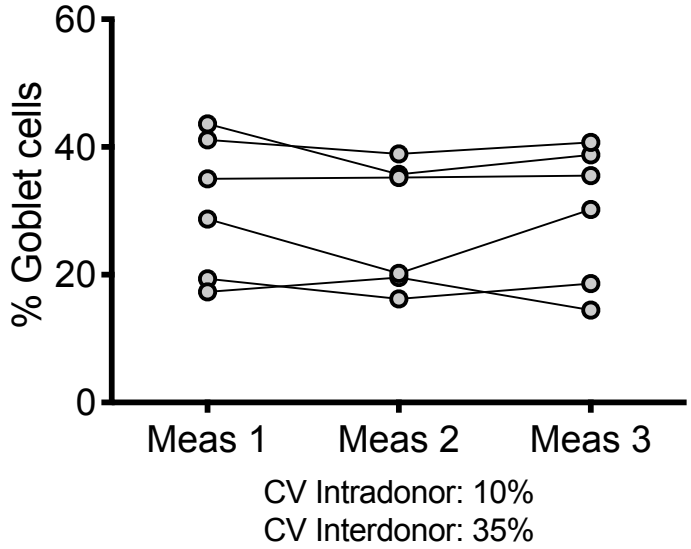
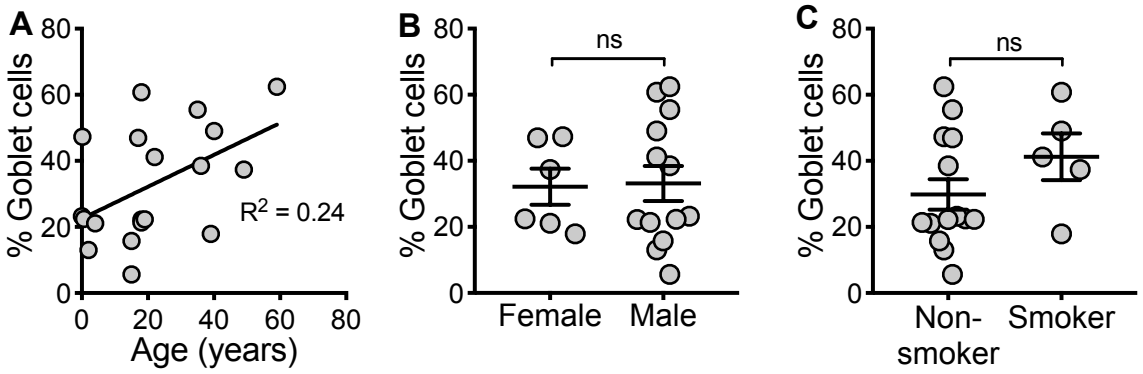
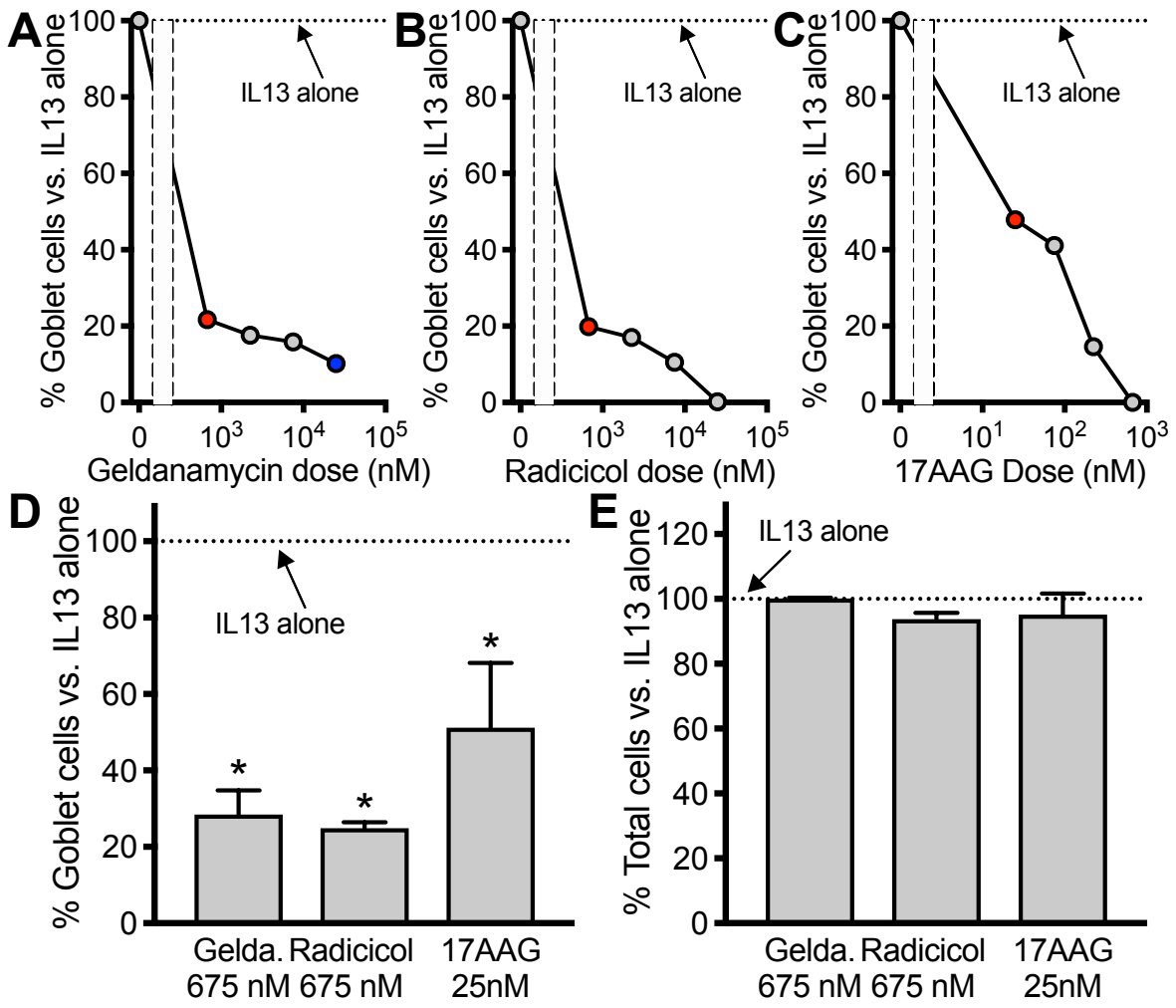


