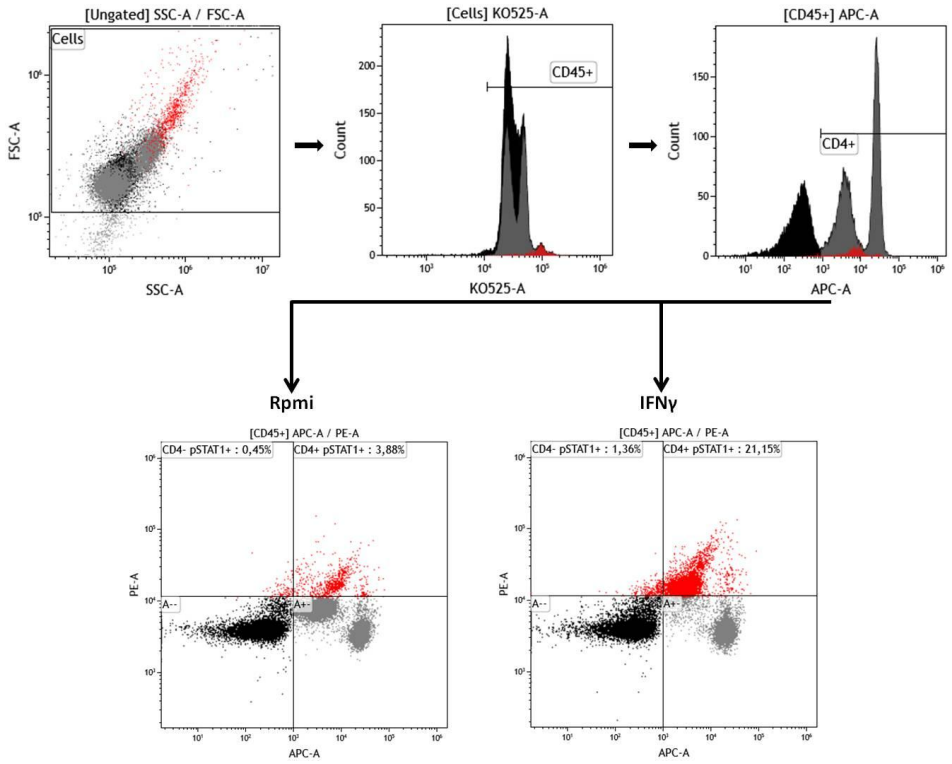
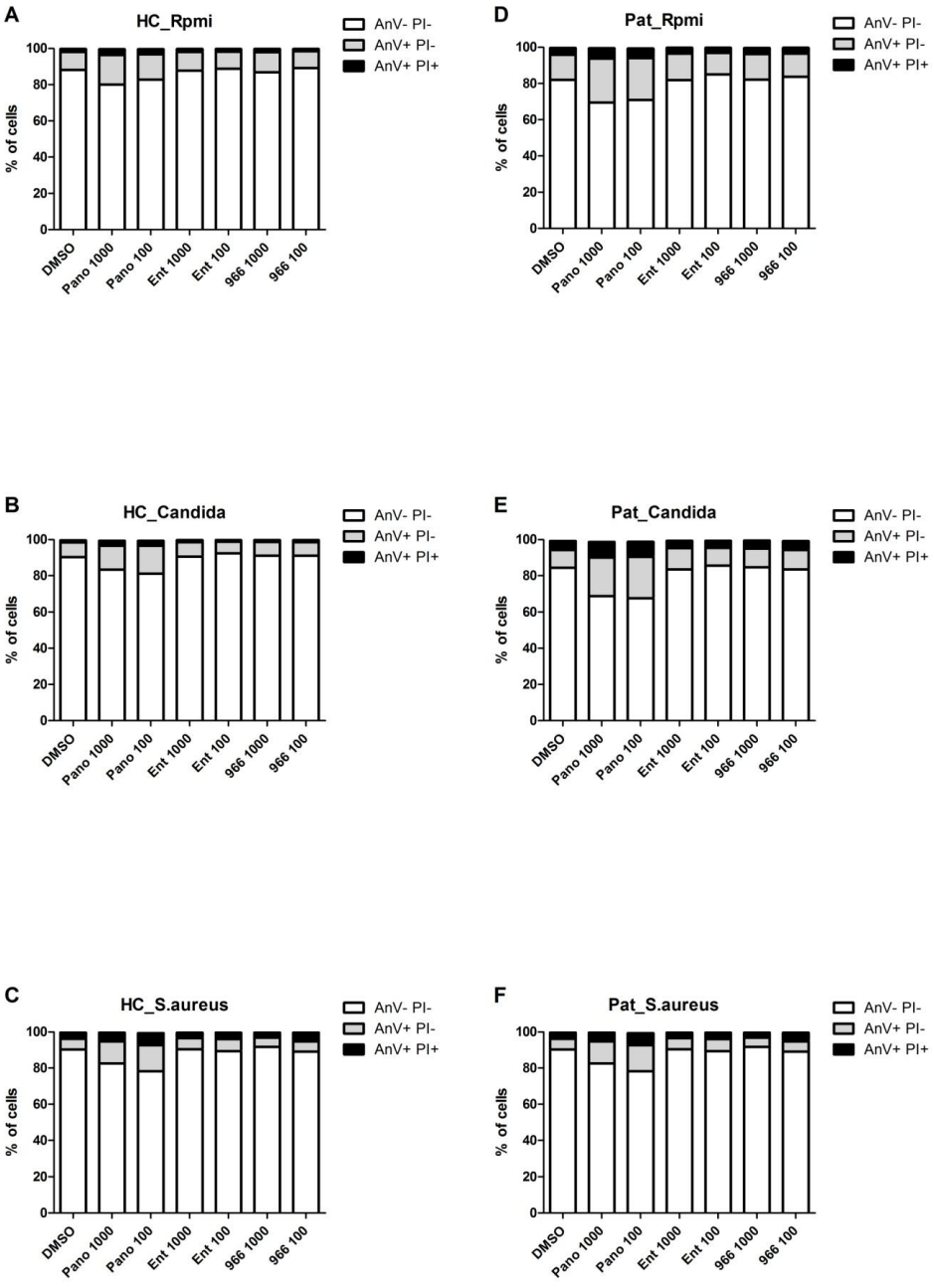
S1: Gating strategy to measure intracellular pSTAT1 /pSTAT3.



