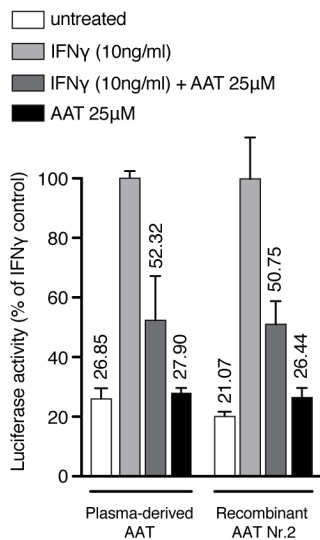


Figure S1. Rotarod Latency (A) Grip strength (B) At 8 weeks of age, CMT1A+ vehicle mice exhibited impaired neuromuscular performance relative to the wild type animals. CMT1A+hAAT mice presented a positive but not significant tendency in both neuromuscular test compared to CMT1A+vehicle. Nerve Conduction velocity (C) positive but not significant trend was observed in CMT1A mice treated with hAAT for this electric measurement. Number of axons (D) Slight increase of the total number of axons per surface was observed in the CMT+hAAT compared to CMT1A+vehicle. (F) Plasma TNF- α and IL-6 ELISA measurements. Mean \pm SEM, n=3 per group; 2-way ANOVA with repeated measures and Bonferroni t-test *, **,***: p<0.05; p<0.01; p<0.001 vs WT control. WT: wild type, not significative (ns) vs CMT1A+vehicle. For TNF- α and IL-6 concentration Mean \pm SEM, Student t-test *, **, ***: p<0.05; p<0.01; p<0.001 vs WT control at this timepoint. For IL-6 concentration value see also Table 3 in the main text. For all the experiments n=3 mice per group.

