Supplementary Material and Methods

Generation of SNAs

Liposomes were synthesized using a high-pressure homogenizer (Avestin, Ottawa, OH) set to 20,000 Psi using 20 discrete passes until 20 nm liposomes were formed. The liposomes were filtered using 0.2 µm sterile filters. The liposome size was measured by dynamic light scattering using a Zetasizer Nano ZS (Malvern Instruments, Malvern, United Kingdom). The lipid concentration of the liposome solution was measured using a phosphatidylcholine assay kit (Sigma-Aldrich, St. Louis, MO). The liposome concentration was calculated using the measured phospholipid concentration, liposome diameter, and the known area of a phosphatidylcholine headgroup.

Mouse Il17ra, human IL17RA, and Scr Control (with or without Cy5) L-SNAs were synthesized by adding a 30-fold molar excess of cholesterol-conjugated oligonucleotides to 21 ± 2 nm DOPC liposomes in 1 × PBS and incubated overnight at 4 °C to obtain approximately 30 oligonucleotides per liposome. The oligonucleotides were: Mouse IL17RA Sequence: mAmGmUmCmAmUC*A*C*C*A*T*mGmUmUmUmCmU/isp18//isp18//3CholTEG/; Human IL17RA Sequence proprietary; Cy5-Scr Control Sequence: /5Cy5/mGmUmUmUmCmAC*C*A*C*C*C*mAmAmUmUmCmC/iSp18//iSp18//3CholTEG/, where mA, mG mU, mC = RNA with 2’ methoxy modification, * = phosphorothioate, iSp18 = spacer 18 (hexaethylene glycol), and 3CholTEG = 3’ cholesterol. The SNA size was measured by DLS, and the formation of the SNA was confirmed using a 0.5% agarose gel with 0.5 µg/ml ethidium bromide. The SNAs were mixed 1:1 (v/v %) with 2 × concentrated proprietary hydrogel vehicle.

Knockdown of IL17RA in human explants

Normal human abdominoplasty skin was collected and was dissected to mid-dermis within 8 hours using a dermatome (Zimmer Biomet, Warsaw, IN). The collection of otherwise discarded abdominoplasty tissue was approved by the Northwestern University Institutional Review Board. The explants were treated topically with 30 μM Cy5-labeled L-SNA for 24 hours prior to embedding in optimal cutting temperature (OCT) and assessed by immunofluorescent microscopy. For quantifying knockdown in the tissue, the skin was cut into 3 cm diameter disks and mounted in 1 cm diameter jacketed Franz diffusion chambers (Laboratory Glass Apparatus, Berkeley, CA). Receptor chambers were filled with culture medium as described (Lenn et al., 2018). And the water jacket was set to 32 ˚C. The SNAs and vehicles were applied topically using positive displacement pipets (Rainin, Emeryville, CA) such that the gels were evenly distributed over the skin surface. The donor chamber lids were sealed to prevent drying during the 24 hour dosing period. After the skin disks were removed from the Franz cells, three 4-mm punch biopsies were collected from each dosed area for immediate processing or storage in RNALater (ThermoFisher Scientific Waltham, MA). The biopsies were homogenized using a Beadruptor 12 homogenizer (Omni International, Kennesaw, GA), and the total RNA was extracted using the Rneasy 96-Kit (Qiagen, Germantown, MD). cDNA was synthesized using a High-Capacity cDNA Reverse Transcription Kit with Rnase Inhibitor (ThermoFisher Scientific). The samples were analyzed referencing glyceraldehyde 3-phosphate dehydrogenase expression as the normalization factor.

