

Supplementary Figures

Supplementary Figure 1: The flow cytometry gating strategy for myeloid populations, validated with

additional surface markers. (a) Briefly, AMs were defined as CD11b⁺CD11c⁺Siglec F⁺; > 90% of these AMs also express CD64⁺. Neutrophils were defined as CD11b⁺CD11c⁻Gr-1^{hi} cells; neutrophils also express Ly6G, but not Ly6C. Monocytes were defined as CD11b⁺CD11c⁻Gr-1^{lo} cells; the majority of them expressed Ly6C and CX3CR1. RMs were defined as CD11b⁺CD11c⁻Gr-1⁻; RMs also expressed CX3CR1, but not CD64 or Ly6C. Red boxes define the criteria used for gating subsets in all figures.

Supplementary Figure 2: Accumulation of lung innate and adaptive cell populations upon H37Rv or HN878 infection in B6 and CCR2^{-/-} mice

(a-e) B6 and CCR2^{-/-} mice (n=5) were aerosol-infected with 100 CFU of H37Rv and lung innate immune populations were determined at 30 dpi by flow cytometry. (f-h) B6 and CCR2^{-/-} mice were infected with H37Rv or HN878 and accumulation of total CD4⁺ T cells and CD44^{hi} activated CD4⁺ T cells producing IFN- γ were determined using flow cytometry. Un.=uninfected, Monos=Monocytes, AMs=Alveolar Macrophages, RMs=Recruited Macrophages, mDCs=Myeloid Dendritic Cells, Neuts=Neutrophils. n=5, (a-h) 1-Way ANOVA with Tukey's post test.

Supplementary Figure 3: CCL2 deficient mice are susceptible to HN878 infection.

(a) B6 and CCL2^{-/-} (n=5) were infected with HN878 and lung bacterial burden was analyzed at 30 dpi. (b) Chemokines protein levels were measured in lung homogenates of HN878 infected IKK2^{fl/fl} Sftpc-Cre mice and littermate controls at 21 dpi. (a-b) Student's t-test.

Supplementary Figure 4: Validation of airway labeling technique using the HCl lung injury model.

B6 mice were treated IT with 50 μ L of sterile water (vehicle, n=4) or HCl (pH 1.5, n=5) and rested 24 hours

prior to airway CD45.2 labelling and lung harvest. (a) The percentage of total lung cells stained with airway CD45.2 was determined by flow cytometry. (b) Total cell counts for lung myeloid populations were determined by flow cytometry. (c) The percentage of each myeloid cell type positive for airway labelled CD45.2 in vehicle and HCl treated mice is shown. (d) Airway label CD45.2 PE localization was by IHC in PBS treated and HCl treated mice. (e) BAL samples were collected ~10 min after airway labelling with CD45.2 Ab from uninfected and infected mice at 45 dpi. The proportion of AMs stained with airway CD45.2 (left panel, uninfected average= 98.6%, infected =97.5%) as well as the proportion of AMs of the total collected BAL sample (right panel, uninfected average= 48.6%, infected=15.3%). (a-d) Student's t-test was used to compare between groups separately for each myeloid cell type. (e) Student's t-test.

Supplementary Figure 5: Sorting strategy of airway AMs and non-airway AMs.

Single cell lung suspensions from airway CD45.2 labelled, uninfected (n=4) and infected mice (n=4-5) were prepared and (a) the gating strategy for airway and non-airway AMs is shown. Briefly, CD11c⁺SiglecF⁺CD45.2⁺ cells were gated as airway AMs, while CD11c⁺SiglecF⁺ CD45.2⁻ cells were gated as non-airway AMs. (b) Enrichment of AMs by CD11c magnetic bead sorting for adoptive transfer into mice was carried out using the Miltenyi CD11c+ sorting kit. Expression of SiglecF and CD11c on sorted cells was determined by flow cytometry.

Supplementary Table 1: Gene expression values of airway and non-airway AM transcriptional signatures from *Mtb*-infected mice.

RNA sequencing datasets of populations of sorted airway (CD45.2⁺ CD11c⁺ SiglecF⁺) and non-airway AMs (CD45.2⁻ CD11c⁺ SiglecF⁺) from infected (n=4-5, 100 CFU HN878, 30 dpi) and uninfected mice (n=4) were analyzed for expression (Log FPKM) of the common AM gene signature (Gautier et al 2012, Misharin et al 2017) (i.e. *Siglecf*, *Pparg*, *Tgfbr2*, *Csf2r*, *Mertk*, *Itgax*, *Lyz2*, *Sftpc*, and *Fcgr1*) and genes associated with monocyte-derived interstitial or recruited macrophages (i.e. *Ly6c1*, *Itgam*, *Cx3cr1*, and *CD163*).

Supplementary Table 2: Pearson correlation of gene expression levels between sorted airway and non-airway AMs from infected mice.

RNA sequencing datasets of populations of sorted airway (CD45.2⁺ CD11c⁺ SiglecF⁺) and non-airway AMs (CD45.2⁻ CD11c⁺ SiglecF⁺) from infected (n=4-5, 100 CFU HN878, 30 dpi) and uninfected mice (n=4) were compared by Pearson correlation for expression of all genes (a) and the AM signature genes (b).

Supplementary Table 3: Descriptions of the 116 genes significantly overexpressed in non-airway AMs compared to airway AMs during infection.

RNA-sequencing of sorted airway AMs (CD45.2⁺ CD11c⁺ SiglecF⁺) and non-airway AMs (CD45.2⁻ CD11c⁺ SiglecF⁺) from HN878 infected B6 mice (n=4-5 per group) harvested at 30 dpi. DESeq2 was used to determine significantly overexpressed genes compared to airway samples. FPKM average expression levels and adjusted p values displayed for each.

Supplementary Table 4: KEGG pathways significantly enriched among the 116 genes overexpressed in non-airway AMs compared to airway AMs during infection.

Differentially expressed genes overexpressed in non-airway samples were tested for significant enrichment among KEGG pathways using WebGestalt (default settings, adjusted $P = 0.05$ threshold for enrichment).

Supplementary Table 5: Descriptions of the 12 genes significantly overexpressed in airway AMs compared to non-airway AMs in HN878-infected mice.

