Pathological consequences of chronic olfactory inflammation on neurite morphology of olfactory bulb projection neurons

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ABSTRACT

Background: Chronic olfactory inflammation (COI) in conditions such as chronic rhinosinusitis significantly impairs the functional and anatomical components of the olfactory system. COI induced by intranasal administration of lipopolysaccharide (LPS) results in atrophy, gliosis, and pro-inflammatory cytokine production in the OB. Although chronic rhinosinusitis patients have smaller olfactory bulbs (OBs), the consequences of olfactory inflammation on OB neurons are largely unknown.

Methods: In this study, we investigated the neurological consequence of COI on OB projection neurons, mitral cells (MCs) and tufted cells (TCs). To induce COI, we performed unilateral intranasal administration of LPS to mice for 4 and 10 weeks. Effects of COI on the OB were examined using RNA-sequencing approaches and immunohistochemical analyses.

Results: We found that repeated LPS administration upregulated immune-related biological pathways in the OB after 4 weeks. We also determined that the length of TC lateral dendrites in the OB significantly decreased after 10 weeks of COI. The axon initial segment of TCs decreased in number and in length after 10 weeks of COI. The lateral dendrites and axon initial segments of MCs, however, were largely unaffected. In addition, dendritic arborization and axon initial segment reconstruction both took place following a 10-week recovery period.

Conclusion: Our findings suggests that olfactory inflammation specifically affects TCs and their integrated circuitry, whereas MCs are potentially protected from this condition. This data demonstrates unique characteristics of the OBs ability to undergo neuroplastic changes in response to stress.

KEY MESSAGES

- Tufted cells undergo neurite dysregulation in response to chronic olfactory inflammation, whereas mitral cells are largely unaffected.
- Tufted cells experience complete recovery from neurite dysregulation following a period of ceased inflammation.

KEY WORDS

Chronic rhinosinusitis; chronic olfactory inflammation; olfactory system; projection neurons; neurite; lipopolysaccharide

INTRODUCTION

Individuals are exposed to chemicals and environmental agents on a daily basis, some of which are capable of entering the body and inducing an immune response. Bacteria, viruses, and allergens such as dust, mold, or pollen are common agents that can enter the nasal cavity and induce inflammation of the olfactory mucosa, mucous membranes lining the olfactory epithelium (OE), and the paranasal sinuses^{1, 2}. This inflammatory state is the foundation to the disease known as rhinosinusitis³. Rhinosinusitis is one of the most common medical conditions in the world⁴, currently affecting about 12.5% of individuals in the United States alone⁵. Symptoms of rhinosinusitis can include thick nasal mucus, stuffy nose and congestion, facial pain, headache, cough, fever, and hyposmia/anosmia⁶⁻⁸. Rhinosinusitis can be an acute or chronic disease^{9, 10}, yet when the condition lasts longer than 12 weeks it is considered chronic rhinosinusitis (CRS) and is typically due to a bacterial infection^{4, 8, 11, 12}.

Although immune responses are an essential first line of defense for the body against invading pathogens, chronic inflammation can act as a significant stressor on an organ or system and may result in damage of the affected tissue¹³⁻¹⁵. Although airflow obstruction within the nasal cavity has been linked to hyposmia, clinical studies have demonstrated that the immune response induced during CRS can severely damage the olfactory mucosa and olfactory epithelium, another major contributor to the loss of smell¹⁶⁻¹⁹. Patients with CRS also exhibit a decrease in the volumetric size of their olfactory bulbs (OBs)^{20, 21}. Nonetheless, the extent to which the CRS-induced inflammatory responses affect the central nervous system (CNS) including the OB is currently not well understood.

Preclinical research using rodents has established that intranasal (i.n.) administration of various chemical entities can induce inflammation of the olfactory epithelium in the form of immune cell activation, infiltration, and pro-inflammatory cytokine release resulting in apoptosis of olfactory sensory neurons²²⁻²⁸. Our previous studies have also demonstrated that i.n. administration of lipopolysaccharide (LPS) has severe implications on the CNS including OB gliosis and atrophy^{23, 29, 30}. More specifically, beginning as early as 3 weeks of i.n. LPS administrations, a significant upregulation of microglial and astrocytic activity as well as the presence of pro-inflammatory cytokines can be detected in the superficial OB layers including the olfactory nerve layer (ONL), glomerular layer (GL), and the superficial external plexiform layer (sEPL). Interestingly, after 10 weeks of administrations, OB atrophy takes place primarily in the same three superficial OB layers

in which the layers are significantly thinner than in controls^{29, 30}. In this study, and in conjunction with our previous studies, we administered LPS into the mouse nostril repetitively over the course of 4 and 10 weeks to induce a state of chronic inflammation of the olfactory epithelium (or chronic olfactory inflammation, COI). We report that COI induces a decrease in the activity of projection neurons residing in the EPL (tufted cells, TCs), as well as dendritic retraction and axonal instability of the same neurons. Mitral cells (MCs) residing in the mitral cell layer (MCL), however, appear to be almost entirely unaffected. Finally, we report that the COI-induced TC impairments return to homeostasis following a recovery period. These results provide further evidence that the OB consists of highly plastic components capable of undergoing severe stress.

METHODS

Animals

In this study, we used eight-week-old C57BL/6J (stock #000664) and YFP knockin (stock #006148; C57BL/6J background) mice purchased from The Jackson Laboratory, as well as Pcdh21-CreER knockin (BRC #RBRC02410; C57BL/6J background) mice purchased from Riken BRC. Pcdh21-CreER x YFP mice were created by crossing Pcdh21-CreER-positive mice with YFP homozygotes to create Cre-positive/YFP heterozygotes (+/Het mice; this was the only genotype used for this mouse line in this study). Among the +/Het mice, a yellow fluorescent protein (YFP) is specifically expressed in MC/TCs in the OBs following tamoxifen injections. All mice were deeply anesthetized with isoflurane and intranasally administered 10 μ L of LPS from *Escherichia coli* (Sigma; product #L2880; lot #025M4040V) in physiologic saline (1 mg/ml; Sigma). LPS administrations took place three times per week for 4 or 10 weeks and were carried out unilaterally to the left naris of each mouse, with the right side serving as an internal control. For analyses of recovery, one group of eight-week-old +/Het mice (n=3) underwent unilateral 10-week LPS administrations as discussed previously^{23, 29, 30} and were subsequently housed for 10 weeks with no additional treatment.

Three days prior to being sacrificed for immunohistochemical analyses, mice were intraperitoneally injected with tamoxifen (30 mg/kg). The dose for tamoxifen was selected after multiple trials at different doses in order to observe optimal YFP expression in fewer OB projection neurons allowing us to trace individual neuron apical and lateral dendrites (data not shown). For histologic preparation, mice were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and transcardially perfused with PBS, followed by 4% (wt/vol) paraformaldehyde in PBS. Heads were removed and placed in the same fixative at 4°C overnight. The rostral half of the calvaria (anterior to the bregma) and the nasal bone were then placed in 0.45 mol/L EDTA in PBS at 4°C for 2 days for decalcification, cryoprotected with 30% sucrose (wt/vol) at 4°C overnight, embedded in OCT compound (Sakura Finetek USA, Torrance, Calif), and maintained at -80°C until use. All protocols were approved by and all methods were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Penn State College of Medicine.

RNA sequencing analysis

RNA Extraction: OBs were microdissected from fixed and cryopreserved whole mouse brains. Approximately 5 mg of frozen tissue was incubated with proteinase K (500 μ g/ml) in 500 μ l of 10

139 mM NaCl, 500 mM Tris (pH 8.0), 20 mM EDTA, and 1% SDS at 55 °C for 3 hours until the tissue
140 was completely dissolved³¹. The acid phenol-chloroform method was applied for RNA extraction
141 using the Direct-zol™ RNA Micro prep Kit (Zymo Research). RNA quality and quantity were
142 determined by RNA Pico BioAnalyzer (Agilent technologies).

143 *RNA-sequencing and Analysis:* The cDNA libraries were prepared using the QuantSeq 3'mRNA-
144 Seq Library Prep Kit FWD for Illumina (Lexogen) as per the manufacturer's instructions. Briefly,
145 total RNA was reverse transcribed using oligo (dT) primers. The second cDNA strand was
146 synthesized by random priming, in which DNA polymerase is efficiently stopped when reaching
147 the next hybridized random primer allowing only the fragment closest to the 3' end being captured
148 for later indexed adapter ligation and PCR amplification. The processed libraries were assessed
149 for their size distribution and concentration using the BioAnalyzer High Sensitivity DNA Kit (Agilent
150 Technologies). The libraries were pooled and diluted to 3 nM using 10 mM Tris-HCl, pH 8.5, and
151 then denatured using the Illumina protocol. The denatured libraries were loaded onto an S1 flow
152 cell on an Illumina NovaSeq 6000 (Illumina) and run for 53-101 cycles according to the
153 manufacturer's instructions. After the quality and polyA trimming by BBDuk and alignment by
154 HISAT2 (version 2.1.0)³², read counts were calculated using HTSeq³³ by supplementing Ensembl
155 gene annotation (GRCm38.78). DESeq2 R package³⁴ was used to determine differentially
156 expressed genes by taking into account a paired design where each mouse individual was
157 compared between ipsilateral and contralateral. Significance was defined to be those with
158 adjusted p-value < 0.1 calculated by the Benjamini-Hochberg method to control the false
159 discovery rate (FDR). The ggplot2 R package³⁵ was used for generating a heatmap. The list of
160 differentially expressed genes was analyzed with Ingenuity Pathway Analysis (IPA). Fastq files
161 and raw read counts generated during this study are available at GEO (GSE185945).