Quantitative real-time-PCR (qRT-PCR) analysis

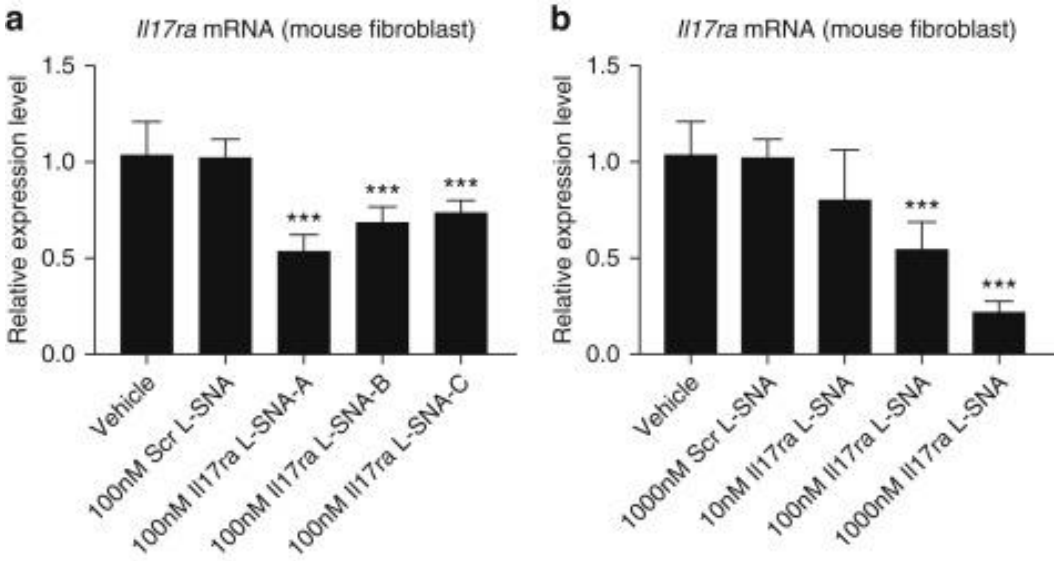
Frozen mouse tissue was homogenized using an Omni Bead Ruptor (Omni International) for 3 minutes, and the tissue extract was centrifuged at 1,000 rpm. The total RNA was extracted using the RNeasy Mini Kit (Qiagen). The gene expression was quantified using pre-designed primers purchased from Integrated DNA Technology(Integrated DNA Technology, Coralville, IA) (Mouse: *Tnfa,* Mm.PT.58.12575861; *Il17ra,* Mm.PT.53a.17621116; *S100a7a,* Mm.PT.58.41637317; *Defb4,* Mm.PT.58.29993789; *Pi3,* Mm.PT.58.43208182; *Il17c,* Mm.PT.58.30030128; *Krt1,* Mm.PT.58.42223107; *Lor,* Mm.PT.58.12882060; *Gapdh,* Mm.PT.39a.1; *Rplp0,* Mm.PT.58.43894205. Human: *TNFA,* Hs.PT.58.45380900; *S100A7,* Hs.PT.58.2437923.g; *DEFB4,* Hs.PT.58.40718840; *PI3,* Hs.PT.58.40210702.g; *IL17C,* Hs.PT.58.1093657; *KRT10,* Hs.PT.58.38635764; *LOR,* Hs.PT.58.27761511; *GAPDH,* Hs.PT.39a.22214836; *RPLP0,* Hs.PT.39a.22214824) and ThermoFisher (Thermofisher Scientific) (*IL17RA,* Hs01064648_m1). All the samples were analyzed using the average of glyceraldehyde 3-phosphate dehydrogenase and 60S acidic ribosomal protein P0 expression for normalization.