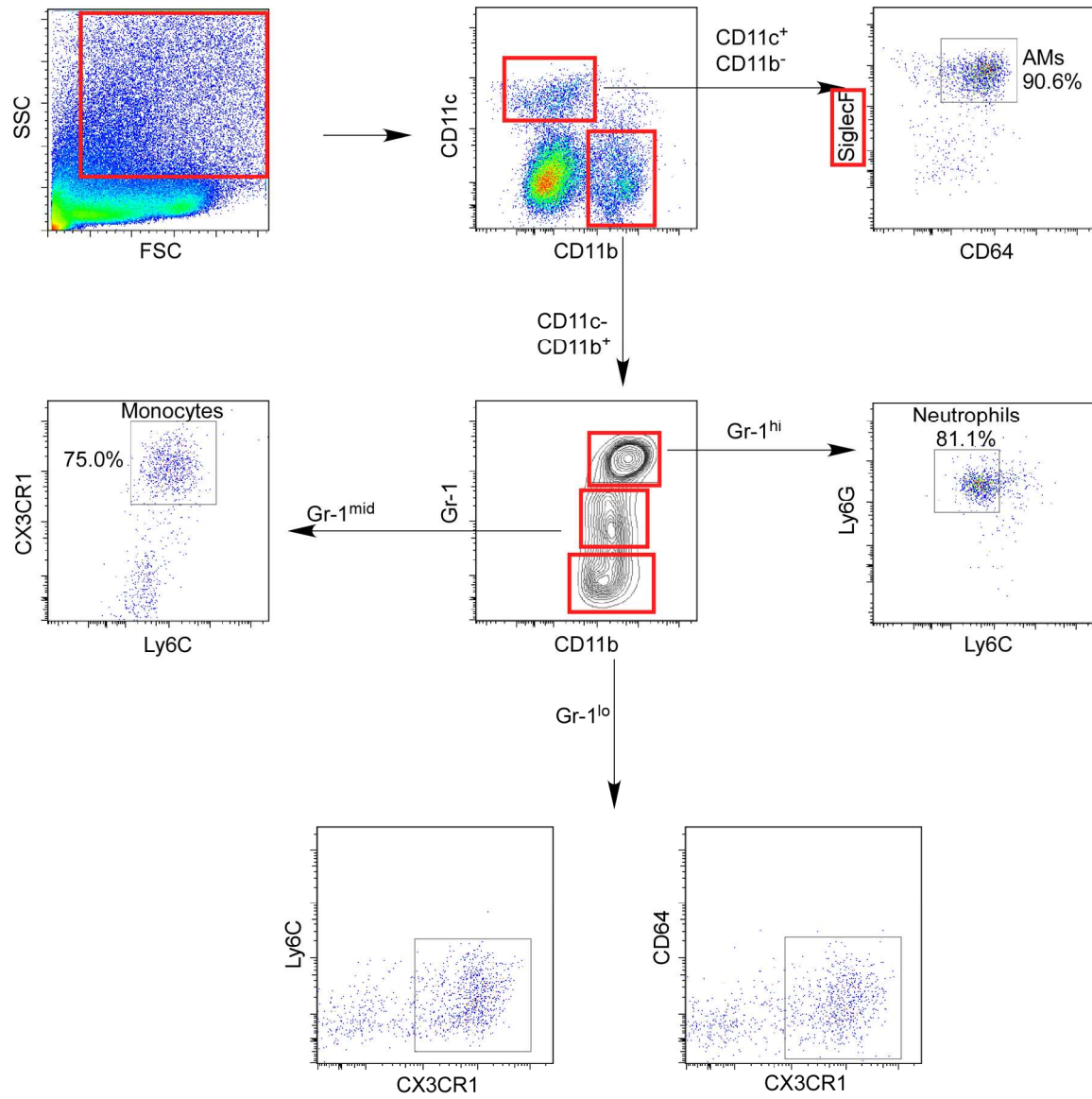
RNA-sequencing of sorted airway AMs (CD45.2⁺ CD11c⁺ SiglecF⁺) and non-airway AMs (CD45.2⁻ CD11c⁺ SiglecF⁺) from HN878 infected B6 mice (n=4-5) at 30 dpi. DESeq2 was used to determine overexpressed genes compared to non-airway samples. FPKM average expression levels and adjusted p values displayed for each.

Supplementary Table 6: KEGG pathways significantly enriched among the 3517 genes overexpressed in infected airway AMs compared to uninfected airway AMs.

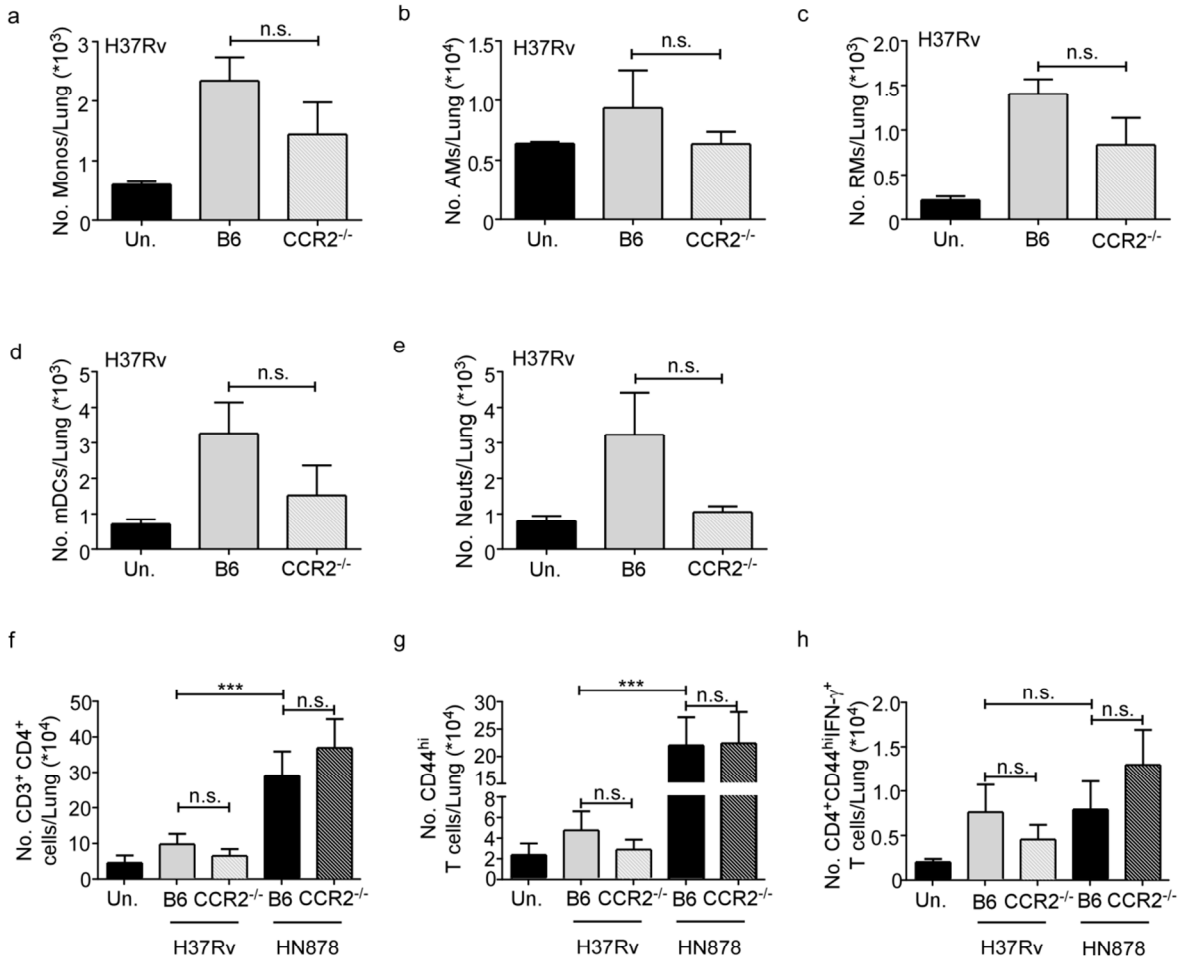
Differentially expressed genes overexpressed in infected airway samples were tested for significant enrichment among KEGG pathways using WebGestalt (default settings, adjusted $P = 0.05$ threshold for enrichment).

Supplementary Table 7: KEGG pathways significantly enriched among the 4442 genes overexpressed in uninfected airway AMs compared to infected airway AMs.