163 Immunostaining

164 Olfactory tissues were coronally cut on a cryostat into 20µm slices, mounted on slide glasses,
165 dried and stored at -80°C until use. The sections were rehydrated with TBST (10 mmol/L Tris-
166 HCl [pH 7.4] and 100 mmol/L NaCl with 0.3% Triton-X100 [vol/vol]), blocked with blocking buffer
167 (5% normal donkey serum [vol/vol] in TBST) at room temperature for one hour, and incubated
168 with primary antibodies diluted in blocking buffer overnight at 4°C. The antibodies and dilutions
169 used in the present study are as follows: mouse anti-Ankyrin G IgG2a (NeuroMab, catalog #75-
170 146, 1:500), chicken anti-green fluorescent protein (GFP; Abcam, catalog #ab13970, 1:1000)
171 which also recognizes YFP, mouse anti-Calretinin (NeuroMarkers, catalog #MA5-14540, 1:400),
172 Alexa Fluoro 488 mouse anti-Tbx21 (Biolegend, catalog #644830, 1:300), rabbit anti-Phospho-

S6 Ribosomal Protein (PS6; Cell Signaling Technology, catalog #4854S, 1:1000), rabbit anti-Parvalbumin (Millipore Sigma, catalog #MAB1572, 1:300), and rabbit anti-Somatostatin (ImmunoStar, catalog #20067, 1:300). For double immunostaining with fluorescence, Alexa Fluoro 488-conjugated or 555-conjugated donkey antispecies IgGs (Thermo Fisher Scientific) were used as secondary antibodies (1:300) and incubated on tissue sections at room temperature for one hour. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI). The sections were coverslipped with fluorescence mounting medium (Dako Agilent) and imaged using the Zeiss Axio Imager M2 fluorescent microscope with an automated motorized XY stage. All images were acquired using the same excitation light intensity, exposure time, and numerical aperture of the objective lens.

Image analyses and morphometry

Five OB sections were stained from each mouse brain with calretinin and DAPI and divided into each OB sublayer (including the superficial and deep EPL) to measure their area. Cells that were positive for DAPI, Tbx21, and YFP in the MCL and EPL were defined as MCs and TCs, respectively, and were subsequently counted to determine the numbers in their respective layers. The area of the superficial and deep (s/d)EPL were measured separately by using Photoshop software. The lengths of YFP-positive (YFP+) dendrites were measured in the sEPL and dEPL separately by manual tracing in the FIJI/ImageJ software using the ROI Manager tool with the freehand line tracer. The primary method of normalizing the dendrite data was to divide the total length of dendrites per OB (in μm) by the number of YFP+ somata in that OB (final units in $\mu\text{m}/\text{cell}$). Similarly, we also normalized this data with respect to dendrite density by converting the sEPL and dEPL areas to square millimeters (mm^2) and divided the total length of dendrites (in μm) in each layer of each OB section by the respective area in mm^2 (resulting units of $\mu\text{m}/\text{mm}^2$). Axon initial segments (AISes) were measured in a region defined by a rectangle with an area of $650 \times 450 \mu\text{m}^2$ in both the medial and lateral portion of the OB. AISes were defined by positive Ankyrin G staining and all AISes in the region were counted and measured in length (μm), and were analyzed via manual tracing in the FIJI/ImageJ software using the ROI Manager tool with the freehand line tracer.

Experimental design and statistical analysis

Comparisons of the relative OB sizes and AIS length/count among contralateral and ipsilateral OBs were statistically analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Comparisons of dendrite length among contralateral and

207 ipsilateral OBs were statistically analyzed by paired t-tests due to differences in inherent cre-
208 recombination and subsequent expression of YFP. A p-value ≤ 0.05 indicated a significant
209 difference. Statistical analyses were performed using Prism software (GraphPad Software, Inc.).
210 Values are reported as means $\pm$ SEM.

211

RESULTS

Upregulation of interferon- γ -driven inflammatory pathways following 4-week COI

We first aimed to examine gene expression signatures affected by early stage COI. To induce COI, LPS administrations took place three times per week for 4 weeks and were carried out unilaterally to the left naris of each mouse, with the right side serving as an internal control. The OB ipsilateral to the side of the injected naris is referred to as *ipsilateral (ipsi)*, and the opposite OB (control) as *contralateral (contra)*. Differential gene expression analysis was performed between the ipsilateral and contralateral OB from mice administered LPS (n=3). We identified 47 genes upregulated and 18 downregulated in the ipsilateral OBs compared to contralateral OBs (Fig. 1A). To understand the functional relevance of these clusters, we performed functional annotation analysis for these genes using Ingenuity Pathway Analysis (IPA, Qiagen). The Core Analysis highlighted the most significantly enriched and activated Canonical Pathway as “Neuroinflammation Signaling Pathway” ($-\log(p\text{-value}) = 5.95$, $z\text{-score} = 2.646$, Fig. 1B). Molecules directly involved in this pathway include B2M, CCL5, CYBB, HLA-A, HLA-DQA1, HLA-DQB1, HLA-DRB5, and RAC2.

Next, we examined the upstream regulator in the IPA Core Analysis and identified interferon- γ (IFN- γ) as the most significant upstream regulator with the largest z-score ($p\text{-value} = 5.04\text{E-}20$, $z\text{-score} = 4.749$, Supplementary Table 1). Although the expression level of IFN- γ itself is not altered, the significant number of related downstream molecules including B2M, Bst2, C1QA, C1QB, C4A/C4B, CCL5, CD74, CTSS, Cxcl9, CYBB, GBP2, GFAP, HLA-A, HLA-DQA1, HLA-DQB1, HLA-DRB5, Ifi47, IFITM3, Igtf, ligp1, IRF1, IRF8, LGALS3BP, PARP14, PENK, RAC2, TAP1, and TAPBP are upregulated. The Mechanistic Network (Fig. 1C), a method to predict signaling cascades that connect other significantly represented upstream regulators to elicit the observed gene expression changes, demonstrated that IFN- γ may orchestrate with other cytokines such as TNF- α and IL-1 β and regulate cascades of intracellular signaling to lead to activations of multiple transcription regulators such as IRF1, NF-kB complex, CREBBP, RELA, IRF8, STAT1, and STAT3. NR3C1, on the other hand, is downregulated and its inhibition is predicted to be mediated by TNF- α .

Finally, we summarize our findings by IPA’s Graphical Summary (Fig. 1D) to provide an overview of the major biological themes in the IPA analysis by selecting the most significant entities identified in the Core Analysis such as Canonical Pathways, Upstream Regulators, and Disease

and Biological Functions, further representing how they relate to each other. The Graphical Summary demonstrates how upregulated/activated (shown in orange) and downregulated/inhibited (shown in blue) genes, pathways, or diseases interact with each other. In addition to the activation of Neuroinflammation Signaling Pathway observed in the Canonical Pathway analysis (Fig. 1B) and IFN- γ which was depicted in the Upstream Regulator analysis (Fig. 1C), we revealed that many pathways associated with immune responses and leukocyte activities are activated, while infectious status is predicted to be inhibited.

Reduction of tufted cell lateral dendrites following 10-week COI

The presence of proinflammatory cytokines such as IFN- γ and TNF- α are capable of causing dendritic atrophy, retraction, and loss of synapses in primary neuronal cultures³⁶. It is important to note that LPS-induced COI does not cause the death of OB projection neurons (MCs/TCs) at any point up to the 24-week time point^{23, 29, 30}. Therefore, we aimed to explore the potential phenomenon of dendritic retraction of MC/TCs following our COI paradigm.

The distribution of projection neuron somata and lateral dendrites is unique based on cell type. TC somata are located in the EPL and extend their lateral dendrites throughout the sEPL, whereas MC somata exist in the MCL and extend their lateral dendrites in the dEPL³⁷. In order to observe changes to the somata and dendritic morphology of MCs/TCs in the OB, we used Pcdh21-CreER x YFP (+/Het) transgenic mice unilaterally administered with LPS (i.n.) for 10 weeks. Protocadherin-21 (Pcdh21) is a member of the protocadherin homophilic cell-adhesion protein family uniquely expressed in MCs/TCs in the mouse OB³⁸. On the final LPS-administration day, the mice were treated with tamoxifen (i.p., 30 mg/kg) to activate CreER for the YFP expression from the ROSA site and sacrificed 3 days after the injection.

As expected, the overall shape of the ipsilateral OB appears to be atrophied and narrower compared to the contralateral OB (Fig. 2A). Cell bodies and dendrites expressing YFP were observed in the GL, EPL, and MCL of both OBs (Fig. 2B, C). There were no differences in the total number of TCs, YFP+ cells in the EPL, counted from 5 coronal OB sections (contra., 72.00 ± 17.58 vs ipsi., 72.67 ± 21.39). The number of MCs, YFP+ cells in the MCL, was smaller than that of TCs but not significantly different comparing the contralateral to the ipsilateral OBs (contra., 23.67 ± 12.86 vs ipsi., 29.00 ± 16.92). This data suggests that the +/Het transgenic model preferentially labels TCs over MCs in the OB, and LPS treatment does not influence the expression of YFP in OB projection neurons.