Freshly isolated peripheral blood mononuclear cells were stained with CD45-KO, CD4-APC pSTAT1-PE or pSTAT3-PE. The debris was removed from the cell population based on SSc and FSc. From the cell population, CD45+ cells were defined as leukocytes and within this population CD4+ cells were identified. Finally, percentages of pSTAT1 or pSTAT3 positive cells were assessed as shown above.

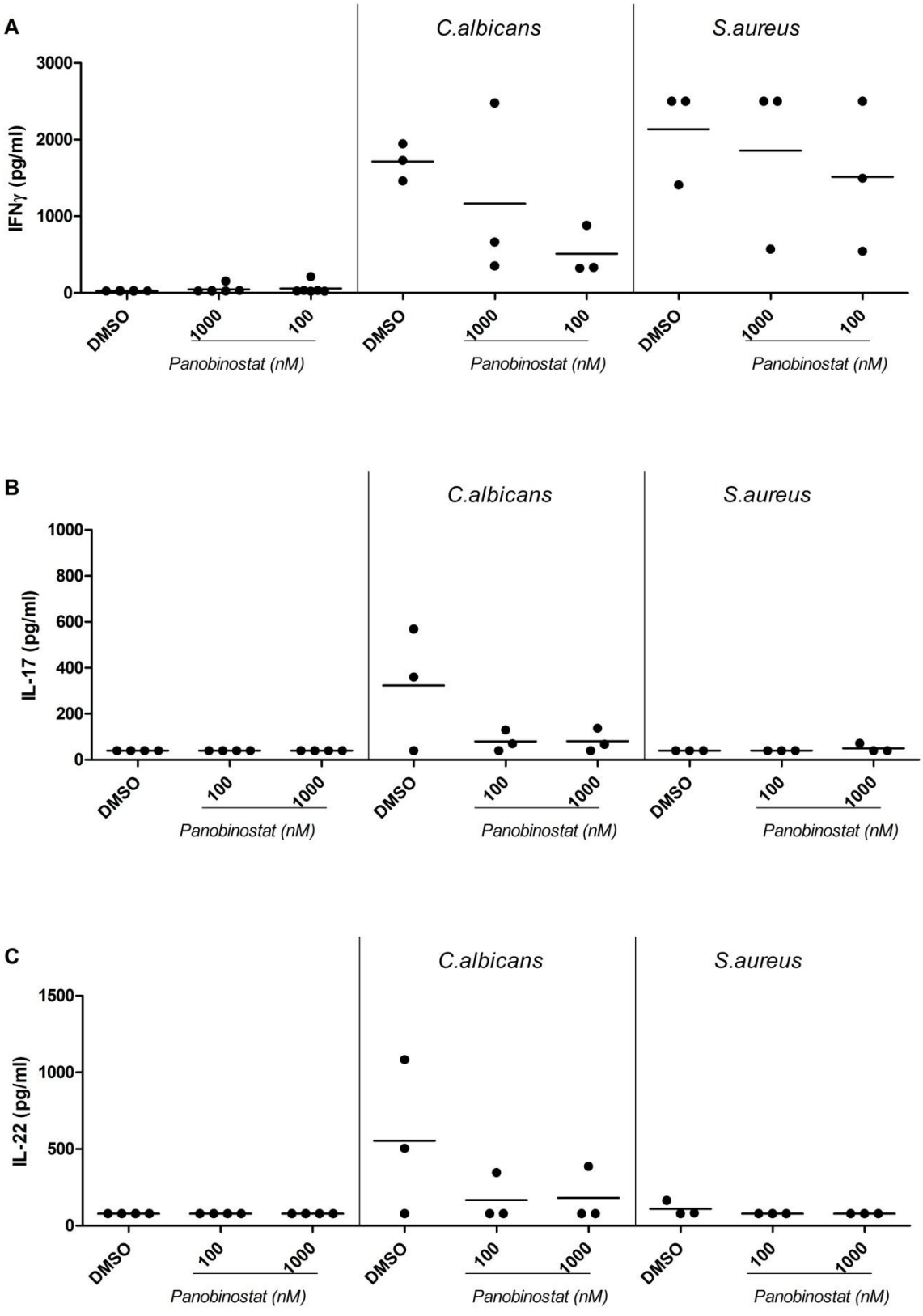
S2: PBMC viability STAT1 GOF cells.