Immunoblotting

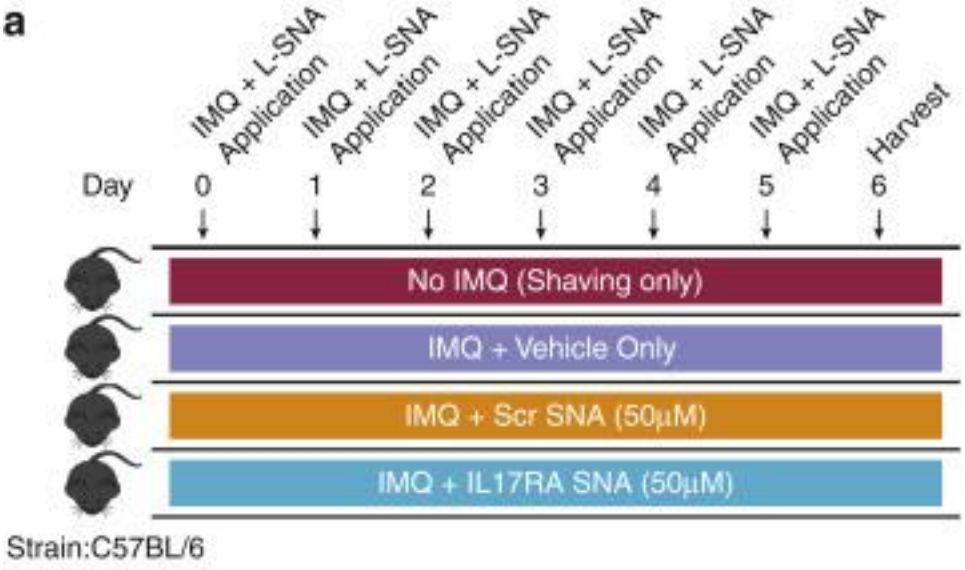
The mouse skin was homogenized in RIPA buffer (10 nM Tris-Cl (pH 8.0), 1 mM EDTA, 1% Triton X-100, 0.1% sodium deoxycholate, 0.1% SDS, 140 mM NaCl, and 1 mM PMSF), and the lysate was loaded onto SDS-PAGE gels (Mini-PROTEAN TGX Stain Free Gels, Bio-Rad, Hercules CA) per standard protocol. Anti-Il17ra and -Gapdh antibodies were purchased from Thermofisher Scientific.

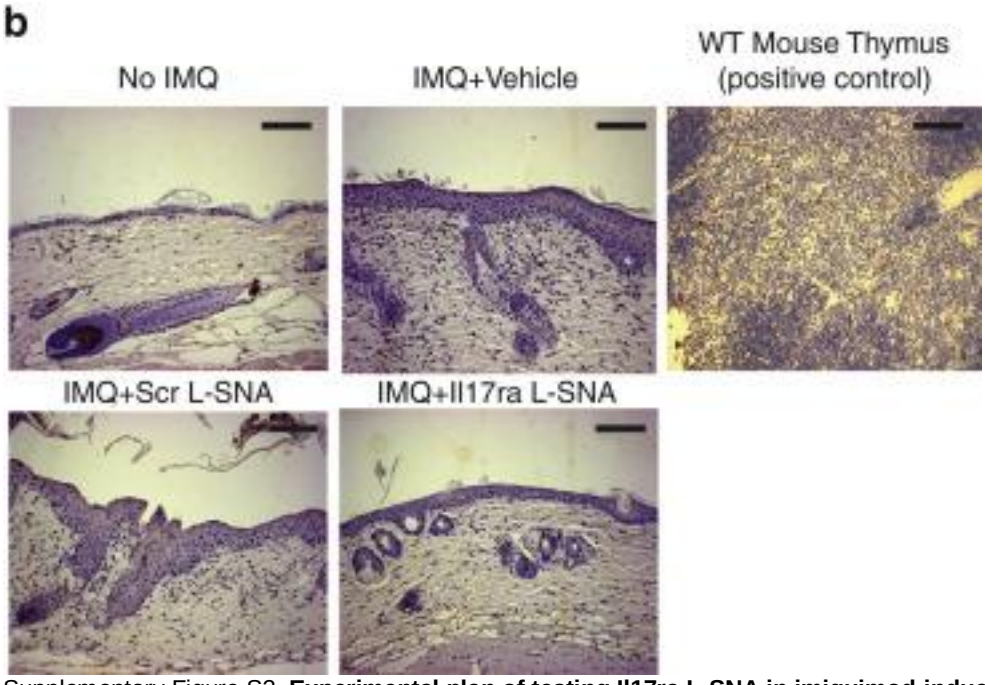
Image analysis

Quantification of the epidermal thickness and number of Ki67-positive cells was performed by three blinded reviewers using the HistoQuest image analysis software (Tissuegnostic Image Solutions, Vienna, Austria). Twelve fields were viewed for each sample.