Next, we analyzed the YFP+ dendrites in the EPL. In the contralateral OB, the total length of YFP+ dendrites counted from 5 coronal sections was significantly greater in the sEPL than in the dEPL (Fig. 2B; $15217 \pm 1332 \mu\text{m}$ vs $7421 \pm 1905 \mu\text{m}$, respectively; $p=0.0014$). However, the length of YFP+ dendrites in the ipsilateral OB was not statistically different between sEPL and dEPL (Fig. 2C; $10095 \pm 1470 \mu\text{m}$ vs $7327 \pm 1588 \mu\text{m}$, respectively; $p=0.2210$). The total length of YFP+ dendrites in the sEPL was significantly reduced in the ipsilateral OB compared to that of contralateral OBs ($p=0.0178$). However, the densities of YFP+ dendrites were not significantly different in the sEPL ($p=0.7458$) nor in the dEPL ($p=0.9751$) between contralateral and ipsilateral OBs, which is consistent with the area reduction of the sEPL but not dEPL in the ipsilateral OB^{29, 30}.

In order to normalize the effects of COI on the dendrites of MCs and TCs, we calculated ratios of YFP+ dendrites (length in μm) to YFP+ cell bodies measured in each OB ($\mu\text{m}/\text{cell}$). This allows us to normalize for variability in our data that may exist due to animal differences in CreER expression. Upon analysis, we observed a significant reduction of dendrites in the sEPL (Fig. 2D; contra., $223.1 \pm 74.70 \mu\text{m}/\text{cell}$ vs ipsi., $152.4 \pm 69.77 \mu\text{m}/\text{cell}$; $p=0.0073$). However, we did not observe any changes to dendrite density in the dEPL (Fig. 2E; contra., $382.5 \pm 190.6 \mu\text{m}/\text{cell}$ vs ipsi., $345.2 \pm 244.4 \mu\text{m}/\text{cell}$; $p=0.3594$). These results suggest that the overall length of TC, but not MC, dendrites has been reduced.

Alterations in the axon initial segment of tufted cells following 10-week COI

Our findings of decreased TC dendrites have led us to believe that there may be further physiological impairments to TCs following COI. The AIS is the site of a neuron that separates its somatodendritic and axonal compartments, and is primarily responsible for maintaining the neuron's polarity and initiating action potentials³⁹. One of the most essential components of the AIS is the cytoskeletal-associated protein, Ankyrin-G (AnkG)⁴⁰. Previous studies have shown that shorter or fewer AISes measured by AnkG are indicative of impairments to the neurons physiology, such as a decrease in excitability^{39, 41, 42}. We first co-stained OB sections with AnkG and Tbx21, an OB projection neuron-specific marker, and confirmed that the vast majority of AnkG+ AISes present in the EPL and MCL are derived from TCs and MCs, respectively (Supplementary Fig. 1).

We, then, measured the length of each individual AIS, as well as the number in each OB. Since our previous studies primarily investigated the response of LPS-treatment on the medial and lateral OBs, we chose to focus on these regions as well. Through this analysis, we observed a significant reduction in the number of AISes in the ipsilateral OB EPL (Fig. 3A, B). Our data demonstrated that fewer AISes were present in the lateral EPL of the ipsilateral OB (Fig. 3B2). The number of AISes in the lateral OB EPL decreased from 165.6 ± 47.45 AISes in the contralateral OB to 94.20 ± 29.24 in the ipsilateral OB (Fig. 3F histogram; $p=0.0175$). This phenomenon, however, was not found in the medial OB EPL (Fig. 3E histogram; contra., 165.4 ± 26.47 vs ipsi., 130.8 ± 24.81 ; $p=0.3829$). For both OBs, there were no differences in the number of MCL AISes counted, regardless of laterality (Fig. 3C, D histograms; medial contra., 119.2 ± 12.76 ; lateral contra., 122.6 ± 23.09 ; medial ipsi., 120.2 ± 16.25 ; lateral ipsi., 120.6 ± 24.17).

We further analyzed the length of the AISes that were present in each OB. Since TCs reside solely in the EPL and MCs in the MCL, we have classified the AISes measured in the EPL as belonging primarily to TCs and AISes in the MCL as those of MCs. It was determined that the TC AISes in the lateral OB significantly decreased in their length (Fig. 3F; contra., $12.05 \pm 1.079 \mu\text{m}$ vs ipsi., $9.399 \pm 1.100 \mu\text{m}$; $p=0.0009$). This phenomenon was not found for the TC AISes in the medial OB (Fig. 3E; contra., $14.84 \pm 0.6815 \mu\text{m}$ vs ipsi., $13.58 \pm 0.3369 \mu\text{m}$; $p=0.1370$). Although there was no change in the number of MC AISes in the medial OB, it did appear that the AISes present in the medial region of the OB significantly decreased in length (Fig. 3C; contra., $21.88 \pm 4.978 \mu\text{m}$ vs ipsi., $19.49 \pm 4.964 \mu\text{m}$; $p=0.0006$). However, the length of MC AISes in the lateral OB did not appear to shorten (Fig. 3D; contra., $15.84 \pm 0.7814 \mu\text{m}$ vs ipsi., $16.29 \pm 0.8635 \mu\text{m}$; $p=0.7684$). Collectively, these results suggest that COI has the most significant effect on TCs morphologically and physiologically in the lateral OB.

Reduction in tufted cell activity following 10-week COI

To examine the alterations in cellular activity of the OB projection neurons, we stained OBs with an antibody against phospho-S6 ribosomal protein (pS6), one of neuronal activity markers⁴³. A recent study demonstrated that pS6 is an exceptional activity marker for OB projection neurons, and that naris occlusion is capable of significantly reducing the expression of pS6 among projection neurons on the ipsilateral OB⁴¹. It is also worth noting that the vast majority of pS6-expressing projection neuron somata were double-positive for Tbx21 (Supplementary Fig. 2). Upon immunohistochemical analysis of mice that underwent the 10-week unilateral COI paradigm, we observed robust pS6 staining throughout the entire MCL and EPL of the

contralateral OB (Fig. 4). In contrast, we observed fewer pS6-positive projection neuron somata throughout the EPL in the ipsilateral OB. The MCL, however, did not appear to have any reduction in pS6 signal (Fig. 4B, C). These findings further suggest that functional impairments may be occurring to TCs rather than MCs throughout the ipsilateral OB.

No apparent loss of OB interneurons following 10-week COI

Olfactory information is not only processed by OB projection neurons, but requires substantial communication with a variety of OB interneurons. Based on their location in the OB, interneurons play a major role in fine-tuning of olfactory information before it even reaches the cortex. OB interneurons can also be further differentiated by their immunoreactivity³⁷. For example, the parvalbumin-positive (PV+) and somatostatin-positive (SST+) interneurons are found in the EPL and are distributed primarily throughout the sEPL and dEPL, respectively^{37, 44-46}. Here, we investigated whether the effects of COI on TCs would extend to interneurons residing throughout the sEPL and dEPL. Figure 5 shows PV+ and SST+ interneurons in the sEPL and dEPL of the contralateral and ipsilateral OBs following the 10-week COI paradigm. To quantify the effects of COI on these interneurons, we counted the numbers from 5 coronal sections (n=5 mice). Consistent with previous literature, there were more PV+ interneurons in the sEPL than in the dEPL of the contralateral OB (333.0 ± 29.04 vs 256.0 ± 30.55 , respectively; $p=0.0037$)⁴⁰. However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB (Fig. 5A, B; sEPL: contra., 333.0 ± 29.04 vs ipsi., 298.8 ± 33.91 , $p=0.2874$; dEPL: contra., 274.0 ± 22.15 vs ipsi., 256.0 ± 30.55 , $p=0.7660$). Similarly, as SST+ interneurons are not present in the sEPL⁴⁷, we counted only from the dEPL. No differences were observed in the number of SST+ interneurons following 10-week COI (Fig. 5C, D; contra., 167.4 ± 16.83 vs ipsi., 169.4 ± 12.64 ; $p=0.3859$). Collectively, this data suggests that there is no change in the number of PV+ or SST+ interneurons in the OB following the 10-week COI paradigm.

Remodeling of tufted cell lateral dendrites after recovery period following 10-week COI

Our previous studies demonstrated that a 10-week period of no LPS treatment following the 10-week COI paradigm resulted in a recovery of the OB atrophy and depletion of inflammatory responses³⁰. Therefore, we sought to investigate if the recovery phenomenon would extend to the OB on a cellular level. For this experiment, we used male +/-Het mice (n=3) treated with LPS for 10 weeks followed by a 10-week recover period of no treatment. We first investigated if TC lateral dendrites recover from their reduction caused by COI.

Consistent with our previous studies, the overall shape of the ipsilateral OB appears to undergo a complete recovery^{29, 30}. We counted the total number of YFP+ cells in the EPL of the contralateral and ipsilateral OBs and observed more YFP+ TC soma in the ipsilateral OB compared to the contralateral (contra., 64.00 ± 15.52 vs ipsi., 79.00 ± 14.42 ; $p=0.0131$). The number of YFP+ MCs, however, was not significantly different (contra., 16.00 ± 6.083 vs ipsi., 17.33 ± 1.528 ; $p=0.6667$). To compensate the difference in the numbers of labeled YFP+ cells, the total number of YFP+ dendrites in the sEPL and dEPL were divided by the total number of YFP+ TCs and MCs, respectively. Surprisingly, even after this normalization, we still observed a slightly significant increase of dendrites in the ipsilateral sEPL compared to contralateral (Fig. 6D; contra., $202.1 \pm 41.38 \mu\text{m}/\text{cell}$ vs ipsi., $222.8 \pm 37.70 \mu\text{m}/\text{cell}$; $p=0.0357$). We did not observe any changes to dendrite length in the dEPL (Fig. 6E; contra., $294.0 \pm 88.64 \mu\text{m}/\text{cell}$ vs ipsi., $340.6 \pm 101.2 \mu\text{m}/\text{cell}$; $p=0.1139$). Thus, our results suggest that the overall length of TC dendrites has not only recovered, but the TCs may have more dendrites in the ipsilateral OB following the 10-week recovery period.