The viability of peripheral blood mononuclear cells was assessed after 6 days of stimulation followed by 24 hours of co-incubation of fresh stimuli (Rpmi, *C. albicans* or *S. aureus*) and HDAC inhibitors. (**A-C**) Healthy control cells showed increased apoptosis in the presence of Panobinostat. Entinostat as well as RGFP966 do not induce apoptosis when compared to

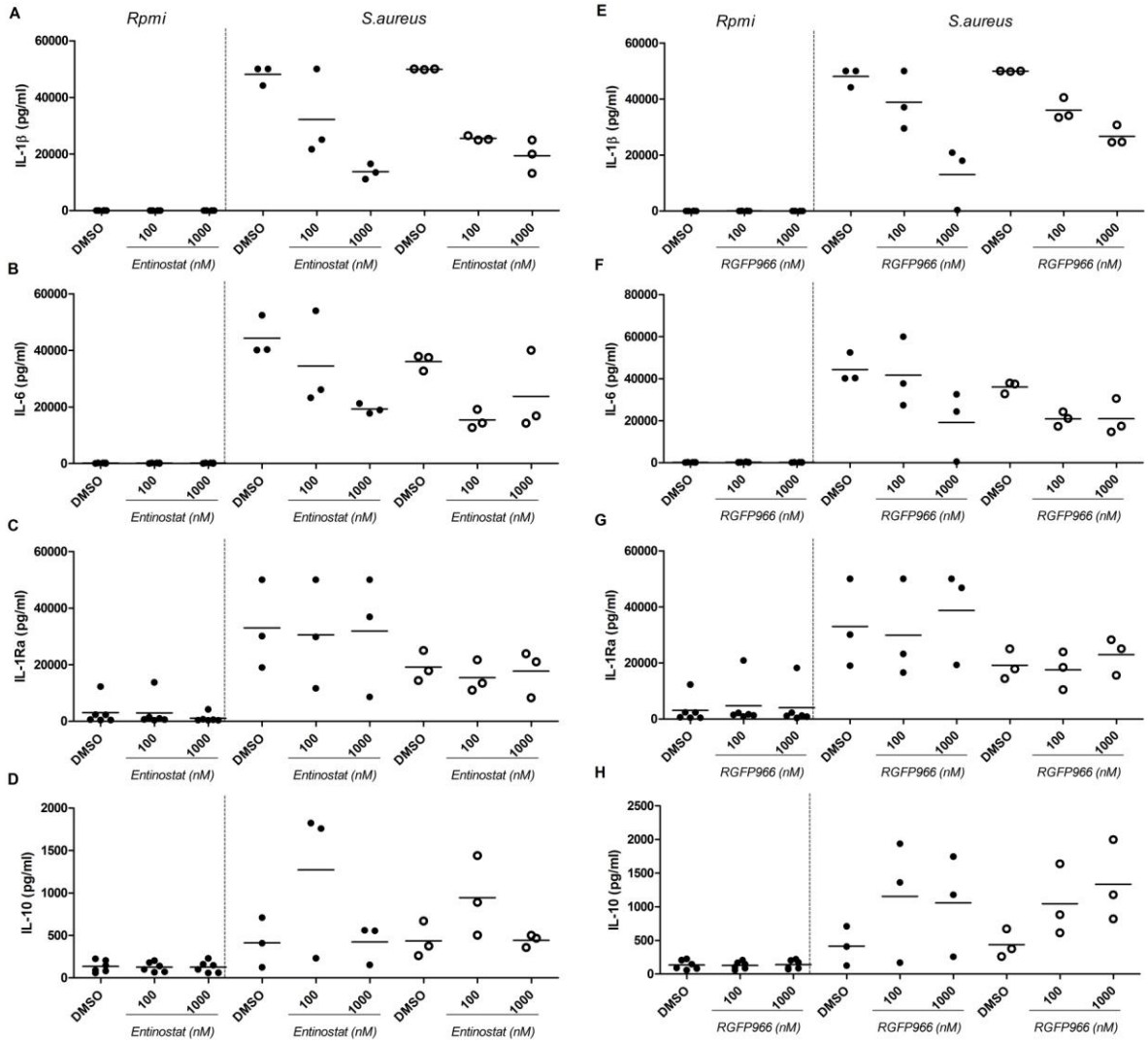
vehicle (DMSO) controls. (**D-F**) STAT1 GOF cells behave similar to healthy control cells. Panobinostat induced cell death, whereas Entinostat and RGFP966 are comparable to DMSO control. In general, patient cells showe slightly higehr percentages of apoptotic cells compared to healthy control cells.