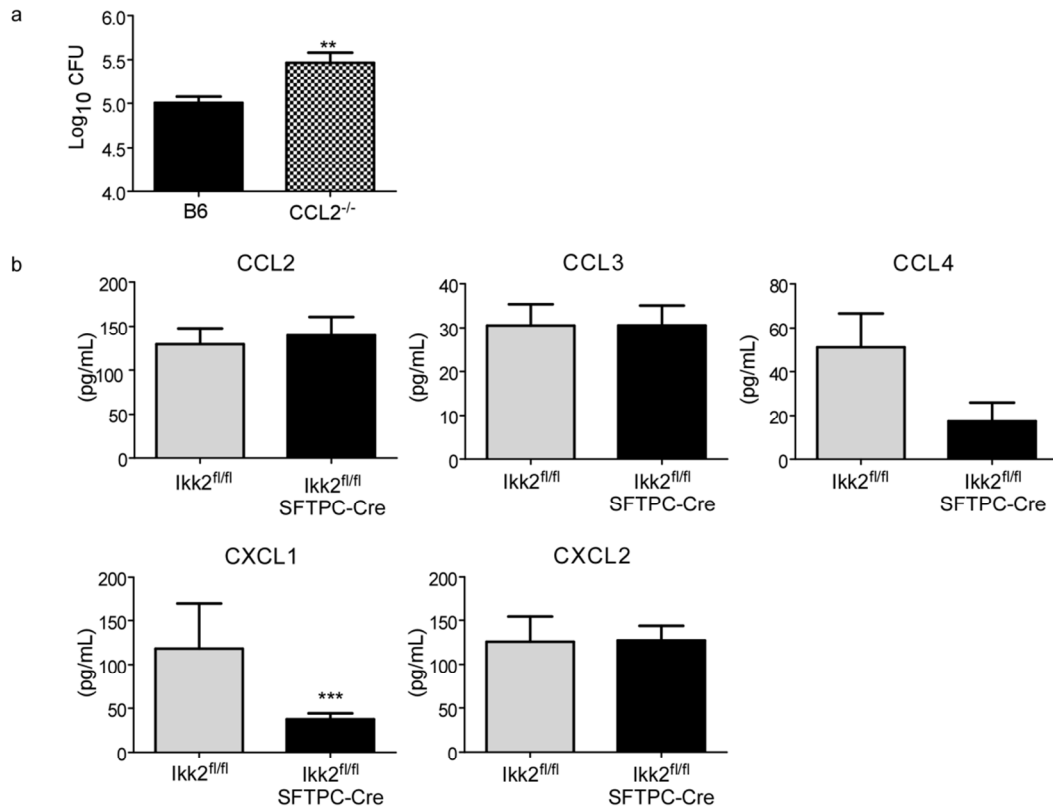
Differentially expressed genes overexpressed in uninfected airway samples were tested for significant enrichment among KEGG pathways using WebGestalt (default settings, adjusted $P = 0.05$ threshold for enrichment).



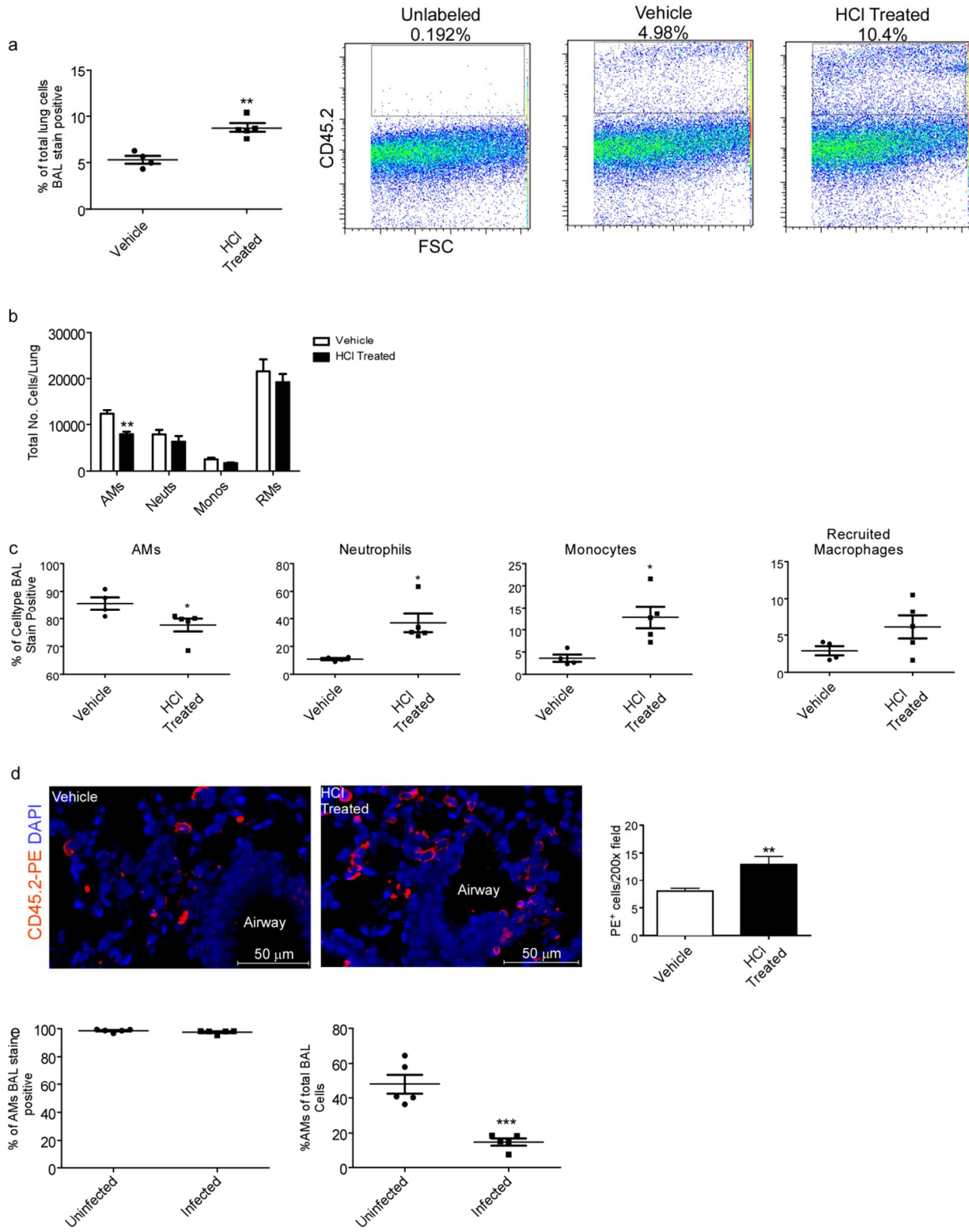
Dunlap et al., Supplementary Figure 1



Dunlap et al., Supplementary Figure 2

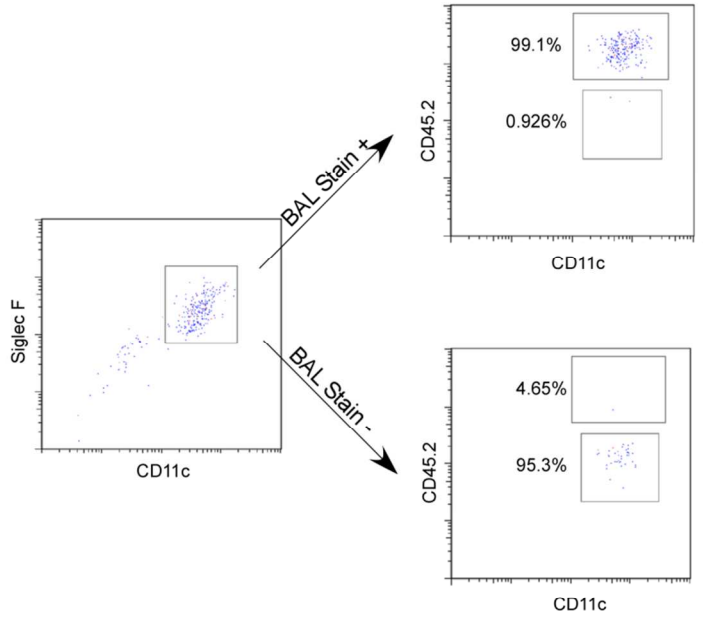


Dunlap et al., Supplementary Figure 3

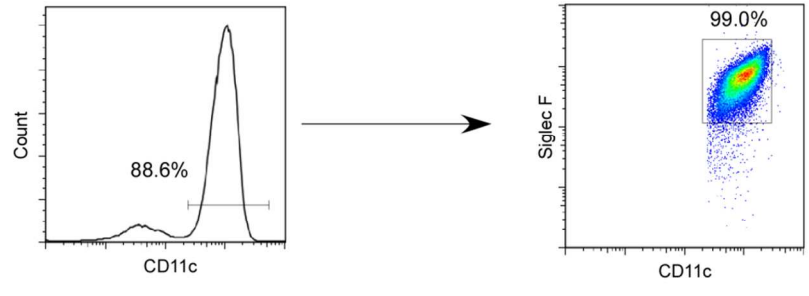


Dunlap et al., Supplementary Figure 4

a



b



Dunlap et al., Supplementary Figure 5

Supplementary Table 1: Gene expression values of airway and non-airway AM transcriptional signatures from *Mtb*-infected mice.