Stabilization of tufted cell activity and axon initial segment integrity after recovery period following 10-week COI

Lastly, we investigated the effect of a recovery period on the integrity of the AIS of MCs and TCs following COI. We performed the same analysis as previously stated, and observed no significant differences between the ipsilateral and contralateral OBs in either the length or number of AISes for both MCs and TCs (Fig. 7). These results indicate that no apparent “over-recovery” phenomenon occurs with respect to TC AIS integrity. Combined with our previous findings, these results suggest that the TC AISes in the lateral OB that are damaged following COI are capable of returning back to appropriate lengths, essentially re-stabilizing, allowing for a restoration in the transfer of OB information. Consistent with this observation, there was no apparent reduction of the pS6 expression in the EPL of the ipsilateral OB in mice who underwent the 10-week COI paradigm followed by a 10-week recovery period of no treatment (Fig. 8). These results suggest that a functional recovery of TCs occurs after a sufficient period without exposure to LPS.

DISCUSSION

In this study, we found that COI induced by i.n. administration of LPS causes dendritic retraction and axonal instability of TCs, but not MCs, in the mouse OB. The superficial OB layers (GL, ONL, sEPL) are the primary region of OB atrophy and inflammation at 10 weeks of LPS administrations^{29, 30}. Our results suggest that the reduction of dendrites that was observed in the ipsilateral OB is primarily attributed to a reduction in the sEPL. Similarly, the shortening and loss of AISes takes place primarily in the lateral EPL of the ipsilateral OB, a region that has been proven to be most susceptible to COI at this time point.

The signaling cascades downstream of proinflammatory cytokines such as IFN- γ and TNF- α has been demonstrated to occur in the OB as early as at 4 weeks of i.n. LPS administrations. These cytokines are capable of inducing the retraction of neuronal dendrites and synaptic degradation in primary neuronal cultures³⁶. We anticipate that a similar phenomenon is taking place in our current paradigm in which the presence of proinflammatory cytokines and activated glial cells among the superficial OB layers induce neuronal stress and subsequent structural dysregulation. Our previous study, however, demonstrated that cessation of COI results in a reduction of immune responses in the OB. This suggests that anti-inflammatory mechanisms may take place following the absence of persistent inflammation. Microglia and astrocytes are well established to engage in both pro- and anti-inflammatory activities⁴⁸⁻⁵⁰. Our research thus far has established that signaling cascades activated by cytokines such as TNF- α , IFN- γ , IL-1 β , and IL-10 are significantly upregulated in the OB following COI. Although the former three are pro-inflammatory, IL-10 is an anti-inflammatory cytokine released by astrocytes which may act to maintain (or restore) neuronal homeostasis^{51, 52}. The release of IL-10 and other neuroprotective agents may be a necessary step in evading, or recovering from, potential TC degeneration. Similarly, astrocytes and microglia are capable of mediating and amplifying axonal and dendrite growth through mechanisms including the release of fibroblast growth factor and purinergic signaling, respectively⁵³⁻⁵⁶. The present study demonstrating a recovery effect of the observed TC dendritic retraction may be attributed to similar neuroprotective mechanisms via glial cell activity.

Our findings of reduced TC AIS number and length is highly suggestive of functional impairments to TC-integrated neural circuits. AISes are responsible for action potential initiation and maintenance of neuronal polarity^{39, 57}. The actual assembly of the AIS is coordinated primarily by AnkG, a cytoskeletal-associated protein^{40, 58}. It remains unknown whether the mechanisms of AIS

445 maintenance and AIS assembly (or reassembly) as controlled by AnkG are related⁵⁹. However,
446 we speculate that the ability of TCs to reconstruct their AISes in the recovery period following COI
447 is possibly also coordinated by AnkG-mediated mechanisms. Nonetheless, dysfunctional AISes
448 induced by diminished AnkG integrity will likely contribute to a decrease in excitability and signal
449 transmission to a neuron's downstream targets⁶⁰. It is also interesting to note that AnkG is
450 necessary to maintain the structural and functional segregation of a neurons axon from its
451 dendrites⁶¹. These implications suggest a potential biological connection between axon
452 destabilization and dendritic retraction in our COI paradigm.

453
454 All of our sensory systems are comprised of first-, second-, and third-order neurons which
455 uniquely relay sensory information to the CNS at each level. Therefore, it is plausible to assert
456 that damage to the neural components at any of these levels will impair sensory processing in the
457 CNS. Multiple clinical studies reported cortical atrophy and altered brain activity in response to
458 spinal cord injury⁶²⁻⁶⁴. Similarly, clinical studies investigating the role of diabetic retinopathy on
459 CNS have found remapping and impairments of the primary visual cortex following disease
460 onset⁶⁵⁻⁶⁷. This phenomenon, however, has yet to be thoroughly investigated with respect to the
461 olfactory system. COI causes ablation to the first-order neurons of the olfactory system, olfactory
462 sensory neurons, which can occur after only one day of i.n. LPS administration²³, and this
463 phenotype will persist for the duration of COI. Our current findings which model CRS suggest that
464 olfactory information processing and transmission at the level of the second-order neurons
465 (specifically, TCs) may be disrupted due to structural and functional pathophysiology. While the
466 olfactory second-order neurons (MCs/TCs) share a multitude of features, they differ in two distinct
467 ways, anatomically; (1) somata location within the OB, and (2) neurite projection patterns. MCs
468 project their axons to most structures within the olfactory cortex (OC), whereas TC axons are
469 more localized to targets including the anterior olfactory nucleus, olfactory tubercle, and anterior
470 piriform cortex⁶⁸⁻⁷¹. When drawing comparisons to other sensory systems, this information leads
471 us to speculate that the differences in axonal projection patterns of MCs and TCs may also be a
472 component of the olfactory system impacted by the pathophysiological nature of COI. More
473 specifically, the third-order neurons of the olfactory system residing in the TC-targeted OC regions
474 may also be impacted by COI in the form of cortical atrophy or even immune responses. Further
475 studies are needed to address whether these OC regions are also susceptible to the
476 neuropathological effects of COI.

CONCLUSIONS

In conclusion, the findings presented in this report demonstrate that TCs undergo significant neurite dysregulation following COI primarily in the forms of lateral dendrite retraction and AIS shortening, whereas MCs, as well as PV+ and SST+ interneurons, are largely unaffected. Our study also suggests that the mechanisms underlying neurite dysregulation are induced through common pathways involving the pro-inflammatory cytokine, IFN- γ . Furthermore, the pathological responses of TCs to COI was shown to recover following a period without olfactory inflammation. In summary, this study provides a strong foundation for investigating the cellular and molecular mechanisms responsible for regulating the reversible changes occurring in TC-integrated OB neural circuits. Overall, we have revealed some of the major consequences of inflammation on the homeostatic functioning of olfactory bulb projection neurons, as well as unveiled a novel pathway of neuroinflammation from the periphery to the CNS. Developing a deeper understanding of the biological mechanisms underlying CRS and the consequences of inflammation-induced hyposmia is a vital next step to the overarching goal of enhancing human health.

ABBREVIATIONS

AIS: axon initial segment; AnkG: Ankyrin G; CNS: central nervous system; COI: chronic olfactory inflammation; CRS: chronic rhinosinusitis; dEPL: deep external plexiform layer; EPL: external plexiform layer; GL: glomerular layer; i.n.: intranasal; IFN- γ : interferon- γ ; LPS: lipopolysaccharide; MC: mitral cell; MCL: mitral cell layer; OB: olfactory bulb; OC: olfactory cortex; OE: olfactory epithelium; ONL: olfactory nerve layer; Pcdh21: protocadherin-21; pS6: phoso-S6 ribosomal protein; PV: parvalbumin; sEPL: superficial external plexiform layer; SST: somatostatin; TC: tufted cell; YFP: yellow fluorescent protein.

DECLARATIONS

Ethics approval and consent to participate

All protocols were approved by and all methods were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Penn State College of Medicine.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors contributions

B.J.L. and F.I. designed research; B.J.L., Y.I., and A.I. performed research; B.J.L., Y.K., and F.I. analyzed data; B.J.L., Y.K., and F.I. wrote the paper.

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FIGURE LEGENDS

Figure 1: Differentially expressed genes in the OB following 4-week COI.

(A) Heatmap of differentially expressed genes. (B) Most significant Canonical Pathways of differentially expressed genes. (C) Mechanistic Network of the most significantly activated Upstream Regulator, IFN- γ . (D) Graphical summary of differentially expressed genes illustrated with their subcellular localizations. Each entity has passed a fisher's exact test p-value cut-off of 0.05 and absolute z-score cut-off of 2 or greater. In panels (B-D), orange represents upregulated genes or activated pathways, where blue represents downregulated genes or inhibited pathways. Details for shapes of nodes and colors or patterns of lines can be found in the IPA's website (https://qiagen.secure.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Legend).

Figure 2. Reduction of tufted cell lateral dendrites following 10-week COI.

(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. The Pcdh21-CreER x YFP transgenic mouse model (+/Het) preferentially labels TCs and their lateral dendrites compared to MCs. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites decreased significantly in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: $**p < 0.01$ compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 3. Reduction and shortening of tufted cell axon initial segments following 10-week COI.