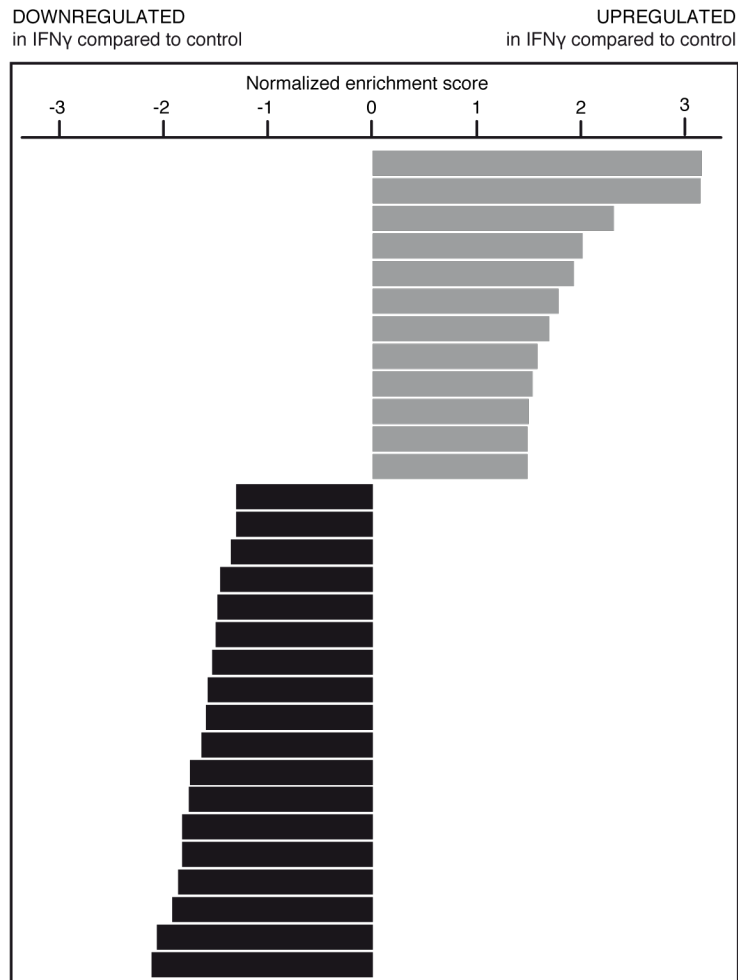
B

Hallmark pathway Enrichment Score from GSEA

A



IFN γ response
IFN α response
 Allograft rejection
TNF α signaling via NF κ B
Inflammatory response
IL-6 JAK/STAT3 signaling
KRAS signaling
 Apoptosis
 Unfolded protein response
P53 pathway
 Complement
 IL-2 STAT5 signaling
 Mitotic spindle
 Hypoxia
 Xenobiotic metabolism
 Protein secretion
 Peroxisome
 Epithelial mesenchymal transition
 Bile acid metabolism
 MTORC1 signaling
 Oestrogen response late
 Adipogenesis
 Androgen response
 Apical surface
 Oxydative phosphorylation
 Myogenesis
 Glycolysis
 Fatty acid metabolism
 Apical junction
 Cholesterol homeostasis



DOWNREGULATED in AAT compared to control

UPREGULATED in AAT compared to control

Protein secretion
 Myc targets V1
 Androgen response
 UV response
 MTORC1 signaling
 E2F targets
 G2M check points
TNF α signaling via NF κ B
Inflammatory response
 Myogenesis
IL-6 JAK/STAT3 signaling
KRAS signaling
IFN γ response
IFN α response

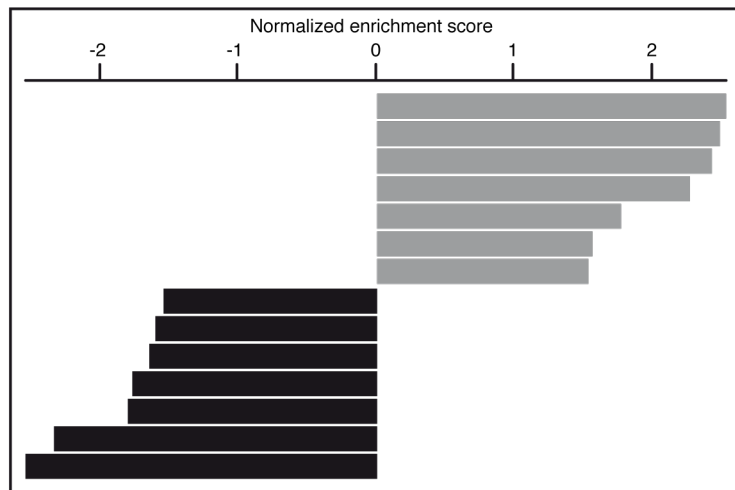
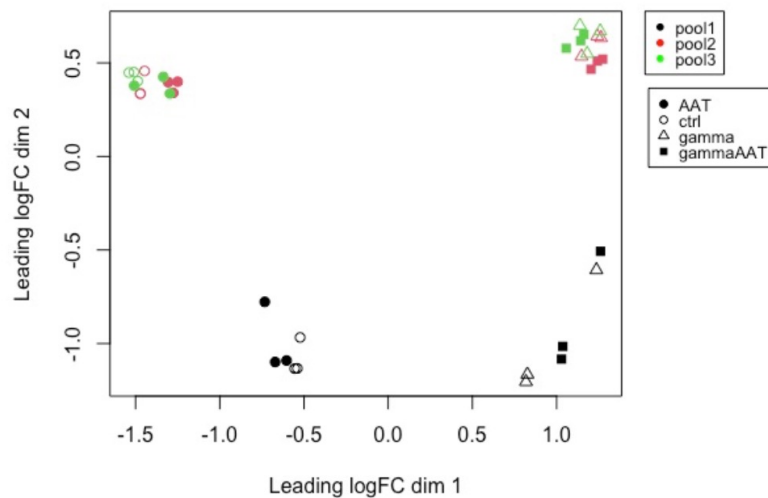