Supplementary Figure 1: **IL13-induced goblet cell metaplasia severity is donor-dependent.** Primary human airway epithelia in vitro were exposed to vehicle or 20 ng/mL IL13 for 21 days in triplicate. Immunofluorescence MUC5AC staining was performed to quantify goblet cells as a proportion of total cells. Each data point set corresponds to epithelia from a different donor (n= 6 biological replicates/donors). Coefficient of variation shown (10% intra-donor, 35% inter-donor).



<u>Supplementary Figure 2</u>: Impact of age, sex and smoking status on severity of IL13-induced goblet cell metaplasia. We evaluated the severity of IL13-induced goblet cell metaplasia in cultures from 19 individuals. Age **(A)**, sex **(B)**, and smoking status **(C)** defined as >100 cigarettes life-long or smoking at time of death are plotted. Unpaired two-tailed t-test (n=19 biological samples).



<u>Supplementary Figure 3</u>: Dose-response curves of various HSP90 inhibitors. We exposed human airway epithelia from a single donor to IL13 for three weeks with or without geldanamycin, its synthetic analog 17-AAG / tanespimycin, or the structurally unrelated HSP90 inhibitor radicicol. Dose-response curves are shown in (**A-C**). Red data points are lowest dose that induced >50% decrease in goblet cell metaplasia. Blue data point is 25 μM. Data are % goblet cells normalized to IL13 alone (100%). **D** and **E:** We exposed human airway epithelia from 3 different donors to IL13 and the selected dose (blue data points in **A-C**) of each drug for three weeks. Data are mean and SEM for % goblet cells and total cells normalized to IL13 alone. * = $p<0.05$ for paired t-test (n = 3 biological replicates / human donors for figure 3, **D-E**. n = 1 biological replicate for **A-C**).