S3: Panobinostat decreases adaptive immune responses towards *C. albicans* and *S. aureus*.



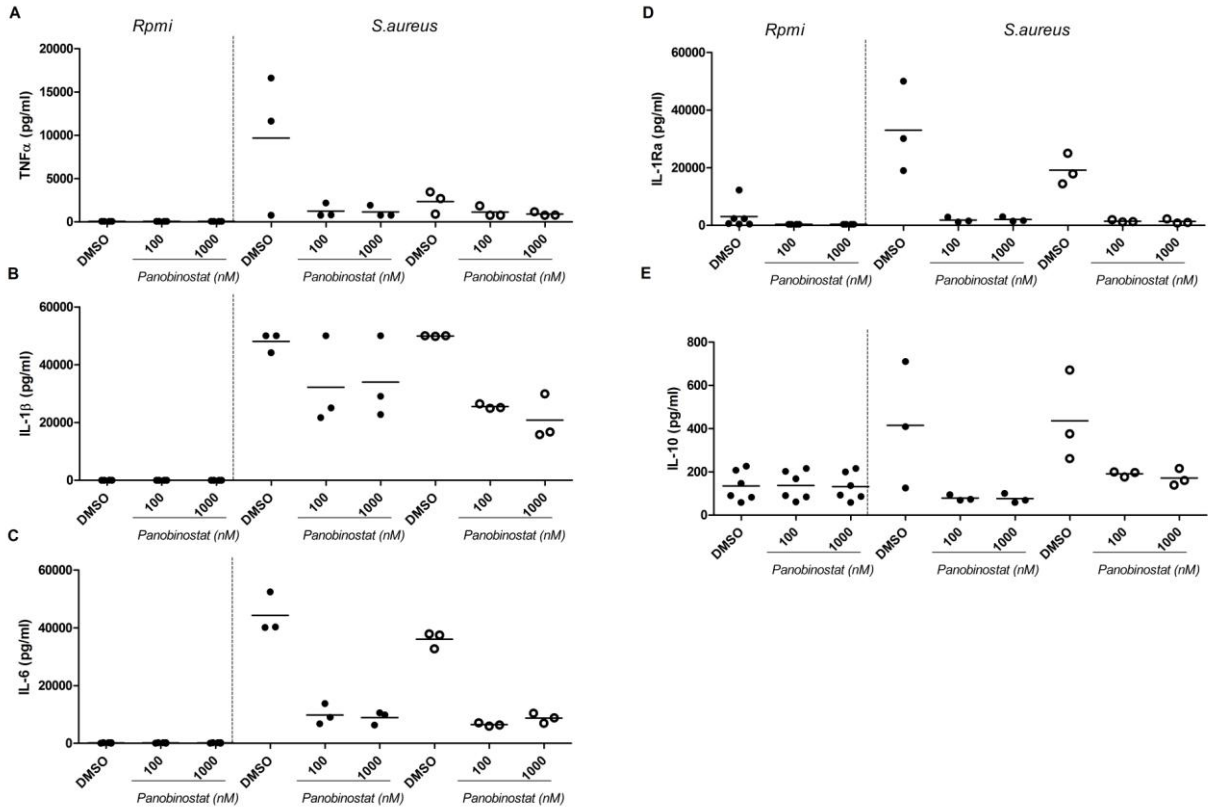
Peripheral blood mononuclear cells were freshly isolated from healthy controls (black) or STAT1 GOF patients (clear). Cells were incubated for 6 days in the presence or absence of *C. albicans* ($1*10^6$ CFU/ml) or heat killed *S. aureus* ($1*10^7$ CFU/ml). At day 6, supernatants were removed and replaced with freshly prepared stimuli (*C. albicans* or *S. aureus*) in combination with or without Panobinostat. Cells were kept in these conditions for an additional 24 hours before supernatants were collected and stored at -20°C until (**A and B**) IFN-γ, (**C and D**) IL-17 or (**E and F**) IL-22 induction was measured by ELISA (median, n=3 for patients and controls, no statistical analysis was performed).