(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. (A) Enlarged views of the medial (A1) and lateral (A2) contralateral OB. (B) Enlarged views of the medial (B1) and lateral (B2) contralateral OB. (C-F) Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse ($n=5$). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean $\pm$ SEM. There were no differences in the number of MC AISes counted in either the medial (C; histogram) or lateral OBs (D; histogram). MC AISes in the medial OB appeared to have shortened in length (C; graph),

whereas those in the lateral OB did not change in length (D; graph). There were no differences in the number of TC AISes counted in medial OB (E; histogram). The TC AISes in the lateral OB were the only AISes to significantly decrease in number (F; histogram). TC AISes in the medial OB did not change in length (E; graph), whereas those in the lateral OB significantly decreased (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons: * $p < 0.05$, *** $p < 0.001$ compared to contralateral OB (control). Scale bars, 100 μm .

Figure 4. Reduced cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. TCs express less pS6 in the ipsilateral OB compared to the contralateral OB following 10-week COI, whereas MCs are unaffected. **(B)** Enlarged view of the medial (B1) and lateral (B2) contralateral OB. **(C)** Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 5. No changes in the number of OB interneurons following 10-week COI.

(A, B) Coronal sections of the OBs stained for PV and DAPI. More PV+ interneurons exist in the sEPL than in the dEPL of the untreated OB. However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB. **(C, D)** Coronal sections of the OBs stained for SST and DAPI. There were no differences in the number of SST+ interneurons in the dEPL between the contralateral and ipsilateral OBs. Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Scale bars, 100 μm .

Figure 6. 10-week recovery period restores tufted cell lateral dendrites following 10-week COI.

(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. **(B)** Enlarged view of the medial (B1) and lateral (B2) contralateral OB. **(C)** Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. **(D, E)** Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites were greater in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: * $p < 0.05$ compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 7. 10-week recovery period restores tufted cell axon initial segments following 10-week COI.

(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. **(A)** Enlarged views of the medial (A1) and lateral (A2) contralateral OB. **(B)** Enlarged views of the medial (B1) and lateral (B2) contralateral OB. **(C-F)** Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse (n=5). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean $\pm$ SEM. There were no differences in the number of MC AISes counted in either the medial (C; histogram) or lateral (D; histogram) OBs. No differences were observed in the lengths of MC AISes in either the medial (C; graph) nor lateral (D; graph) OBs. There were also no differences in the number of TC AISes counted in medial (E; histogram) or lateral (F; histogram) OBs. TC AISes in the medial OB did not change in length (E; graph), nor did those in the lateral OB (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Scale bars, 100 μ m.

Figure 8. 10-week recovery period restores cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. The expression of pS6 among TCs has recovered in the ipsilateral OB after the 10-week recovery period following 10-week COI. **(B)** Enlarged view of the medial (B1) and lateral (B2) contralateral OB. **(C)** Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μ m (A), and 100 μ m (B, C).

Supplementary Figure 1.

Labelling of the AIS using AnkG preferentially occurs in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.

Supplementary Figure 2.

Using pS6 as a marker for OB projection neuron cellular activity was demonstrated to occur in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.

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Figure 1: Differentially expressed genes in the OB following 4-week COI.

(A) Heatmap of differentially expressed genes. **(B)** Most significant Canonical Pathways of differentially expressed genes. **(C)** Mechanistic Network of the most significantly activated Upstream Regulator, IFN- γ . **(D)** Graphical summary of differentially expressed genes illustrated with their subcellular localizations. Each entity has passed a fisher's exact test p-value cut-off of 0.05 and absolute z-score cut-off of 2 or greater. In panels (B-D), orange represents upregulated genes or activated pathways, where blue represents downregulated genes or inhibited pathways. Details for shapes of nodes and colors or patterns of lines can be found in the IPA's website (https://qiagen.secure.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Legend).

YFP

Calretinin

DAPI

Contra

Ipsi

Medial OB

B1

GL

sEPL

dEPL

C1

GL

sEPL

dEPL

Lateral OB

B2

GL

sEPL

dEPL

C2

GL

sEPL

dEPL

D

E

Figure 2. Reduction of tufted cell lateral dendrites following 10-week COI.

(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. The *Pcdh21-CreER* x YFP transgenic mouse model (+/Het) preferentially labels TCs and their lateral dendrites compared to MCs. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites decreased significantly in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: ** $p < 0.01$ compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 4. Reduced cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. TCs express less pS6 in the ipsilateral OB compared to the contralateral OB following 10-week COI, whereas MCs are unaffected. **(B)** Enlarged view of the medial (B1) and lateral (B2) contralateral OB. **(C)** Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μ m (A), and 100 μ m (B, C).

Figure 5. No changes in the number of OB interneurons following 10-week COI.

(A, B) Coronal sections of the OBs stained for PV and DAPI. More PV+ interneurons exist in the sEPL than in the dEPL of the untreated OB. However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB. (C, D) Coronal sections of the OBs stained for SST and DAPI. There were no differences in the number of SST+ interneurons in the dEPL between the contralateral and ipsilateral OBs. Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Scale bars, 100 μ m.

Figure 6. 10-week recovery period restores tufted cell lateral dendrites following 10-week COI.

(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites were greater in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: * $p < 0.05$ compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 7. 10-week recovery period restores tufted cell axon initial segments following 10-week COI.

(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. (A) Enlarged views of the medial (A1) and lateral (A2) contralateral OB. (B) Enlarged views of the medial (B1) and lateral (B2) contralateral OB. **(C-F)** Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse ($n=5$). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean $\pm$ SEM. There were no differences in the number of MC AISes counted in either the medial (C; histogram) or lateral (D; histogram) OBs. No differences were observed in the lengths of MC AISes in either the medial (C; graph) nor lateral (D; graph) OBs. There were also no differences in the number of TC AISes counted in medial (E; histogram) or lateral (F; histogram) OBs. TC AISes in the medial OB did not change in length (E; graph), nor did those in the lateral OB (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Scale bars, 100 μm .

Figure 8. 10-week recovery period restores cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. The expression of pS6 among TCs has recovered in the ipsilateral OB after the 10-week recovery period following 10-week COI. **(B)** Enlarged view of the medial (B1) and lateral (B2) contralateral OB. **(C)** Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μ m (A), and 100 μ m (B, C).

AnkG**Tbx21****DAPI**

Supplementary Figure 1.

Labelling of the AIS using AnkG preferentially occurs in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.

pS6**Tbx21****DAPI**

Supplementary Figure 2.

Using pS6 as a marker for OB projection neuron cellular activity was demonstrated to occur in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.