Gene			Infected airway AMs					Infected non-airway AMs				Uninfected airway AMs			
ENSMUSG00000015947	Fcgr1	Fc receptor, IgG, high affinity I	1.8	1.7	1.7	1.7	1.8	1.8	1.8	1.8	1.9	1.5	1.5	1.5	1.3
ENSMUSG00000032440	Tgfb2	transforming growth factor, beta receptor II	1.2	1.1	1.0	1.0	1.0	1.2	1.0	1.0	1.0	1.5	1.4	1.5	1.4
ENSMUSG00000014361	Mertk	c-mer proto-oncogene tyrosine kinase	1.4	1.4	1.4	1.3	1.4	1.4	1.4	1.4	1.2	1.8	1.8	1.8	1.8
ENSMUSG00000000440	Pparg	peroxisome proliferator activated receptor gamma	2.0	1.8	1.8	1.7	1.9	1.9	1.8	1.8	1.8	1.9	2.0	1.8	1.7
ENSMUSG00000030789	Itgax	integrin alpha X	1.7	1.7	1.7	1.7	1.8	1.8	1.7	1.7	1.8	2.1	2.1	2.1	2.0
ENSMUSG00000039013	Siglecf	sialic acid binding Ig-like lectin F	2.1	1.9	1.9	1.8	2.0	2.1	2.0	1.9	2.0	2.2	2.3	2.2	2.1
ENSMUSG00000069516	Lyz2	lysozyme 2	4.8	4.8	4.8	4.8	4.8	4.8	4.9	4.8	4.9	4.6	4.7	4.5	4.3
ENSMUSG00000071714	Csf2rb2	colony stimulating factor 2 receptor, beta 2	1.0	1.0	1.0	1.0	1.2	1.1	1.0	1.1	1.3	1.6	1.4	1.6	1.5
ENSMUSG00000059326	Csf2ra	colony stimulating factor 2 receptor, alpha	2.4	2.4	2.4	2.4	2.5	2.4	2.4	2.3	2.4	2.4	2.4	2.3	2.1
ENSMUSG00000008845	Cd163	CD163 antigen	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.2	0.3	0.3	1.9
ENSMUSG00000030786	Itgam	integrin alpha M	0.3	0.4	0.4	0.6	0.3	0.6	0.6	0.6	0.8	-0.5	-0.4	0.0	0.1
ENSMUSG00000079018	Ly6c1	lymphocyte antigen 6 complex, locus C1	0.4	0.6	0.2	0.5	0.1	0.5	0.2	0.6	0.5	0.6	0.4	0.6	0.9

Supplementary Table 2a: Pearson correlation of gene expression levels between sorted airway and non-airway AMs from infected mice, based on the gene expression levels of all genes.

	Infected Airway AMs					Infected non-airway AMs				Uninfected Airway AMs			
Infected Airway AMs		0.9965	0.9960	0.9773	0.9940	0.9976	0.9866	0.9923	0.9796	0.9067	0.9465	0.8924	0.8575
	0.9965		0.9991	0.9801	0.9966	0.9957	0.9885	0.9971	0.9856	0.9106	0.9468	0.8996	0.8652
	0.9960	0.9991		0.9849	0.9974	0.9952	0.9875	0.9967	0.9863	0.9124	0.9452	0.9014	0.8669
	0.9773	0.9801	0.9849		0.9818	0.9833	0.9820	0.9841	0.9890	0.8719	0.9108	0.8547	0.8206
	0.9940	0.9966	0.9974	0.9818		0.9938	0.9878	0.9962	0.9863	0.9238	0.9502	0.9125	0.8763
Infected non-airway AMs	0.9976	0.9957	0.9952	0.9833	0.9938		0.9939	0.9958	0.9889	0.9016	0.9447	0.8846	0.8463
	0.9866	0.9885	0.9875	0.9820	0.9878	0.9939		0.9918	0.9923	0.9068	0.9530	0.8866	0.8421
	0.9923	0.9971	0.9967	0.9841	0.9962	0.9958	0.9918		0.9934	0.9044	0.9394	0.8917	0.8534
	0.9796	0.9856	0.9863	0.9890	0.9863	0.9889	0.9923	0.9934		0.8856	0.9249	0.8680	0.8262
Uninfected Airway AMs	0.9067	0.9106	0.9124	0.8719	0.9238	0.9016	0.9068	0.9044	0.8856		0.9820	0.9964	0.9596
	0.9465	0.9468	0.9452	0.9108	0.9502	0.9447	0.9530	0.9394	0.9249	0.9820		0.9692	0.9277
	0.8924	0.8996	0.9014	0.8547	0.9125	0.8846	0.8866	0.8917	0.8680	0.9964	0.9692		0.9700
	0.8575	0.8652	0.8669	0.8206	0.8763	0.8463	0.8421	0.8534	0.8262	0.9596	0.9277	0.9700	

Supplementary Table 2b: Pearson correlation of gene expression levels between sorted airway and non-airway AMs from infected mice, based on the gene expression levels of the 12 AM signature genes.

	Infected Airway AMs					Infected non-airway AMs				Uninfected Airway AMs			
Infected Airway AMs		0.999987	0.999994	0.999978	0.999984	0.999991	0.999991	0.999989	0.999987	0.999960	0.999914	0.999908	0.9999474
	0.999987		0.999997	0.999995	0.999990	0.999998	0.999989	0.999987	0.999987	0.9999680	0.9999938	0.9999148	0.9999559
	0.999994	0.999997		0.999988	0.999984	0.999995	0.999997	0.999996	0.999996	0.9999617	0.9999915	0.9999043	0.9999491
	0.999978	0.999995	0.999988		0.999996	0.999994	0.999973	0.999971	0.999971	0.9999717	0.9999942	0.9999214	0.9999594
	0.999984	0.999990	0.999984	0.999996		0.999994	0.999969	0.999965	0.999965	0.9999719	0.9999948	0.9999210	0.9999598
Infected non-airway AMs	0.999991	0.999998	0.999995	0.999994	0.999994		0.999986	0.999983	0.999982	0.9999696	0.9999949	0.9999168	0.9999580
	0.999991	0.999989	0.999997	0.999973	0.999969	0.999986		1.000000	0.999999	0.9999564	0.9999893	0.9998960	0.9999435
	0.999989	0.999987	0.999996	0.999971	0.999965	0.999983	1.000000		1.000000	0.9999545	0.9999882	0.9998931	0.9999413
	0.999987	0.999987	0.999996	0.999971	0.999965	0.999982	0.999999	1.000000		0.9999546	0.9999880	0.9998935	0.9999415
Uninfected Airway AMs	0.999960	0.9999680	0.9999617	0.9999717	0.9999719	0.9999696	0.9999564	0.9999545	0.9999546		0.9999871	0.9999865	0.9999974
	0.999914	0.9999938	0.9999915	0.9999942	0.9999948	0.9999949	0.999893	0.9999882	0.9999880	0.9999871		0.9999473	0.9999804
	0.9999008	0.9999148	0.9999043	0.9999214	0.9999210	0.9999168	0.9998960	0.9998931	0.9998935	0.9999865	0.9999473		0.9999881
	0.9999474	0.9999559	0.9999491	0.9999594	0.9999598	0.9999580	0.9999435	0.9999413	0.9999415	0.9999974	0.9999804	0.9999881	

Supplementary Table 3. Descriptions of the 116 genes significantly overexpressed in non-airway AMs compared to airway AMs during *Mtb* infection.