Detailed Methods

Microarray sample processing

Initial quality control was performed with Nanodrop 2000 (Thermo Fisher Scientific, Wilmington, DE, USA) and Agilent Bioanalyzer 2100 (Agilent, Santa Clara, CA, USA). Microarray hybridizations were performed by the University of Iowa Genomics Division. Briefly, 50 ng total RNA was converted to SPIA-amplified cDNA using the WT-Ovation Pico RNA Amplification System, v2 (3302, NuGEN Technologies, San Carlos, CA) according to the manufacturer's recommended protocol. The amplified SPIA cDNA product was purified through a QIAquick PCR Purification column (28104, Qiagen, Hilden, Germany) according to modifications from NuGEN. Five micrograms of this product were fragmented (average fragment size = 85 bases) and biotin labeled using the NuGEN FL-Ovation cDNA Biotin Module (4200, NuGEN Technologies) per the manufacturer's recommended protocol. The resulting biotin-labeled cDNA was mixed with Affymetrix eukaryotic hybridization buffer (Affymetrix, Santa Clara, CA), placed onto Affymetrix Human Gene 1.0 ST arrays (901085), and incubated at 45º C for 18 h with 60 rpm rotation in an Affymetrix Model 640 Genechip Hybridization Oven. Following hybridization, the arrays were washed, stained with streptavidin-phycoerythrin (Molecular Probes, Eugene, OR), the signal was amplified with anti-streptavidin antibody (Vector Laboratories, Burlingame, CA) using the Affymetrix Model 450 Fluidics Station.

Reagents

Cell Signaling (Danvers, MA, USA)

Rabbit monoclonal anti-acetylated alpha tubulin antibody (5335, Lot 4); dilution of 1:300

Rabbit monoclonal anti-cleaved caspase-3 antibody (9664, Lot 3); dilution of 1:100

Bioss (Woburn, MA, USA), acquired through Sapphire Bioscience (Redfern, NSW, Australia)

Rabbit polyclonal anti-STXBP1/MUNC18 antibody (BS-3954R, Lot 120130); dilution of 1:100

Abcam (Cambridge, UK)

Rabbit polyclonal anti-HSP90 antibody (AB13495, lot GR286091-24); dilution of 1:100

ThermoFisher Scientific (Waltham, MA, USA)

Invitrogen (Carlsbad, CA, USA)

Mouse monoclonal antibody against MUC5AC (MA5-12178, Lot SE2384663A); dilution of 1:5000

Alexa Fluor 633 Phalloidin (A22284); dilution of 1:40 to 1:400

Propidium Iodide from Bacterial Viability Kit (L13152); reconstituted in 10mL of PBS

Triton X-100 Surfactant-Amps Detergent Solution (28314)

Alexa Fluor 488 goat anti-rabbit IgG (A11070); dilution of 1:1000

Alexa Fluor 488 goat anti-mouse IgG (A11017); dilution of 1:1000

Alexa Fluor 568 goat anti-rabbit IgG (A11011); dilution of 1:1000

Alexa Fluor 568 goat anti-mouse IgG (A11019); dilution of 1:1000

Thermo Scientific *(Waltham, MA, USA)*

SuperBlock blocking buffer (37515)

Gibco *(Waltham, MA, USA)*

Dulbecco's Phosphate Buffered Saline (14190144)

Fisher Scientific *(Waltham, MA, USA)*

DMSO (D128, Lot 153792)

NaOH (SS255-1, Lot 042694-24)

HCl (SA48-1, Lot 175004)

Superfrost Plus Microscope Slides precleaned (12-550-15)

Fisherbrand Filter Cards (22-030-410)

Research Products International (Mt Prospect, IL, USA)

Albumin Bovine Fraction V (A30075, Lot 39673-48434)

EGTA (E57060, Lot 30911); used at a concentration of 8mM in water

Vector Laboratories (Burlingame, CA, USA)

Vectashield mounting medium with DAPI (H-1200)

R&D Systems (Minneapolis, MN, USA)

Recombinant Human IL-13 Protein (213-ILB, Lot DCSK0415031)

Recombinant Human IL-17A Protein (317-ILB, Lot SOA2216031)

Note: Both reconstituted with PBS and used a dose of 20ng/mL of culture media

Sigma-Aldrich (St. Louis, MO, USA)

Geldanamycin-Biotin (SML0985. Lot 054M4110V) reconstituted in DMSO at 5mM. Final concentration 25μM. Final concentration of DMSO in media 0.5% v/v.

Methanol (179337)

Axon Medchem (Reston, VA, USA)

HDAC6 inhibitor ISOX (1645) reconstituted in DMSO at 2mM. Final concentration 10μM. Final concentration of DMSO in media 0.5% v/v.

Electron Microscopy Sciences (Hatfield, PA)

Paraformaldehyde 32% Solution (15714-S, Lot 170118)