Supplementary Table1: Upstream Regulator

Upstream Regulator	Expr Fold Change	Molecule Type	Predicted Activation State	Activation z-score	Flags	p-value of overlap	Target Molecules in Dataset	Mechanistic Network
KDM1A	0.088	enzyme				2.9E-21	Bst2,C1QB,C4A/C4B,CCL5,CD74,CTSS,CYBB,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,IFITM3,Igtp,LGALS3BP,LYZ,MPEG1,PARP14,TAP1	
IFNG		cytokine	Activated	4.749		5.04E-20	B2M,Bst2,C1QA,C1QB,C4A/C4B,CCL5,CD74,CTSS,Cxcl9,CYBB,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,Ifi47,IFITM3,IGF1,Igtp,Ilgp1,IRF1,IRF8,LGALS3BP,PARP14,PENK,PTN,RAC2,TAP1,TAPBP	34 (15)
STAT1	1.108	transcription regulator	Activated	2.826	bias	9.4E-20	B2M,C4A/C4B,CCL5,CTSS,Cxcl9,GBP2,HLA-DQA1,HLA-DRB5,Ifi47,IFITM3,IGF1,Igtp,Ilgp1,IRF1,IRF8,NPPA,PTN,SERPINA3,TAP1	34 (15)
Ifnar		group	Activated	3.576	bias	3.16E-19	B2M,Bst2,CCL5,CD74,Cxcl9,GBP2,HLA-A,IFITM3,IRF1,IRF8,TAP1,TAPBP,UNC93B1	35 (17)
MAPT	-0.014	other				7.02E-18	C1QB,C4A/C4B,CD74,CTSS,CYBB,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,IFITM3,Igtp,LGALS3BP,LYZ,MPEG1,PARP14,PENK,TAP1,TUBB2B	36 (11)
DYSF	0.984	other				1.45E-15	B2M,C1QB,CD74,CTSS,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,LYZ,MPEG1,SERPINA3	
SIRT1	0.155	transcription regulator	Inhibited	-3.45		2.18E-14	CCL5,CD74,GNG13,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,Ifi47,IFITM3,IGF1,Igtp,Ilgp1,LGALS3BP,PARP14,PTN,TAP1	35 (10)
ZBTB10	-0.096	other	Activated	3.317	bias	4.19E-13	B2M,Bst2,CCL5,Cxcl9,CYBB,Ifi47,IFITM3,Igtp,Ilgp1,IRF1,UNC93B1	
Interferon alpha		group	Activated	3.537	bias	8.51E-13	B2M,Bst2,CCL5,Cxcl9,GBP2,HLA-A,Ifi47,IFITM3,Ilgp1,IRF1,IRF8,PARP14,TAP1,TAPBP,UNC93B1	26 (12)
STAT3	0.016	transcription regulator		0.931		1.15E-12	CCL5,CD74,Cxcl9,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DRB5,IFITM3,Igtp,IRF1,LYZ,NPPA,OMP,PTN,SERPINA3,TAP1	32 (13)
IL4		cytokine		-1.331	bias	1.25E-12	APOLD1,Bst2,CCL5,CD74,Cxcl9,CYBB,GBP2,HLA-DQA1,HLA-DQB1,HLA-DRB5,IFITM3,IGF1,Igtp,Ilgp1,IRF1,IRF8,LGALS3BP,MPEG1,Nrgn,OMP,TAPBP	38 (14)
IRF1	2.122	transcription regulator	Activated	2.23	bias	2.96E-12	B2M,CCL5,CTSS,Cxcl9,CYBB,GBP2,Ifi47,IFITM3,IRF1,TAP1,TAPBP	34 (15)
SNCA	0.514	enzyme	Activated	3.138		3.06E-12	Bst2,CD74,CYBB,FABP7,GBP2,GFAP,HLA-DQA1,HLA-DRB5,Ifi47,IGF1,IRF1,NPTX2,Nrgn	34 (9)
QKI	0.205	other		1.941		4.35E-12	CTSS,FABP7,GFAP,HLA-DQA1,HLA-DQB1,HNRNP1,TAP1,TUBB2B	
IL27		cytokine	Activated	2.609		6.28E-12	B2M,CCL5,CD74,Cxcl9,GBP2,HLA-A,HLA-DQA1,HLA-DQB1,IRF1,TAP1	34 (16)
ELAVL1	0.759	other	Activated	2.985	bias	7.53E-12	B2M,Bst2,CTSS,Cxcl9,HLA-A,HLA-DRB5,IFITM3,Ilgp1,IRF1,LGALS3BP,MPEG1	
PIK3CG	2.644	kinase	Inhibited	-2.813		1.03E-11	B2M,CD74,Cxcl9,GBP2,HLA-A,Igtp,Ilgp1,IRF1,TAP1	34 (14)
JAK1/2		group	Activated	2.828	bias	1.54E-11	Bst2,CD74,GBP2,HLA-DQA1,HLA-DRB5,Ifi47,IRF1,Nrgn	
STAT6	1.324	transcription regulator	Inhibited	-2.487		1.68E-11	APOLD1,Bst2,CCL5,Cica3a1/Cica3a2,CTSS,CYBB,GBP2,IFITM3,IGF1,Igtp,Ilgp1,IRF1,LGALS3BP,MPEG1	
TRIM24	0.301	transcription regulator	Inhibited	-2.343	bias	1.85E-11	Bst2,CCL5,GBP2,Ifi47,Igtp,Ilgp1,IRF1,LGALS3BP,TAP1	28 (8)
G protein alphaI		group	Activated	2.795	bias	2.42E-11	Bst2,C4A/C4B,GBP2,HLA-A,IFITM3,Igtp,Ilgp1,TAP1	
lipopolysaccharide		chemical drug	Activated	4.2		3.94E-11	C1QA,CCL5,CD74,Cxcl9,CYBB,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,Ifi47,IGF1,Igtp,Ilgp1,IRF1,IRF8,LGALS3BP,LYZ,NPPA,PARP14,PENK,SERPINA3,TAP1,TAPBP	34 (16)
IRF9	0.37	transcription regulator		-0.277		7.35E-11	Cxcl9,Ifi47,IFITM3,Ilgp1,IRF1,IRF8,NPPA	29 (10)
SLC9A3		ion channel				8.16E-11	B2M,CCL5,CD74,Ifi47,Igtp,IRF8	
inosine		chemical - endogenous mammalian	Activated	2.646	bias	8.48E-11	C1QA,C1QB,C4A/C4B,GFAP,IFITM3,IRF1,LGALS3BP	
IRF3	0.052	transcription regulator	Activated	3.1	bias	1.96E-10	B2M,Bst2,CCL5,Cxcl9,Ifi47,IFITM3,Igtp,IRF1,PARP14,TAP1	31 (13)
IL6		cytokine	Activated	2.93		2.12E-10	CCL5,CD74,Cxcl9,CYBB,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DRB5,IFITM3,IGF1,IRF1,LYZ,PENK,SERPINA3,TAP1	34 (15)
poly rI:C-RNA		biologic drug	Activated	3.648	bias	2.86E-10	B2M,Bst2,CCL5,CD74,Cxcl9,GBP2,HLA-A,IFITM3,IGF1,Igtp,Ilgp1,IRF1,LYZ,PARP14,TAP1	31 (17)
TLR4	1.494	transmembrane receptor	Activated	2.149	bias	5.38E-10	CCL5,Cxcl9,GBP2,GFAP,HLA-DQA1,Ifi47,IFITM3,Igtp,Ilgp1,IRF1,IRF8,NPPA	31 (12)
CIITA		transcription regulator	Activated	2.435		1.03E-09	B2M,CD74,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5	
IL1B	0.77	cytokine	Activated	2.654		1.5E-09	B2M,CCL5,CD74,CTSS,Cxcl9,CYBB,GBP2,HLA-A,Ifi47,IFITM3,IGF1,IRF1,IRF8,NPPA,PENK,RAC2,SERPINA3	30 (15)
Immunoglobulin		complex		0.858		3.02E-09	B2M,CCL5,CD74,Cxcl9,GFAP,HLA-A,HLA-DQB1,IFITM3,IRF1,IRF8,LGALS3BP,PARP14,PENK,RAC2,SERPINA3	34 (18)
NRAS	0.378	enzyme	Inhibited	-2.63		4.29E-09	B2M,CCL5,CYBB,GBP2,HLA-A,Ilgp1,NPPA,PENK,TAP1	27 (11)
NFAT5	0.301	transcription regulator		0.933		6.13E-09	CD74,Cxcl9,CYBB,HLA-DQA1,HLA-DQB1,HLA-DRB5,Ilgp1,IRF1	
Irgm1	1.289	other	Inhibited	-2.588	bias	7.97E-09	B2M,CCL5,Cxcl9,GBP2,IFITM3,Ilgp1,IRF1	33 (17)