Gene ID	Gene short name	Gene Name	Average expression level (FPKM)		Adjusted P value
			Airway	Non-airway	
ENSMUSG00000016283	H2-M2	Histocompatibility 2, M region locus 2	102.7	446.5	4.7E-29
ENSMUSG00000035186	Ubd	Ubiquitin D	52.1	227.4	3.0E-17
ENSMUSG00000030142	Clec4e	C-type lectin domain family 4, member e	42.3	90.8	9.2E-16
ENSMUSG00000022126	Acod1	Aconitate decarboxylase 1	31.6	67.1	1.6E-15
ENSMUSG00000031740	Mmp2	Matrix metalloproteinase 2	4.3	19.2	1.6E-15
ENSMUSG00000027962	Vcam1	Vascular cell adhesion molecule 1	2.3	7.1	1.1E-14
ENSMUSG00000038179	Slamf7	SLAM family member 7	20.0	38.6	9.9E-11
ENSMUSG00000027611	Procr	Protein C receptor, endothelial	21.0	50.6	9.4E-09
ENSMUSG00000005089	Slc1a2	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	0.2	0.7	1.2E-08
ENSMUSG00000053318	Slamf8	SLAM family member 8	41.8	82.3	3.9E-08
ENSMUSG00000018217	Pmp22	Peripheral myelin protein 22	3.8	10.2	6.1E-08
ENSMUSG00000020826	Nos2	Nitric oxide synthase 2, inducible	3.2	11.3	6.4E-08
ENSMUSG00000023224	Serping1	Serine (or cysteine) peptidase inhibitor, clade G, member 1	4.5	16.7	6.4E-08
ENSMUSG00000039395	Mreg	Melanoregulin	7.4	13.5	7.2E-08
ENSMUSG00000025877	Hk3	Hexokinase 3	19.7	32.5	7.7E-08
ENSMUSG00000018796	Acsl1	Acyl-CoA synthetase long-chain family member 1	7.6	14.5	8.6E-08
ENSMUSG00000029816	Gpnmb	Glycoprotein (transmembrane) nmb	47.9	75.7	1.4E-07
ENSMUSG00000076441	Ass1	Argininosuccinate synthetase 1	4.4	10.9	2.3E-07
ENSMUSG00000056054	S100a8	S100 calcium binding protein A8 (calgranulin A)	156.1	251.7	1.0E-06
ENSMUSG00000022303	Dcstamp	Dendrocyte expressed seven transmembrane protein	1.9	5.2	1.0E-06
ENSMUSG00000029417	Cxcl9	Chemokine (C-X-C motif) ligand 9	68.0	144.0	1.6E-06
ENSMUSG00000057191	AB124611	CDNA sequence AB124611	14.9	27.5	1.6E-06
ENSMUSG00000038521	C1s1	Complement component 1, s subcomponent 1	12.7	24.3	1.0E-05
ENSMUSG00000090231	Cfb	Complement factor B	2.7	6.9	1.0E-05
ENSMUSG00000024164	C3	Complement component 3	5.5	13.0	1.5E-05
ENSMUSG00000041324	Inhba	Inhibin beta-A	40.7	77.5	1.5E-05
ENSMUSG00000055546	Timd4	T cell immunoglobulin and mucin domain containing 4	1.7	3.9	4.9E-05
ENSMUSG00000026177	Slc11a1	Solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1	7.4	15.7	5.6E-05
ENSMUSG00000031382	Asb11	Ankyrin repeat and SOCS box-containing 11	1.2	2.6	5.9E-05
ENSMUSG00000021322	Aoah	Acyloxyacyl hydrolase	3.0	5.7	9.0E-05

ENSMUSG00000030605	Mfge8	Milk fat globule-EGF factor 8 protein	3.5	6.6	1.6E-04
ENSMUSG00000036636	Clcn7	Chloride channel, voltage-sensitive 7	21.7	31.2	2.5E-04
ENSMUSG00000046031	Fam26f	Family with sequence similarity 26, member F	138.3	218.0	2.8E-04
ENSMUSG00000017652	Cd40	CD40 antigen	14.7	22.5	3.0E-04
ENSMUSG00000028517	Plpp3	Phospholipid phosphatase 3	3.4	5.7	3.5E-04
ENSMUSG00000032561	Acpp	Acid phosphatase, prostate	0.1	0.3	4.0E-04
ENSMUSG00000025854	Fam20c	Family with sequence similarity 20, member C	1.7	3.4	4.4E-04
ENSMUSG00000028270	Gbp2	Guanylate binding protein 2	181.2	272.2	5.8E-04
ENSMUSG00000044162	Tnip3	TNFAIP3 interacting protein 3	22.0	45.6	6.3E-04
ENSMUSG00000068129	Cst7	Cystatin F (leukocystatin)	1.0	1.6	6.3E-04
ENSMUSG00000024334	H2-Oa	Histocompatibility 2, O region alpha locus	37.0	73.1	6.5E-04
ENSMUSG00000041827	Oasl1	2'-5' oligoadenylate synthetase-like 1	5.8	8.7	6.6E-04
ENSMUSG00000044367	Slc16a13	Solute carrier family 16 (monocarboxylic acid transporters), member 13	0.4	1.0	6.7E-04
ENSMUSG00000023913	Pla2g7	Phospholipase A2, group VII (platelet-activating factor acetylhydrolase, plasma)	49.7	118.4	7.7E-04
ENSMUSG00000050737	Ptges	Prostaglandin E synthase	2.5	3.8	8.0E-04
ENSMUSG00000022586	Ly6i	Lymphocyte antigen 6 complex, locus I	425.8	777.0	8.7E-04
ENSMUSG00000039196	Orm1	Orosomuroid 1	4.7	13.3	8.7E-04
ENSMUSG00000020592	Sdc1	Syndecan 1	1.5	4.2	9.9E-04
ENSMUSG00000070427	Il18bp	Interleukin 18 binding protein	74.4	109.0	1.0E-03
ENSMUSG00000026822	Lcn2	Lipocalin 2	1.2	2.7	1.1E-03
ENSMUSG00000020407	Upp1	Uridine phosphorylase 1	3.3	6.2	1.2E-03
ENSMUSG00000069515	Lyz1	Lysozyme 1	92.5	146.1	1.2E-03
ENSMUSG00000020010	Vnn3	Vanin 3	1.7	3.6	1.4E-03
ENSMUSG00000025161	Slc16a3	Solute carrier family 16 (monocarboxylic acid transporters), member 3	5.8	8.7	1.4E-03
ENSMUSG00000049723	Mmp12	Matrix metalloproteinase 12	6.2	10.0	1.7E-03
ENSMUSG00000018920	Cxcl16	Chemokine (C-X-C motif) ligand 16	61.7	97.7	1.8E-03
ENSMUSG00000037966	Ninj1	Ninjurin 1	42.1	67.0	2.1E-03
ENSMUSG00000036103	Colec12	Collectin sub-family member 12	3.3	5.4	2.8E-03
ENSMUSG00000019122	Ccl9	Chemokine (C-C motif) ligand 9	11.0	17.9	3.2E-03
ENSMUSG00000036067	Slc2a6	Solute carrier family 2 (facilitated glucose transporter), member 6	35.5	57.3	3.2E-03
ENSMUSG00000033192	Lpcat2	Lysophosphatidylcholine acyltransferase 2	37.5	62.8	4.1E-03
ENSMUSG00000006205	Htra1	HtrA serine peptidase 1	1.1	2.5	5.1E-03
ENSMUSG00000031722	Hp	Haptoglobin	29.3	46.0	5.7E-03
ENSMUSG00000054203	Ifi205	Interferon activated gene 205	12.3	18.0	7.0E-03
ENSMUSG00000037419	Endod1	Endonuclease domain containing 1	2.6	3.8	7.5E-03
ENSMUSG00000055172	C1ra	Complement component 1, r subcomponent A	22.3	31.4	8.1E-03
ENSMUSG00000030786	Itgam	Integrin alpha M	2.6	4.5	9.6E-03