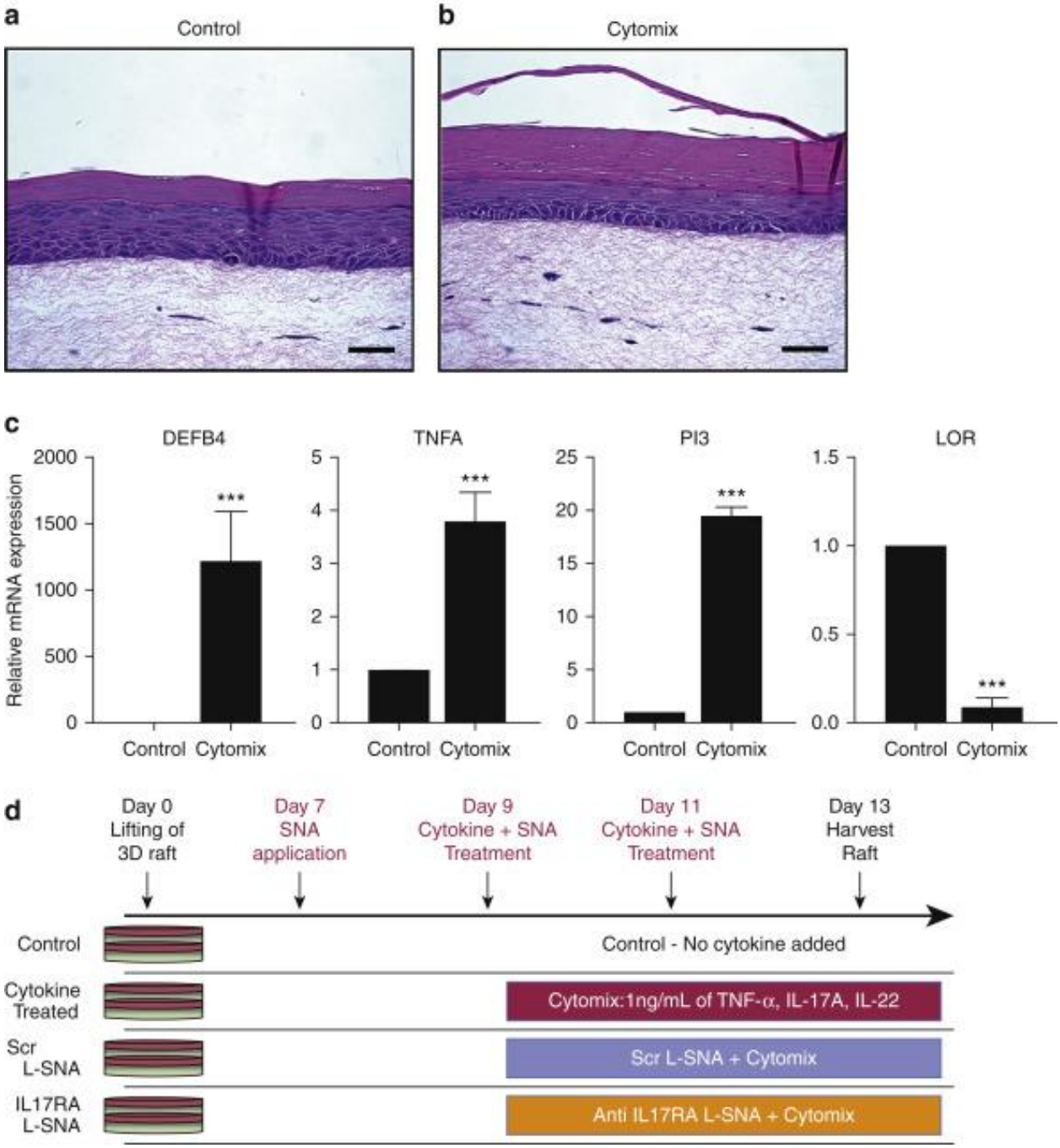


Supplementary Figure S1. **Selection of Il17ra L-SNA for in vivo studies.** Selection was based on Il17ra gene knockdown in mouse fibroblasts after 48 hours, as measured by qRT-PCR. (**a**) Three different sequences of antisense DNA L-SNAs targeting *Il17ra* were tested versus control Scr L-SNA and vehicle. (**b**) Dose-dependent reduction in *Il17a* expression by the selected L-SNA. Values reported as mean ± standard error of the mean. ***$P < 0.001$. IL17ra L-SNA, IL-17A receptor liposomal spherical nucleic acid; L-SNA, liposomal spherical nucleic acid; qRT-PCR, quantitative real-time reverse transcriptase–PCR; Scr L-SNA, scrambled liposomal spherical nucleic acid.