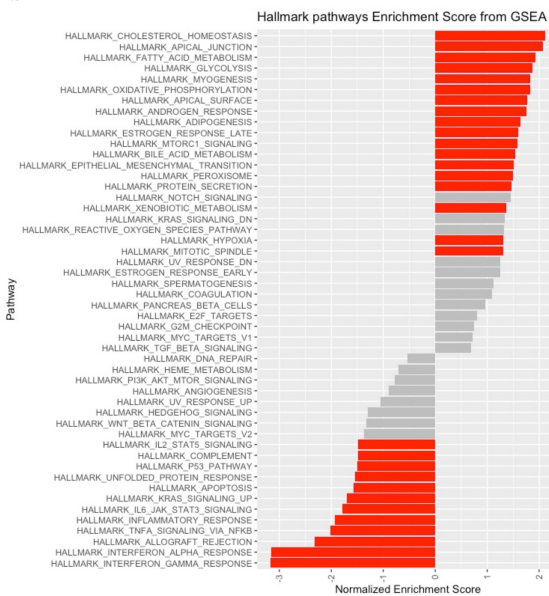
Figure S2. MHCII luciferase activation after IFN γ induction followed by plasma hAAT and recombinant AAT (rhAAT) (A). Luciferase activity is normalized over cell viability. Bars represented percentage of control for all conditions. Gene Set Enrichment Analysis (GSEA) of RNAseq data from plasma and rhAAT treated cells (B). Upregulated gene families (grey bars) and downregulated ones (black bars) are shown according to normalized enrichment score. The inflammatory profile induced by IFN γ was confirmed by the upregulation of several processes related to inflammation (bold italic), AAT in absence or presence (see Figure 9) of inflammation was able to downregulate some of these pathways (bold italic).

A

MDSplot

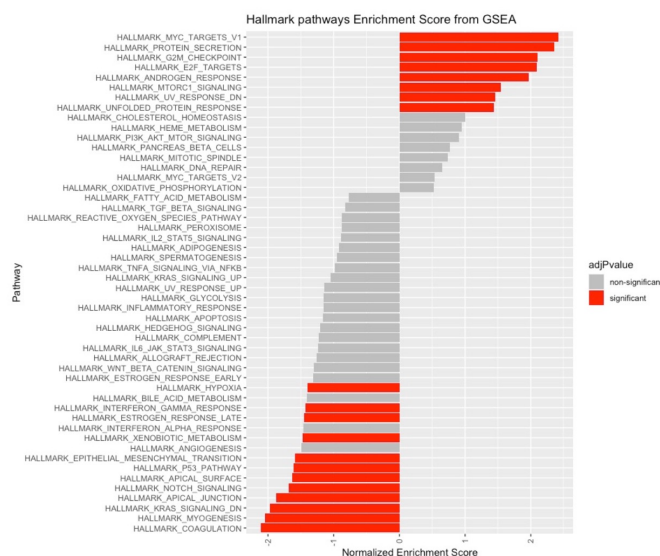


B



C

Enriched molecular signatures: gamma versus gammaAAT (pool2 and pool3)



Enriched molecular signatures: control versus AAT (pool2 and pool3)