ENSMUSG00000039699	Batf2	Basic leucine zipper transcription factor, ATF-like 2	13.3	18.9	1.0E-02
ENSMUSG00000011752	Pgam1	Phosphoglycerate mutase 1	23.1	30.2	1.0E-02
ENSMUSG00000024899	Papss2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	0.9	2.0	1.1E-02
ENSMUSG00000024187	Fam234a	Family with sequence similarity 234, member A	3.4	4.8	1.1E-02
ENSMUSG00000030760	Acer3	Alkaline ceramidase 3	7.9	11.0	1.1E-02
ENSMUSG00000024084	Qpct	Glutamyl-peptide cyclotransferase (glutamyl cyclase)	16.6	22.5	1.4E-02
ENSMUSG00000039062	Anpep	Alanyl (membrane) aminopeptidase	1.1	1.9	1.4E-02
ENSMUSG00000000957	Mmp14	Matrix metalloproteinase 14 (membrane-inserted)	16.4	23.8	1.4E-02
ENSMUSG00000030144	Clec4d	C-type lectin domain family 4, member d	21.9	30.7	1.4E-02
ENSMUSG00000028327	Stra6l	STRA6-like	0.7	1.0	1.8E-02
ENSMUSG00000020077	Srgn	Serglycin	208.0	287.7	1.8E-02
ENSMUSG00000027555	Car13	Carbonic anhydrase 13	133.4	167.6	1.8E-02
ENSMUSG00000033880	Lgals3bp	Lectin, galactoside-binding, soluble, 3 binding protein	2.6	4.3	1.8E-02
ENSMUSG00000028645	Slc2a1	Solute carrier family 2 (facilitated glucose transporter), member 1	9.5	13.1	1.8E-02
ENSMUSG00000027737	Slc7a11	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 11	1.7	3.0	1.9E-02
ENSMUSG00000079442	St6galnac4	ST6 (alpha-N-acetylneuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	4.7	6.4	2.2E-02
ENSMUSG00000009585	Apobec3	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide 3	8.9	11.3	2.2E-02
ENSMUSG00000037820	Tgm2	Transglutaminase 2, C polypeptide	58.3	74.0	2.2E-02
ENSMUSG00000020057	Dram1	DNA-damage regulated autophagy modulator 1	44.8	58.0	2.3E-02
ENSMUSG00000037405	Icam1	Intercellular adhesion molecule 1	62.1	86.1	2.4E-02
ENSMUSG00000079057	Cyp4v3	Cytochrome P450, family 4, subfamily v, polypeptide 3	23.5	29.2	2.4E-02
ENSMUSG00000025791	Pgm2	Phosphoglucomutase 2	10.3	12.8	2.6E-02
ENSMUSG00000062300	Nectin2	Nectin cell adhesion molecule 2	1.5	2.3	2.6E-02
ENSMUSG00000015340	Cybb	Cytochrome b-245, beta polypeptide	9.9	16.2	2.7E-02
ENSMUSG00000032294	Pkm	Pyruvate kinase, muscle	115.1	141.3	2.7E-02
ENSMUSG00000045827	Serpinb9	Serine (or cysteine) peptidase inhibitor, clade B, member 9	286.8	336.2	2.7E-02
ENSMUSG00000023947	Nfkbie	Nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, epsilon	13.2	16.8	2.9E-02
ENSMUSG00000007891	Ctsd	Cathepsin D	2006.3	2618.4	2.9E-02
ENSMUSG00000026866	Kynu	Kynureninase (L-kynurenine hydrolase)	13.6	16.7	2.9E-02
ENSMUSG00000028965	Tnfrsf9	Tumor necrosis factor receptor superfamily, member 9	2.6	6.2	2.9E-02
ENSMUSG00000046879	Irgm1	Immunity-related GTPase family M member 1	50.1	65.5	3.1E-02
ENSMUSG00000031438	Rnf128	Ring finger protein 128	6.2	8.8	3.4E-02
ENSMUSG00000041515	Irf8	Interferon regulatory factor 8	42.6	52.4	3.7E-02
ENSMUSG00000047414	Flrt2	Fibronectin leucine rich transmembrane protein 2	0.0	0.1	3.7E-02
ENSMUSG00000004952	Rasa4	RAS p21 protein activator 4	3.5	4.7	3.8E-02
ENSMUSG00000002103	Acp2	Acid phosphatase 2, lysosomal	16.8	19.6	3.9E-02

ENSMUSG00000044309	Apol7c	Apolipoprotein L 7c	1.3	2.6	4.0E-02
ENSMUSG00000032802	Srxn1	Sulfiredoxin 1 homolog (S. cerevisiae)	11.7	15.0	4.2E-02
ENSMUSG00000026879	Gsn	Gelsolin	14.4	18.3	4.2E-02
ENSMUSG00000094724	Rnaset2b	Ribonuclease T2B	49.2	63.4	4.2E-02
ENSMUSG00000024770	Lipn	Lipase, family member N	0.7	1.5	4.3E-02
ENSMUSG00000024621	Csf1r	Colony stimulating factor 1 receptor	48.3	60.7	4.3E-02
ENSMUSG00000023991	Foxp4	Forkhead box P4	0.3	0.6	4.4E-02
ENSMUSG00000031266	Gla	Galactosidase, alpha	20.9	25.3	4.4E-02
ENSMUSG00000036086	Zranb3	Zinc finger, RAN-binding domain containing 3	1.0	1.4	4.7E-02
ENSMUSG00000029860	Zyx	Zyxin	32.3	43.9	4.7E-02
ENSMUSG00000021451	Sema4d	Sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	3.4	5.9	4.8E-02
ENSMUSG00000064358	mt-Co3	Mitochondrially encoded cytochrome c oxidase III	0.7	8.9	4.8E-02
ENSMUSG00000053030	Spink2	Serine peptidase inhibitor, Kazal type 2	22.3	37.3	5.0E-02

Supplementary Table 4: KEGG pathways significantly enriched among the 116 genes overexpressed in non-airway AMs compared to airway AMs during infection.

KEGG ID		# genes in pathway	# genes in test set	Expected # genes	Enrichment Ratio	Adjusted P value
mmu05150	Staphylococcus aureus infection	52	7	0.42	16.63	4.9E-05
mmu05133	Pertussis	75	7	0.61	11.53	3.2E-04
mmu04610	Complement and coagulation cascades	87	7	0.70	9.94	5.8E-04
mmu04514	Cell adhesion molecules (CAMs)	169	8	1.37	5.85	4.5E-03
mmu05230	Central carbon metabolism in cancer	66	5	0.53	9.36	1.1E-02
mmu05144	Malaria	49	4	0.40	10.09	2.9E-02
mmu04145	Phagosome	184	7	1.49	4.70	2.9E-02

Supplementary Table 5: Descriptions of the 12 genes significantly overexpressed in airway AMs compared to non-airway AMs in HN878-infected mice.