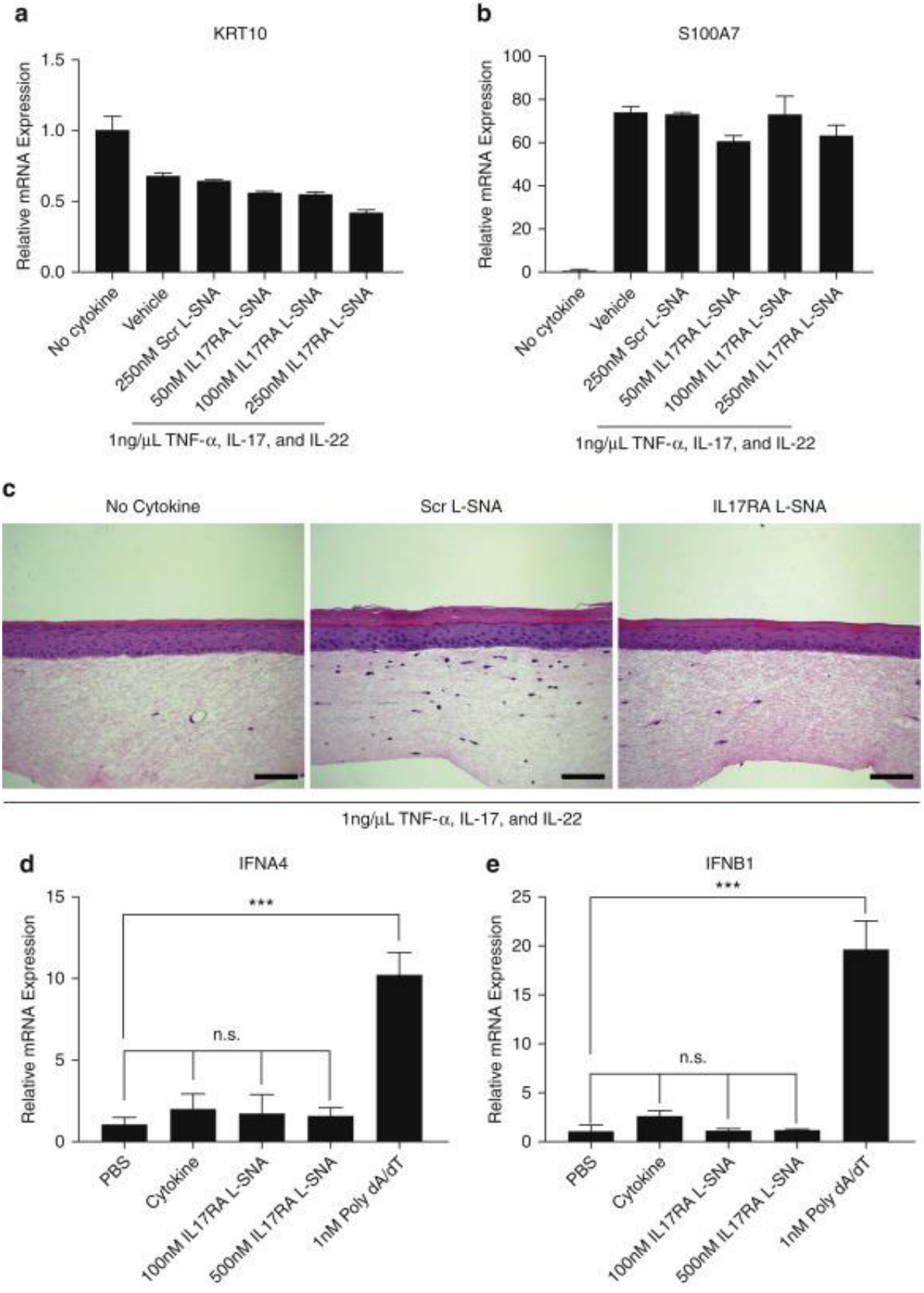




Supplementary Figure S2. **Experimental plan of testing Il17ra L-SNA in imiquimod-induced psoriatic mice.** (**a**) Schematic for testing Il17ra L-SNAs in the IMQ-treated mouse. C57BL/6 mice were treated with (or without) 62.5 mg/cm^2 imiquimod (IMQ) daily for 6 days to induce the psoriasis-like phenotype. Vehicle, 50 μM Scrambled (Scr) L-SNAs, and 50 μM Il17ra L-SNAs were applied before IMQ application to the same site. N = 6 mice per treatment group. (**b**) TUNEL staining of mouse skin harvested at day 6. WT mouse thymus tissue was used as a positive control (top right). Bars = 100 μm. IL17ra L-SNA, IL-17A receptor liposomal spherical nucleic acid; IL17RA SNA, IL-17A receptor spherical nucleic acid; IMQ, imiquimod; L-SNA, liposomal spherical nucleic acid; Scr L-SNA, scrambled liposomal spherical nucleic acid; Scr SNA, scrambled spherical nucleic acid; WT, wild-type.



Supplementary Figure S3. **Psoriasis-like 3-dimensional model and experimental plan.** (**a, b**) The psoriatic organotypic raft was generated by adding 1 ng/ml of TNF-α, IL-17A, and IL-22 to 3-dimensional raft culture medium for six days. Hematoxylin and eosin (H&E) staining of 3-dimensional organotypic rafts after 6 days of (**a**) untreated control versus (**b**) cytokine mix (Cytomix). (**c**) qRT-PCR showing the reduction of psoriasis-associated mRNA expression (*DEFB4*, *TNFA*, *PI3*, and *LOR*) mRNA expression in 3-dimensional organotypic rafts after 1 ng/ml each of TNF-α, IL-17A and IL-22 beginning 4 days before harvest. Values reported as the mean ± standard deviation of the mean. ***$P < 0.001$. (**d**) Experimental design for treating with IL17RA SNAs during 3-dimensional psoriatic organotypic raft generation. IL17RA L-SNA, IL-17A receptor liposomal spherical nucleic acid; qRT-PCR, quantitative real-time reverse transcriptase–PCR; SNA, spherical nucleic acid; Scr L-SNA, scrambled liposomal spherical nucleic acid; TNF-α, tumor necrosis factor α.