S4: The effect of Entinostat and RGFP966 inhibitors on the innate cytokine profile.



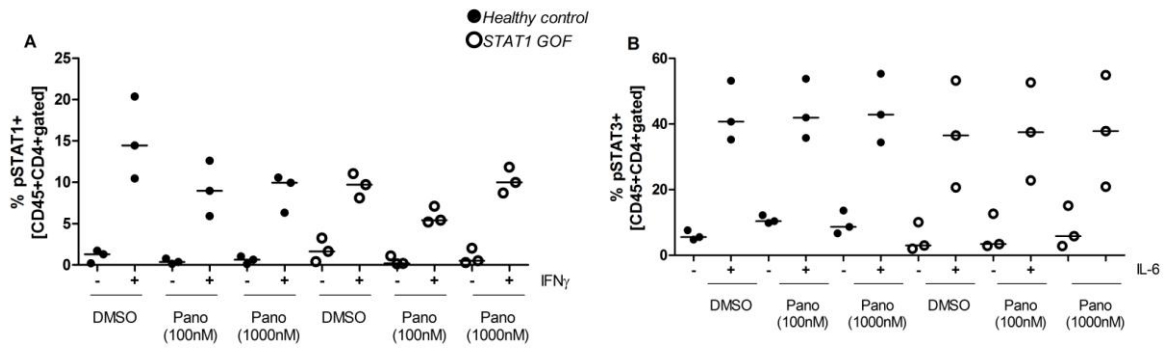
Peripheral blood mononuclear cells were freshly isolated from healthy controls (black) or STAT1 GOF patients (clear). Cells were pre-incubated for one hour with Entinostat (**A-D**) or RGFP966 (**E-H**) and subsequently stimulated for an additional 24 hours in the presence or absence of heat killed *S. aureus* ($1*10^7$ CFU/ml) . Supernatants were collected and stored at -20°C until IL-1β, IL-6, IL-1Ra and IL-10 production were measured by ELISA (negative controls for controls and patients were pooled. Median, n=3 for patients and controls, no statistical analysis was performed).

S5: The effect of Panobinostat on innate cytokine responses.