D

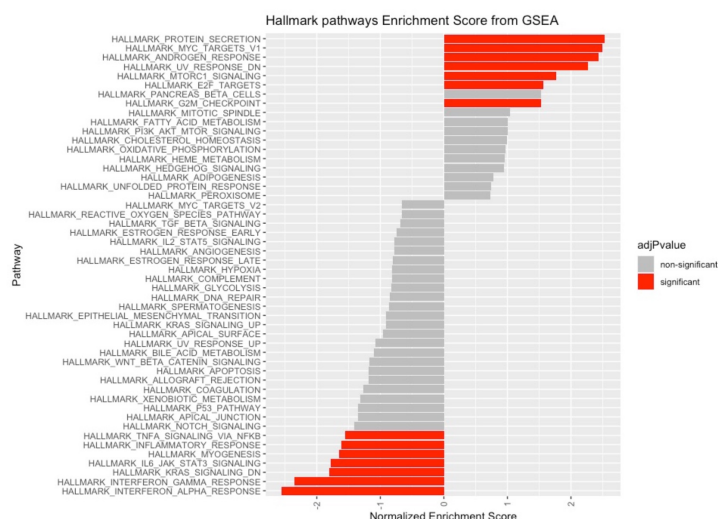


Figure S3. The MDS plot (multi-dimensional scaling) of the samples is shown (A). The MDS plot gives an indication of the similarity, based on the fold changes between all the pairs of samples. Enriched molecular signatures: control versus gamma (pool2 and pool3) (B). Enriched molecular signatures: control versus AAT (pool2 and pool3) (C). Enriched molecular signatures: gamma (IFN γ) versus gammaAAT (IFN γ + AAT) (pool2 and pool3) (D). A negative score (NES) means that the genes belonging to that gene set are mostly down regulated in the comparison tested and a positive NES that they are upregulated in the tested comparison.

Antigen presentation

Top Gene	p-value	FC	p-value	FC
	Up in inflammation		DOWN (Inflammation+AAT)	
CD74	4.15E-14	75.81		
LAMP3	9.39E-12	7.94		
TAP1	5.99E-11	6.12		
PSMB9	<u>5.73E-11</u>	<u>5.96</u>	<u>3.11E-02</u>	<u>-1.23</u>
HLA-DOB	<u>5.11E-04</u>	<u>4.48</u>	<u>6.82E-03</u>	<u>-4.49</u>
PSMB8	5.18E-11	4.22		
<i>HLA-DRA</i>	<i>4.99E-10</i>	<i>4.76</i>	<i>4.68E-02</i>	<i>-2.22</i>
SOCS1	1.21E-05	3.99		
TAP2	8.97E-13	3.54		
NCF2	2.57E-05	2.88		
CTSS	2.29E-05	3.71		
HLA-DPA1	8.31E-09	3.22		
BATF3	1.45E-06	2.55		
NFKB1	6.21E-10	2.41		
IL1B	<u>5.54E-04</u>	<u>2.08</u>	<u>1.11E-03</u>	<u>-2.07</u>
FYN	2.18E-07	1.80		
BCL10	3.21E-05	1.65		
MALT1	1.75E-04	1.62		
	DOWN in inflammation		UP in inflammation+AAT	
TUBA1A	2.29E-12	-5.00		
KIF20A	7.29E-12	-3.75		
CALR	<u>6.15E-11</u>	<u>-3.53</u>	<u>4.74E-04</u>	<u>1.35</u>
PYCARD	<u>6.92E-03</u>	<u>-2.86</u>	<u>1.53E-02</u>	<u>2.20</u>
CDC20	1.05E-08	-2.80		
Other Gene	p-value	FC	p-value	FC
	Down in inflammation		UP in inflammation+AAT	
NFATC2	<0.05	-1.37	<0.05	1.63
MRC2	<0.05	-1.61	<0.05	1.47
CTSD	<0.05	-1.34	<0.05	1.47
HLA-DPB1	<0.05	-1.23	<0.05	1.31
TAPBP	<0.05	-1.90	<0.05	1.23
SOCS3	<0.05	-1.99	<0.05	1.20
CTSA	<0.05	-1.31	<0.05	1.17
	Regulated in inflammation		Regulated in AAT	
NFATC1	<0.05	-1.29	<0.05	1.44
TRAF6	<0.05	1.08	<0.05	-1.26

Figure S4. Gene related to antigen presentation. Inflammatory top gene (FC>2; p-value<0.05; left column), were defined by differential expression between untreated and IFN γ -treated cells (inflammation; middle column). Top genes that were significantly and oppositely regulated by AAT treatment are highlighted (right column; underline).