a
KRT10
Relative mRNA Expression
1.5
1.0
0.5
0.0
No cytokine
Vehicle
250nM Scr L-SNA
50nM IL17RA L-SNA
100nM IL17RA L-SNA
250nM IL17RA L-SNA
1ng/μL TNF-α, IL-17, and IL-22
b
S100A7
Relative mRNA Expression
100
80
60
40
20
0
No cytokine
Vehicle
250nM Scr L-SNA
50nM IL17RA L-SNA
100nM IL17RA L-SNA
250nM IL17RA L-SNA
1ng/μL TNF-α, IL-17, and IL-22
c
No Cytokine
Scr L-SNA
IL17RA L-SNA
1ng/μL TNF-α, IL-17, and IL-22
d
IFNA4
Relative mRNA Expression
15
10
5
0
***
n.s.
PBS
Cytokine
100nM IL17RA L-SNA
500nM IL17RA L-SNA
1nM Poly dA/dT
e
IFNB1
Relative mRNA Expression
25
20
15
10
5
0
***
n.s.
PBS
Cytokine
100nM IL17RA L-SNA
500nM IL17RA L-SNA
1nM Poly dA/dT

Supplementary Figure S4. **Human IL17RA L-SNA treatment of cytokine-induced 3-dimensional organotypic rafts.** (**a, b**) qRT-PCR showing that IL17RA L-SNA cannot reverse the reduction in *KRT10* expression or increase *S100A7* expression in cytokine-induced 3-dimensional rafts. Values reported as the mean ± standardd deviation of the mean (**c**) Hematoxylin and eosin staining of 3-dimensional organotypic rafts. Bars = 100 μm. (**d, e**) qRT-PCR showing IL17RA L-SNA did not induce IRF3-dependent activation of IFNA4 and IFNB1 expression in cytokine-induced 3-dimensional keratinocyte cell culture. One nanomolar poly dA/dT was used as the positive control. Values reported as mean ± standard deviation of the mean. ***$P < 0.001$. IL17RA L-SNA, IL-17A receptor liposomal spherical nucleic acid; n.s, not significant; PBS, phosphate buffered saline; qRT-PCR, quantitative real-time reverse transcriptase–PCR; Scr L-SNA, scrambled liposomal spherical nucleic acid; TNF-α, tumor necrosis factor α.