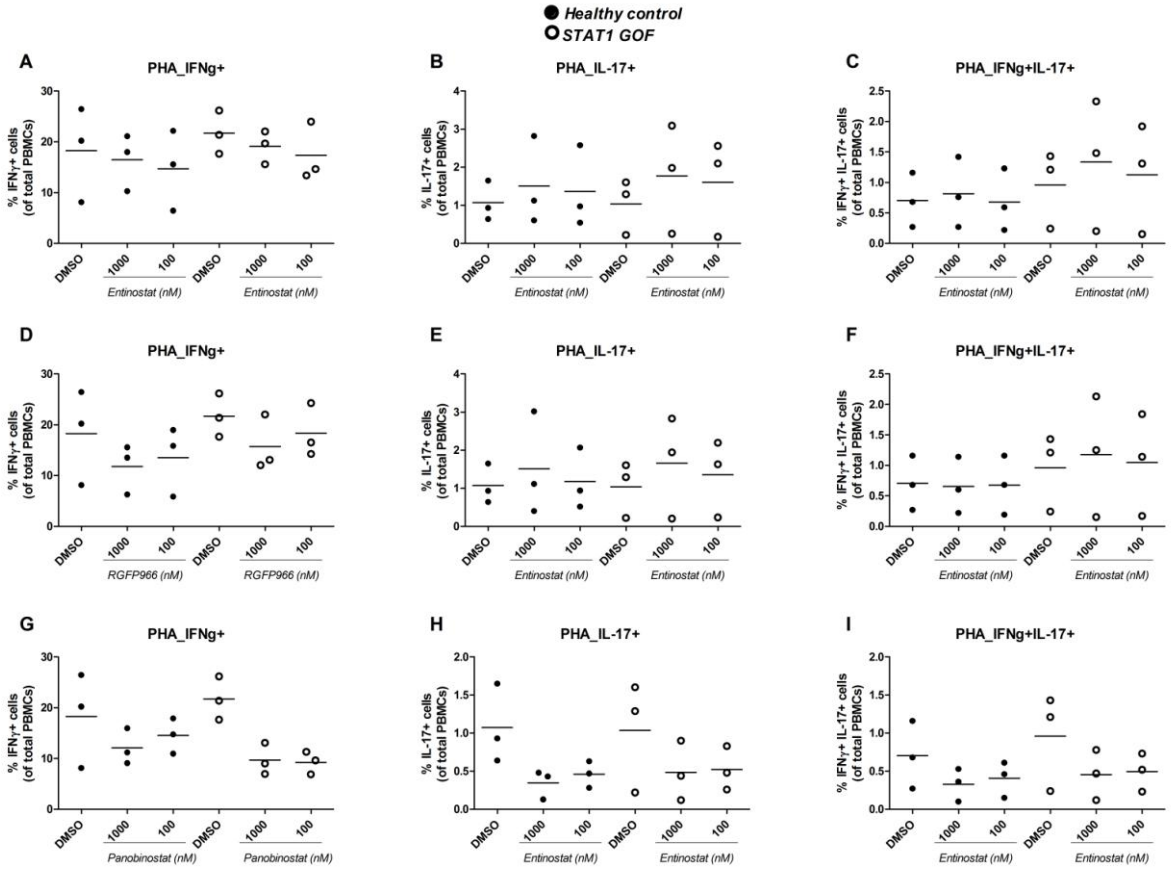
Peripheral blood mononuclear cells were freshly isolated from healthy controls (black) or STAT1 GOF patients (clear). Cells were pre-incubated for one hour with Panobinostat and the stimulated with or without heat killed *S. aureus* ($1*10^7$ CFU/ml) for 24 hours. Supernatants were collected and stored at -20°C until TNF-α (**A**), IL-6 (**B**), IL-1β (**C**), IL-1Ra (**D**) and IL-10 (**E**) production were measured by ELISA (median, n=3 for patients and controls, no statistical analysis was performed).

S6: Panobinostat downregulates pSTAT1 levels but do not influence pSTAT3.



Intracellular levels of (**A**) phosphorylated STAT1 (pSTAT1) upon IFN-γ (50 ng/ml) and (**B**) phosphorylated STAT3 (pSTAT3) upon IL-6 (20 ng/ml) were measured in freshly isolated peripheral blood mononuclear cells of healthy controls (black) and STAT1 GOF patients (clear). Peripheral blood mononuclear cells were pre-treated for one hour with Panobinostat or DMSO control. All samples were stained for CD45 and CD4 in combination with either anti-pSTAT1 or anti-pSTAT3 and measured by flow cytometry (median, n=3 for patients and controls, no statistical analysis was performed (median, n=3 for patients and controls, no statistical analysis was performed).

S7. Intracellular IL-17 and IFN-γ in peripheral blood mononuclear cells of healthy controls and STAT1 GOF are affected similarly by HDAC inhibitors.



(**A-C**) Intracellular levels of IFN-γ, (**D-F**) IL-17 or (**G-I**) IL-17/ IFN-γ were measured in freshly isolated peripheral blood mononuclear cells of healthy controls and STAT1 GOF patients. Cells were pre-incubated for one hour with HDAC inhibitors and subsequently all samples were activated with phytohaemagglutinin (PHA) (10 μg/ml) for 4 hours. Cells were collected immediately and stained for intracellular IL-17 and IFN-γ. All samples were measured on the same day by flow cytometry (median, n=3 for patients and controls, no statistical analysis was performed).