.0 assay). Source data are provided as a Source Data file.