dexamethasone		chemical drug		-1.963		8.72E-09	B2M,C1QB,CCL5,CD74,C1ca3a1/C1ca3a2,Cxcl9,CYBB,GBP2,HLA-A,HLA-DQB1,HLA-DRB5,HNRNPH1,IFITM3,IGF1,IRF1,IRF8,LGALS3BP,MPEG1,NPPA,PARP14,PENK,PTN,SERPINA3	37 (17)
EBI3	0.996	cytokine	Activated	2.425	bias	1.05E-08	B2M,GBP2,HLA-A,HLA-DQA1,IRF1,TAP1	26 (8)
B2M	1.931	transmembrane receptor	Activated	2.2	bias	1.32E-08	HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,TAPBP	
IFNA2		cytokine	Activated	2.79	bias	1.91E-08	B2M,CCL5,GBP2,HLA-A,IFITM3,IRF1,LGALS3BP,NPTX2,TAP1	27 (11)
IRF7	3.615	transcription regulator	Activated	2.777	bias	2.16E-08	CCL5,Ifi47,IFITM3,Igtp,IRF1,IRF8,PARP14,TAP1	25 (9)
APP	0.006	other	Activated	3.073		2.34E-08	C4A/C4B,CCL5,CD74,Cxcl9,CYBB,GBP2,GFAP,Ifi47,IGF1,Igtp,IRF1,Nrgn,PARP14,PENK,TUBB2B	33 (16)
POR	0.265	enzyme		-1.912		2.81E-08	CD74,GBP2,HLA-A,HLA-DQA1,HLA-DQB1,HLA-DRB5,SERPINA3,TUBB2B	
PARP1	-0.331	enzyme		0.749		3.27E-08	CCL5,Cxcl9,GBP2,IGF1,Igtp,Igtp1,LGALS3BP	32 (9)
IFN Beta		group		1.404	bias	3.34E-08	Bst2,CCL5,CD74,Cxcl9,CYBB,HLA-A,IRF1,TAPBP	34 (17)
Ifn		group	Activated	2.588	bias	3.67E-08	B2M,HLA-A,IFITM3,IGF1,IRF1,IRF8,TAP1	31 (9)
E. coli B4 lipopolysaccharide		chemical toxicant	Activated	2.183	bias	6.34E-08	C1QB,CCL5,C1ca3a1/C1ca3a2,GBP2,HLA-A,IFITM3,Igtp,Igtp1,TAP1	14 (3)
IRF2	0.249	transcription regulator				6.66E-08	B2M,CTSS,Ifi47,IRF1,IRF8,TAP1,TAPBP	28 (11)
EIF4E	0.15	translation regulator	Activated	2.795	bias	8.89E-08	B2M,Bst2,CYBB,HLA-A,HLA-DQB1,LGALS3BP,LYZ,TAPBP	
IRF8	2.169	transcription regulator		1.911		0.000000115	B2M,CCL5,CD74,CTSS,Cxcl9,CYBB,IRF8	32 (14)
pembrolizumab		biologic drug	Activated	2.236	bias	0.000000117	B2M,CCL5,HLA-A,HLA-DQA1,IRF1	
PARP9	0.59	enzyme		0.762	bias	0.000000139	CD74,HLA-DQA1,HLA-DQB1,IRF1	
vinorelbine		chemical drug		-1.718		0.000000139	B2M,CCL5,CD74,RAC2	
TCL1A		transcription regulator				0.000000141	C1QA,C1QB,CTSS,CYBB,FABP7,MPEG1	
IgG		complex		0.475		0.000000157	B2M,CCL5,Cxcl9,GFAP,IFITM3,IRF1,NPPA,TAP1,TAPBP	30 (16)
PTGER4	-0.566	G-protein coupled receptor	Inhibited	-2.621		0.000000208	Cxcl9,CYBB,GBP2,Ifi47,Igtp,IRF1,PARP14	32 (7)
HRG		other	Activated	2	bias	0.000000219	C1QA,C1QB,CD74,HLA-DQA1	
PNPT1	0.524	enzyme	Inhibited	-2	bias	0.000000226	Bst2,CCL5,GBP2,LGALS3BP,PARP14	
lactosylceramide		chemical - endogenous mammalian				0.00000033	CCL5,Cxcl9,GFAP,HLA-DQA1	25 (4)
TNF		cytokine	Activated	3.761		0.000000378	B2M,C4A/C4B,CCL5,CD74,CTSS,Cxcl9,CYBB,GBP2,GFAP,HLA-A,IGF1,IRF1,IRF8,NPPA,PARP14,PENK,SERPINA3,TAP1,TAPBP	34 (17)
IL10		cytokine		-1.916		0.000000407	CCL5,CD74,CTSS,Cxcl9,HLA-DQB1,HLA-DRB5,Igtp,Igtp1,IRF1,TAP1	34 (14)
ITPR2	0.207	ion channel	Activated	2	bias	0.000000477	Bst2,Ifi47,Igtp,Igtp1	
IGF1	-1.406	growth factor		1.603		0.000000491	C1QA,C4A/C4B,CCL5,CD74,CYBB,GFAP,IFITM3,IGF1,NPPA,PENK,TAP1	34 (16)
rosiglitazone		chemical drug		0.937		0.000000645	C1QA,C1QB,C4A/C4B,CCL5,Cxcl9,GBP2,IGF1,IRF1,NPPA,PENK	30 (12)
beta-estradiol		chemical - endogenous mammalian		-1.415		0.000000815	BRINP2,C4A/C4B,CCL5,CD74,CYBB,ERBB4,GBP2,GFAP,HLA-A,HLA-DQA1,HLA-DRB5,IFITM3,IGF1,IRF1,LGALS3BP,LYZ,MPEG1,NPPA,PENK,RAC2,SERPINA3	33 (11)
RNA polymerase II		complex				0.000000816	B2M,CCL5,GBP2,HLA-DQA1,Ifi47,IGF1,TAP1,TAPBP	
EGFR	0.84	kinase		-0.432		0.000000818	CCL5,ERBB4,FABP7,GFAP,HNRNPH1,IGF1,IRF1,NPPA,PCDH1,SERPINA3	24 (5)
TLR2	2.269	transmembrane receptor		0.448	bias	0.000000868	CCL5,Cxcl9,CYBB,HLA-DQA1,HLA-DRB5,IRF1,NPPA	31 (14)
methylprednisolone		chemical drug		0.728		0.00000097	B2M,C1QB,CD74,CTSS,CYBB,FABP7,GBP2,IGF1,IRF1,SERPINA3,TAPBP	
CREBBP	0.162	transcription regulator		1.718	bias	0.00000104	B2M,CCL5,Cxcl9,CYBB,IRF1,LGALS3BP,NPPA,SERPINA3,TAPBP	27 (12)
NFkB (complex)		complex	Activated	2.58	bias	0.00000111	CCL5,CD74,Cxcl9,CYBB,GBP2,GFAP,HLA-A,IRF1,NPPA,SERPINA3,TAP1	31 (14)
IFNB1		cytokine	Activated	2.405		0.0000013	Bst2,CCL5,GBP2,HLA-A,Ifi47,Igtp,IRF1,PARP14	33 (13)
TGFB1	0.071	growth factor		0.919		0.0000015	B2M,C1QA,C1QB,CCL5,CD74,CTSS,CYBB,GBP2,GFAP,HLA-DQA1,HLA-DQB1,HLA-DRB5,HNRNPH1,IGF1,IRF1,NPPA,S100A5,SERPINA3	35 (16)
IL2	2.116	cytokine	Activated	2.104	bias	0.00000158	CCL5,CD74,Cxcl9,GFAP,HLA-DQA1,HLA-DQB1,HLA-DRB5,IRF1,NPTX2,Nrgn,PENK	35 (13)
ZC3H12C	-0.19	other	Inhibited	-2	bias	0.00000159	GBP2,Igtp,Igtp1,MPEG1	
ERK1/2		group		-1.222	bias	0.00000166	B2M,CCL5,CYBB,HLA-A,NPPA,PTN,TAP1,TAPBP	28 (10)
CX3CL1	0.594	cytokine		1.067		0.0000018	BRINP2,FABP7,GFAP,IGF1,LGALS3BP,LYZ	
IL10RA	2.135	transmembrane receptor	Inhibited	-2.813		0.00000183	CCL5,Cxcl9,GBP2,HLA-A,Ifi47,Igtp1,IRF1,TAP1	27 (10)
ETV6-RUNX1		fusion gene/product	Inhibited	-2.03	bias	0.00000201	APOLD1,Bst2,CCL5,CYBB,GBP2,IRF1,IRF8,RAC2	
AGN194204		chemical drug	Activated	2.646	bias	0.0000024	GBP2,Ifi47,IFITM3,Igtp,IRF1,PENK,TAP1	
JUND	0.106	transcription regulator				0.00000257	C1QB,CCL5,Cxcl9,CYBB,PENK	9 (3)
IFN alpha/beta		group	Activated	2	bias	0.00000273	CCL5,Cxcl9,HLA-A,IRF1,IRF8	27 (10)
MEF2A	-0.036	transcription regulator		0.907	bias	0.00000273	Cxcl9,GBP2,Ifi47,IRF1,NPPA	
CpG ODN 1826		chemical reagent	Activated	2.194		0.0000029	CCL5,Cxcl9,CYBB,HLA-DQB1,PARP14	
IL6R	0.299	transmembrane receptor		0.528	bias	0.00000345	CCL5,IGF1,IRF1,PENK,SERPINA3	28 (8)
JAK2	0.591	kinase	Activated	2.423	bias	0.00000369	CCL5,CYBB,GBP2,GFAP,IRF1,TAP1	30 (12)
SSB	-0.031	enzyme	Inhibited	-2.236		0.00000387	C4A/C4B,CD74,CYBB,HLA-DQA1,HLA-DQB1	
17-alpha-ethinylestradiol		chemical drug		-0.896		0.00000398	C1QB,CCL5,CD74,CTSS,FABP7,IGF1	7 (2)