Gene ID	Gene short name	Gene Name	Average expression level (FPKM)		Adjusted P value
			Airway	Non-airway	
ENSMUSG00000028680	Plk3	Polo-like kinase 3	41.95	24.46	3.0E-04
ENSMUSG00000038508	Gdf15	Growth differentiation factor 15	31.3	14.4	3.3E-03
ENSMUSG00000052512	Nav2	Neuron navigator 2	0.7	0.3	4.5E-03
ENSMUSG00000041268	Dmxl2	Dmx-like 2	6.3	4.0	1.8E-02
ENSMUSG00000033705	Stard9	START domain containing 9	0.5	0.3	1.8E-02
ENSMUSG00000037279	Ovol2	Ovo like zinc finger 2	5.0	2.6	2.4E-02
ENSMUSG00000020205	Phlda1	Pleckstrin homology like domain, family A, member 1	26.8	14.3	2.5E-02
ENSMUSG00000038352	Arl5c	ADP-ribosylation factor-like 5C	73.4	33.2	3.1E-02
ENSMUSG00000042745	Id1	Inhibitor of DNA binding 1	33.9	18.9	3.5E-02
ENSMUSG00000033004	Mycbp2	MYC binding protein 2	3.2	1.9	4.1E-02
ENSMUSG00000056708	Ier5	Immediate early response 5	32.3	19.2	4.1E-02
ENSMUSG00000025893	Kbtbd3	Kelch repeat and BTB (POZ) domain containing 3	6.3	4.0	4.9E-02

Supplementary Table 6: KEGG pathways significantly enriched among the 3517 genes overexpressed in the infected airway AMs compared to uninfected airway AMs.

KEGG ID	# genes in pathway	# genes in test set	Expected # genes	Enrichment Ratio	Adjusted P value	
mmu03050	Proteasome	45	39.00	7.65	5.10	0
mmu05168	Herpes simplex infection	215	79.00	36.57	2.16	2.25E-10
mmu04612	Antigen processing and presentation	91	44.00	15.48	2.84	3.78E-10
mmu03040	Spliceosome	133	54.00	22.62	2.39	5.52E-09
mmu01100	Metabolic pathways	1309	301.00	222.62	1.35	3.4E-08
mmu04142	Lysosome	124	47.00	21.09	2.23	8.77E-07
mmu05012	Parkinson's disease	144	52.00	24.49	2.12	8.99E-07
mmu04145	Phagosome	184	60.00	31.29	1.92	4.83E-06
mmu00520	Amino sugar and nucleotide sugar metabolism	49	24.00	8.33	2.88	7.65E-06
mmu00190	Oxidative phosphorylation	134	47.00	22.79	2.06	8.15E-06
mmu04141	Protein processing in endoplasmic reticulum	167	55.00	28.40	1.94	8.15E-06
mmu05169	Epstein-Barr virus infection	221	67.00	37.59	1.78	1.32E-05
mmu05150	Staphylococcus aureus infection	52	24.00	8.84	2.71	2.12E-05
mmu04621	NOD-like receptor signaling pathway	169	54.00	28.74	1.88	2.41E-05
mmu04932	Non-alcoholic fatty liver disease (NAFLD)	153	50.00	26.02	1.92	2.67E-05
mmu05332	Graft-versus-host disease	65	27.00	11.05	2.44	4.7E-05
mmu05140	Leishmaniasis	66	27.00	11.22	2.41	6.28E-05
mmu03013	RNA transport	167	52.00	28.40	1.83	6.97E-05
mmu04130	SNARE interactions in vesicular transport	33	17.00	5.61	3.03	8.91E-05
mmu05152	Tuberculosis	178	54.00	30.27	1.78	9.61E-05
mmu05323	Rheumatoid arthritis	83	31.00	14.12	2.20	9.61E-05
mmu05016	Huntington's disease	194	57.00	32.99	1.73	0.000146
mmu05166	HTLV-I infection	285	76.00	48.47	1.57	0.000258
mmu05330	Allograft rejection	64	25.00	10.88	2.30	0.000265
mmu05164	Influenza A	170	50.00	28.91	1.73	0.00043
mmu04940	Type I diabetes mellitus	70	26.00	11.90	2.18	0.000473
mmu04380	Osteoclast differentiation	132	41.00	22.45	1.83	0.000505
mmu00240	Pyrimidine metabolism	104	34.00	17.69	1.92	0.000679
mmu00100	Steroid biosynthesis	19	11.00	3.23	3.40	0.000679
mmu05416	Viral myocarditis	88	30.00	14.97	2.00	0.000714

mmu04144	Endocytosis	286	74.00	48.64	1.52	0.000727
mmu01200	Carbon metabolism	118	37.00	20.07	1.84	0.000791
mmu04650	Natural killer cell mediated cytotoxicity	120	37.00	20.41	1.81	0.001135
mmu05133	Pertussis	75	26.00	12.76	2.04	0.001377
mmu05010	Alzheimer's disease	175	49.00	29.76	1.65	0.001418
mmu00620	Pyruvate metabolism	38	16.00	6.46	2.48	0.001938
mmu03030	DNA replication	35	15.00	5.95	2.52	0.002326
mmu04210	Apoptosis	138	40.00	23.47	1.70	0.002326
mmu00020	Citrate cycle (TCA cycle)	32	14.00	5.44	2.57	0.002716
mmu04668	TNF signaling pathway	109	33.00	18.54	1.78	0.003092
mmu03420	Nucleotide excision repair	44	17.00	7.48	2.27	0.003716
mmu04659	Th17 cell differentiation	102	31.00	17.35	1.79	0.004046
mmu04120	Ubiquitin mediated proteolysis	140	39.00	23.81	1.64	0.005705
mmu05145	Toxoplasmosis	113	33.00	19.22	1.72	0.005705
mmu00230	Purine metabolism	178	47.00	30.27	1.55	0.006205
mmu05340	Primary immunodeficiency	36	14.00	6.12	2.29	0.009472
mmu05160	Hepatitis C	136	37.00	23.13	1.60	0.011282
mmu04658	Th1 and Th2 cell differentiation	87	26.00	14.80	1.76	0.012486
mmu04660	T cell receptor signaling pathway	105	30.00	17.86	1.68	0.012612
mmu00010	Glycolysis / Gluconeogenesis	66	21.00	11.22	1.87	0.013246
mmu03008	Ribosome biogenesis in eukaryotes	79	24.00	13.44	1.79	0.013246
mmu05320	Autoimmune thyroid disease	79	24.00	13.44	1.79	0.013246
mmu03060	Protein export	30	12.00	5.10	2.35	0.013419
mmu05134	Legionellosis	58	19.00	9.86	1.93	0.013749
mmu03018	RNA degradation	81	24.00	13.78	1.74	0.018042
mmu04640	Hematopoietic cell lineage	95	27.00	16.16	1.67	0.01953
mmu00280	Valine, leucine and isoleucine degradation	56	18.00	9.52	1.89	0.021088
mmu05162	Measles	138	36.00	23.47	1.53	0.022493
mmu00052	Galactose metabolism	32	12.00	5.44	2.20	0.022615
mmu04620	Toll-like receptor signaling pathway	101	28.00	17.18	1.63	0.022812
mmu00072	Synthesis and degradation of ketone bodies	11	6.00	1.87	3.21	0.024919
mmu05142	Chagas disease (American trypanosomiasis)	103	28.00	17.52	1.60	0.029623
mmu05203	Viral carcinogenesis	235	55.00	39.97	1.38	0.031497
mmu03430	Mismatch repair	22	9.00	3.74	2.41	0.03246
mmu04622	RIG-I-like receptor signaling pathway	68	20.00	11.56	1.73	0.035221
mmu04623	Cytosolic DNA-sensing pathway	64	19.00	10.88	1.75	0.037481
mmu01230	Biosynthesis of amino acids	78	22.00	13.27	1.66	0.039805
mmu05132	Salmonella infection	78	22.00	13.27	1.66	0.039805

mmu04672	Intestinal immune network for IgA production	43	14.00	7.31	1.91	0.0406
mmu00900	Terpenoid backbone biosynthesis	23	9.00	3.91	2.30	0.041531
mmu00640	Propanoate metabolism	31	11.00	5.27	2.09	0.043027
mmu03022	Basal transcription factors	44	14.00	7.48	1.87	0.047977
mmu04062	Chemokine signaling pathway	196	46.00	33.33	1.38	0.047977

Supplementary Table 7: KEGG pathways significantly enriched among the 4442 genes overexpressed in the uninfected airway AMs compared to infected airway AMs.