Cytokine signaling				
Top Gene	p-value	FC	p-value	FC
	UP in inflammation		DOWN in inflammation+AAT	
IL6	3.53E-10	17.139		
TNFSF10	2.53E-07	10.595		
TRAF1	4.39E-07	7.789		
CCL5	5.17E-09	7.540		
<u>ATF3</u>	<u>6.86E-13</u>	<u>7.218</u>	<u>1.85E-03</u>	<u>-1.26</u>
<u>PSMB9</u>	<u>6.09E-10</u>	<u>5.963</u>	<u>3.11E-02</u>	<u>-1.23</u>
CEBPB	2.57E-10	5.808		
CSF1	3.52E-09	5.455		
PSMB8	1.63E-10	4.219		
IL23A	6.49E-03	4.218		
STAT1	2.04E-09	4.110		
IL15RA	4.63E-07	3.660		
<u>FGF2</u>	<u>1.66E-06</u>	<u>3.608</u>	<u>9.13E-03</u>	<u>-1.57</u>
CXCL2	6.42E-05	3.467		
IL21R	1.16E-05	3.235		
CEBPG	3.19E-09	2.909		
<u>CXCL1</u>	<u>1.36E-04</u>	<u>2.82</u>	<u>7.22E-03</u>	<u>-2.09</u>
CASP1	1.07E-05	2.740		
<u>TNFRSF9</u>	<u>2.39E-04</u>	<u>2.434</u>	<u>1.23E-03</u>	<u>-2.35</u>
<u>CXCL5</u>	<u>5.07E-05</u>	<u>2.36</u>	<u>5.98E-03</u>	<u>-2.15</u>
<u>IL1B</u>	<u>2.14E-03</u>	<u>2.08</u>	<u>1.11E-03</u>	<u>-2.07</u>
	DOWN in inflammation		UP in inflammation+AAT	
<u>FSCN1</u>	<u>9.42E-08</u>	<u>-6.312</u>	<u>8.09E-04</u>	<u>1.48</u>
CCL2	2.95E-03	-6.086		
<u>IL4I1</u>	<u>3.22E-03</u>	<u>-4.19</u>	<u>3.22E-03</u>	<u>1.95</u>
<u>IL27RA</u>	<u>2.22E-07</u>	<u>-3.848</u>	<u>2.67E-02</u>	<u>1.36</u>
<u>STAT5A</u>	<u>7.66E-04</u>	<u>-3.53</u>	<u>9.78E-03</u>	<u>1.45</u>
CEBPD	5.07E-05	-3.102		
EGF	6.13E-03	-2.973		
FGF18	2.11E-05	-2.754		
IL6R	6.00E-08	-2.630		
<u>IL1R1</u>	<u>1.27E-07</u>	<u>-2.566</u>	<u>3.94E-02</u>	<u>1.18</u>
<u>IAK3</u>	<u>3.03E-08</u>	<u>-2.43</u>	<u>3.20E-03</u>	<u>1.43</u>
<u>RASAL1</u>	<u>1.36E-06</u>	<u>-2.34</u>	<u>4.65E-03</u>	<u>1.52</u>
Other Gene	p-value	FC	p-value	FC
	UP in inflammation		DOWN in inflammation+AAT	
IL18	<0.05	1.83	<0.05	-1.75
NFKBIZ	<0.05	1.94	<0.05	-1.37
ANXA1	<0.05	1.17	<0.05	-1.33
HBEGF	<0.05	1.36	<0.05	-1.30
DUSP6	<0.05	1.96	<0.05	-1.26
	DOWN in inflammation		UP in inflammation+AAT	
CX3CL1	<0.05	-1.38	<0.05	1.61
MAP2K2	<0.05	-1.28	<0.05	1.51

Figure S5. Genes related to cytokines signaling. Analysis was performed as described in Figure S4.