KEGG ID	# genes in pathway	# genes in test set	Expected # genes	Enrichment Ratio	Adjusted P value	
mmu03010	Ribosome	141	73.00	29.0	2.5	3.32E-14
mmu04510	Focal adhesion	203	84.00	41.70	2.01	9.44E-10
mmu04810	Regulation of actin cytoskeleton	218	85.00	44.78	1.90	1.89E-08
mmu05206	MicroRNAs in cancer	141	61.00	28.96	2.11	4.65E-08
mmu04360	Axon guidance	177	70.00	36.35	1.93	2.31E-07
mmu04022	cGMP-PKG signaling pathway	173	67.00	35.53	1.89	1.12E-06
mmu05200	Pathways in cancer	395	125.00	81.13	1.54	2.79E-06
mmu04910	Insulin signaling pathway	143	57.00	29.37	1.94	2.95E-06
mmu04919	Thyroid hormone signaling pathway	117	49.00	24.03	2.04	3.51E-06
mmu04512	ECM-receptor interaction	83	38.00	17.05	2.23	5.45E-06
mmu04320	Dorso-ventral axis formation	26	17.00	5.34	3.18	2.24E-05
mmu04072	Phospholipase D signaling pathway	145	55.00	29.78	1.85	2.24E-05
mmu04931	Insulin resistance	111	45.00	22.80	1.97	2.41E-05
mmu04211	Longevity regulating pathway	95	39.00	19.51	2.00	8.06E-05
mmu04915	Estrogen signaling pathway	98	39.00	20.13	1.94	0.000184
mmu04010	MAPK signaling pathway	252	80.00	51.76	1.55	0.000265
mmu05220	Chronic myeloid leukemia	73	31.00	14.99	2.07	0.000289
mmu04530	Tight junction	140	50.00	28.76	1.74	0.000328
mmu04520	Adherens junction	74	31.00	15.20	2.04	0.000358
mmu01522	Endocrine resistance	95	37.00	19.51	1.90	0.000409
mmu05224	Breast cancer	146	51.00	29.99	1.70	0.000464
mmu05231	Choline metabolism in cancer	101	38.00	20.74	1.83	0.000662
mmu04012	ErbB signaling pathway	87	34.00	17.87	1.90	0.000662
mmu04664	Fc epsilon RI signaling pathway	70	29.00	14.38	2.02	0.000662
mmu04024	cAMP signaling pathway	199	64.00	40.87	1.57	0.000773
mmu04933	AGE-RAGE signaling pathway in diabetic complications	102	38.00	20.95	1.81	0.000773
mmu04310	Wnt signaling pathway	146	50.00	29.99	1.67	0.000773
mmu05215	Prostate cancer	89	34.00	18.28	1.86	0.000964
mmu04152	AMPK signaling pathway	129	45.00	26.50	1.70	0.000964

mmu04270	Vascular smooth muscle contraction	129	45.00	26.50	1.70	0.000964
mmu04330	Notch signaling pathway	49	22.00	10.06	2.19	0.000976
mmu00310	Lysine degradation	59	25.00	12.12	2.06	0.001038
mmu04722	Neurotrophin signaling pathway	123	43.00	25.26	1.70	0.001147
mmu04015	Rap1 signaling pathway	215	67.00	44.16	1.52	0.001147
mmu04070	Phosphatidylinositol signaling system	98	36.00	20.13	1.79	0.001229
mmu00562	Inositol phosphate metabolism	70	28.00	14.38	1.95	0.001229
mmu04392	Hippo signaling pathway -multiple species	26	14.00	5.34	2.62	0.00143
mmu05222	Small cell lung cancer	85	32.00	17.46	1.83	0.001535
mmu05100	Bacterial invasion of epithelial cells	78	30.00	16.02	1.87	0.001535
mmu01521	EGFR tyrosine kinase inhibitor resistance	82	31.00	16.84	1.84	0.001699
mmu05205	Proteoglycans in cancer	204	63.00	41.90	1.50	0.001978
mmu04611	Platelet activation	123	42.00	25.26	1.66	0.001979
mmu04390	Hippo signaling pathway	154	50.00	31.63	1.58	0.002158
mmu04921	Oxytocin signaling pathway	159	51.00	32.66	1.56	0.00256
mmu04068	FoxO signaling pathway	134	44.00	27.52	1.60	0.003529
mmu04925	Aldosterone synthesis and secretion	86	31.00	17.66	1.75	0.003894
mmu04014	Ras signaling pathway	230	68.00	47.24	1.44	0.003978
mmu05213	Endometrial cancer	52	21.00	10.68	1.97	0.005166
mmu04144	Endocytosis	286	81.00	58.74	1.38	0.005166
mmu05214	Glioma	66	25.00	13.56	1.84	0.005166
mmu04666	Fc gamma R-mediated phagocytosis	89	31.00	18.28	1.70	0.006536
mmu04912	GnRH signaling pathway	89	31.00	18.28	1.70	0.006536
mmu04914	Progesterone-mediated oocyte maturation	89	31.00	18.28	1.70	0.006536
mmu05221	Acute myeloid leukemia	57	22.00	11.71	1.88	0.007193
mmu04540	Gap junction	86	30.00	17.66	1.70	0.007289
mmu04151	PI3K-Akt signaling pathway	345	94.00	70.86	1.33	0.007289
mmu04922	Glucagon signaling pathway	102	34.00	20.95	1.62	0.008599
mmu05202	Transcriptional misregulation in cancer	177	53.00	36.35	1.46	0.009026
mmu05212	Pancreatic cancer	66	24.00	13.56	1.77	0.010585
mmu05414	Dilated cardiomyopathy	89	30.00	18.28	1.64	0.012321
mmu04720	Long-term potentiation	67	24.00	13.76	1.74	0.012905
mmu04974	Protein digestion and absorption	90	30.00	18.49	1.62	0.014263
mmu04213	Longevity regulating pathway - multiple species	64	23.00	13.15	1.75	0.014263
mmu05210	Colorectal cancer	64	23.00	13.15	1.75	0.014263
mmu04930	Type II diabetes mellitus	50	19.00	10.27	1.85	0.015371
mmu04724	Glutamatergic synapse	114	36.00	23.42	1.54	0.01573
mmu04725	Cholinergic synapse	112	35.00	23.00	1.52	0.021113

mmu04071	Sphingolipid signaling pathway	124	38.00	25.47	1.49	0.021204
mmu04917	Prolactin signaling pathway	74	25.00	15.20	1.64	0.022886
mmu05223	Non-small cell lung cancer	56	20.00	11.50	1.74	0.025659
mmu02010	ABC transporters	46	17.00	9.45	1.80	0.031272
mmu05161	Hepatitis B	145	42.00	29.78	1.41	0.038827
mmu03460	Fanconi anemia pathway	51	18.00	10.48	1.72	0.041793
mmu04662	B cell receptor signaling pathway	74	24.00	15.20	1.58	0.042552
mmu04971	Gastric acid secretion	74	24.00	15.20	1.58	0.042552
mmu05412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	74	24.00	15.20	1.58	0.042552
mmu05146	Amoebiasis	110	33.00	22.59	1.46	0.044953
mmu05211	Renal cell carcinoma	67	22.00	13.76	1.60	0.047118
mmu04750	Inflammatory mediator regulation of TRP channels	127	37.00	26.09	1.42	0.048553
mmu04150	mTOR signaling pathway	156	44.00	32.04	1.37	0.048581