cyclophosphamide		chemical drug		-1.432		0.00000409	B2M,C4A/C4B,CCL5,CD74,RAC2	
kainic acid		chemical toxicant		1.188	bias	0.0000046	APOLD1,CCL5,ERBB4,GFAP,NPTX2,PENK	
B4GALNT1	0.563	enzyme				0.00000515	C1QA,C1QB,C4A/C4B	
ACKR2		G-protein coupled receptor	Inhibited	-2	bias	0.00000534	CCL5,Cxcl9,Ifi47,Ilgp1	
BMP10		growth factor		-1.342		0.00000536	CD74,HLA-A,NPPA,PTN,SERPINA3	25 (4)
ZNF106	-0.029	other	Inhibited	-2		0.00000586	C4A/C4B,IFITM3,LYZ,SERPINA3	
E. coli B5 lipopolysaccharide		chemical - endogenous non-mammalian	Activated	2.586		0.00000635	B2M,CCL5,CYBB,GBP2,HLA-A,Igtp,IRF1	32 (15)
CSF1	0.589	cytokine		0.184	bias	0.00000651	CCL5,CD74,CYBB,HLA-A,IGF1,Ilgp1,IRF8	32 (15)
fluticasone propionate		chemical drug		-1.747		0.00000695	C1QB,CCL5,CD74,HLA-DQA1,IRF8,TAP1	
SENP3	0.472	peptidase		1.982	bias	0.00000702	Bst2,Cxcl9,HLA-A,TAP1	
Hbb-b2		other	Activated	2	bias	0.00000702	C1QA,CD74,Cxcl9,CYBB	
Pam3-Cys-Ser-Lys4		chemical reagent		1.026	bias	0.00000743	CCL5,Cxcl9,HLA-A,HLA-DRB5,IRF1,PARP14	29 (13)
tretinoin		chemical - endogenous mammalian	Activated	3.639		0.00000744	C1QA,CD74,C1ca3a1/C1ca3a2,CTSS,CYBB,GFAP,HLA-A,IGF1,IRF1,IRF8,LGALS3BP,NPPA,Nrgn,PARP14,PENK,TAP1	36 (17)
F2RL1		G-protein coupled receptor				0.00000762	GBP2,Ilgp1,IRF8,NPTX2,SERPINA3	
aldesleukin		biologic drug	Activated	2	bias	0.00000765	B2M,IRF1,TAP1,TAPBP	
CSF3		cytokine		-0.277		0.00000818	CCL5,CYBB,GFAP,HLA-DQA1,IGF1,LYZ	28 (7)
PSEN2	1.139	peptidase	Inhibited	-2.211		0.00000839	C1QA,C1QB,CD74,CTSS,GFAP	
HOXA9		transcription regulator				0.00000929	CYBB,IGF1,LYZ,NPPA,Nrgn,PCDH1	
PSEN1	0.555	peptidase	Inhibited	-2.205		0.0000105	C1QA,C1QB,CCL5,CD74,CTSS,GFAP,IGF1,TUBB2B	
IFN type 1		group		1.972	bias	0.0000106	Bst2,CCL5,Cxcl9,IRF1	27 (12)
TARDBP	0.555	transcription regulator	Inhibited	-2		0.0000106	C1QA,C1QB,GBP2,HLA-A	
PRL		cytokine	Activated	2.593	bias	0.0000107	B2M,CTSS,ERBB4,IRF1,PARP14,PENK,SERPINA3	
mir-21		microRNA		-1.709	bias	0.0000112	Cxcl9,GBP2,GFAP,Ifi47,Ilgp1,IRF1,TAP1	34 (12)
MYD88	1.446	other		0.292	bias	0.0000115	CCL5,Cxcl9,HLA-A,IGF1,IRF1,IRF8,NPPA	30 (14)
pyrrolidine dithiocarbamate		chemical reagent		-0.492	bias	0.0000126	CCL5,Cxcl9,IGF1,IRF1,NPPA	31 (14)
CCR2		G-protein coupled receptor		1.206	bias	0.0000132	C1QA,C1QB,CCL5,Cxcl9,IGF1	
AR	0.227	ligand-dependent nuclear receptor		-0.294		0.0000144	ACBD7,C4A/C4B,CCL5,FABP7,GFAP,HLA-A,IGF1,Nrgn,PENK,SERPINA3	
SAFB	0.192	other	Inhibited	-2	bias	0.0000144	B2M,CCL5,CD74,IGF1	
BIRC5	3.253	other				0.0000155	CD74,HLA-DQA1,HLA-DQB1,LYZ	
PS-1145		chemical drug				0.0000172	CCL5,IRF1,SERPINA3	22 (6)
PSMB11	-3.84	peptidase		-0.447	bias	0.0000199	CCL5,CTSS,Cxcl9,GFAP,GNG13	
IL1R1	1.744	transmembrane receptor		0.686	bias	0.0000204	CCL5,Cxcl9,GFAP,IGF1	28 (10)
STAT2	0.432	transcription regulator				0.0000204	CCL5,Ifi47,Ilgp1,IRF1	19 (3)
IFI30	2.817	enzyme				0.0000212	CTSS,HLA-A	
valsartan		chemical drug		-1	bias	0.0000218	CTSS,CYBB,GFAP,NPPA	
filgrastim		biologic drug	Inhibited	-2.157		0.0000223	B2M,CCL5,CD74,CYBB,HLA-DQB1,HLA-DRB5,MPEG1,PARP14	
NLRC5	2.976	transcription regulator				0.0000236	B2M,HLA-A,TAP1	
ADORA3		G-protein coupled receptor				0.0000236	CCL5,IRF1,NPPA	22 (6)
ST8SIA1	0.38	enzyme				0.0000236	C1QA,C1QB,C4A/C4B	
OSMR	1.902	transmembrane receptor				0.0000248	Cxcl9,GBP2,Ifi47,Igtp	
BCL3	2.5	transcription regulator	Inhibited	-2		0.0000248	CCL5,Cxcl9,HLA-DQB1,IRF1	18 (5)
LIF		cytokine		1.346		0.0000252	GFAP,IGF1,IRF1,NPPA,OMP,SERPINA3	26 (7)
CD40		transmembrane receptor		1.402	bias	0.0000301	CCL5,Cxcl9,HLA-DQB1,IRF1,TAP1,TAPBP	29 (14)
NFKBIA	0.37	transcription regulator		0.553		0.0000307	CCL5,CD74,GBP2,HLA-A,HLA-DQA1,IRF1,LYZ,NPPA	29 (11)
cuprizone		chemical toxicant				0.0000313	CCL5,GFAP,IGF1	
RHO		G-protein coupled receptor	Inhibited	-2		0.0000316	B2M,C1QA,CD74,CTSS	
trovafloxacin		chemical drug	Activated	2		0.0000335	B2M,HLA-A,Igtp,IRF1	
gentamicin		chemical drug		0.816		0.000041	C1QA,C1QB,C4A/C4B,IRF1,PTN,SEZ6L,TAP1	
ADCYAP1	-1.482	other		-0.293		0.0000432	CCL5,GFAP,IRF1,SERPINA3,SEZ6L,TUBB2B	15 (5)
losartan potassium		chemical drug		0.447		0.0000438	CYBB,GBP2,Ifi47,IGF1,NPPA	26 (7)
RXRB	0.428	ligand-dependent nuclear receptor				0.0000443	C1QA,CTSS,IGF1,LYZ	4 (2)
PLK2	0.294	kinase				0.0000457	Cxcl9,Ilgp1,IRF1	
immethridine		chemical reagent				0.0000457	C4A/C4B,CTSS,SERPINA3	
REL	0.644	transcription regulator				0.0000463	B2M,Cxcl9,HLA-A,Ilgp1,IRF8,PARP14	
APOE	0.129	transporter		-1.964	bias	0.0000465	C1QA,C1QB,CCL5,CTSS,CYBB,IGF1,SERPINA3	11 (3)

NR3C2	2.237	ligand-dependent nuclear receptor		1.091		0.0000468	CCL5,HLA-DQB1,IGF1,NPPA,SERPINA3	27 (7)
KRAS	-0.316	enzyme		-0.378		0.0000504	B2M,CD74,CYBB,GFAP,IFITM3,IRF1,LYZ,PCDH1,SERPINA3,TAP1	30 (9)
PROCR	0.94	other				0.0000513	GBP2,Ilgp1,IRF8	
PLK4	1.739	kinase				0.0000513	Cxcl9,Ilgp1,IRF1	
THRA	0.388	ligand-dependent nuclear receptor		-1.067		0.0000531	IGF1,IRF1,NPPA,Nrgn,PENK	
prostaglandin E2		chemical - endogenous mammalian		-1.52		0.0000572	CCL5,Cxcl9,GFAP,IGF1,Ilgp1,IRF1,PENK	34 (18)
DUSP1	-0.176	phosphatase		-0.528		0.0000602	CYBB,IFITM3,Ilgp1,IRF1,IRF8	20 (4)
MAP3K7		kinase		0.063		0.0000605	CCL5,GBP2,IRF1,NPPA	26 (10)
IFNAR1	0.654	transmembrane receptor	Activated	2.2	bias	0.000062	B2M,CCL5,Cxcl9,HLA-A,IRF1	32 (17)
dehydroisoandrosterone		chemical - endogenous mammalian				0.0000667	B2M,GFAP,IGF1,NPPA	17 (6)
NCOA2	0.137	transcription regulator		1.96		0.0000679	CCL5,Cxcl9,HLA-A,IRF1,LYZ	
finoglimod		chemical drug		-1.969	bias	0.00007	CCL5,Cxcl9,HLA-DQA1,HLA-DQB1	
atenolol		chemical drug				0.0000704	B2M,NPPA	
RPSA	0.035	translation regulator				0.0000708	CCL5,Ifi47,TAP1	
CNTF	-2.154	cytokine				0.0000734	GFAP,IRF1,PENK,SERPINA3	19 (5)
TLR3	0.655	transmembrane receptor		1.941	bias	0.0000734	CCL5,Cxcl9,GBP2,Ifi47,Ilgp1,IRF1	29 (18)
Nuclear factor 1		group				0.0000782	FABP7,GFAP,SERPINA3	
USP18	2.796	peptidase				0.0000782	CCL5,IFITM3,IRF1	
CNOT7	0.147	transcription regulator				0.0000782	B2M,LGALS3BP,TAP1	
MAPK1	0.472	kinase	Inhibited	-2.449		0.0000797	CCL5,GBP2,IFITM3,LGALS3BP,NPPA,NPTX2,TAP1	15 (4)
NPC1	-0.015	transporter				0.0000922	CD74,HLA-DQB1,HLA-DRB5,LYZ	
MARK2	0.161	kinase				0.0000945	IGF1,Ilgp1,IRF1	
IL21		cytokine	Activated	2	bias	0.000113	CCL5,Cxcl9,HLA-DRB5,Igtp,TAP1	27 (7)
RARB	-0.468	ligand-dependent nuclear receptor	Activated	2.236		0.000113	GBP2,Ifi47,Igtp,Ilgp1,LYZ	
ACE2	0.52	peptidase				0.000113	CCL5,Cxcl9,CYBB	
Hbb-b1		transporter	Activated	2	bias	0.000114	C1QA,CD74,Cxcl9,CYBB	
6-hydroxydopamine		chemical toxicant				0.000114	CCL5,CYBB,GFAP,PENK	28 (7)
dextran sulfate		chemical drug				0.000125	C4A/C4B,CCL5,CD74,Cxcl9,IFITM3,PTN	25 (4)
OSM		cytokine	Activated	2.767		0.000127	B2M,CCL5,GBP2,HLA-A,IRF1,SERPINA3,TAP1,TAPBP	26 (13)
hemin		chemical - endogenous mammalian				0.000129	CYBB,GFAP,IGF1,NPPA	
IKBKB	0.151	kinase		1.186	bias	0.00013	CCL5,Cxcl9,GBP2,HLA-A,IRF1,NPPA	28 (13)
CTF1		cytokine				0.000134	IRF1,NPPA,SERPINA3	22 (7)
Ifn gamma		complex				0.000135	CCL5,Cxcl9,CYBB,IRF8	13 (3)
E. coli serotype 0127B8 lipopolysaccharide		chemical - endogenous non-mammalian	Activated	2.219		0.000135	CCL5,Cxcl9,Ifi47,IGF1,IRF1	30 (14)
NR3C1	0.437	ligand-dependent nuclear receptor		-1.446		0.000136	B2M,C4A/C4B,CCL5,Cxcl9,GBP2,IGF1,IRF1,IRF8,NPPA	34 (15)
IL17A		cytokine		0.849	bias	0.000138	B2M,CCL5,Cxcl9,GBP2,IGF1,IRF1	31 (16)
GATA1		transcription regulator		0.152		0.000138	CCL5,C1ca3a1/C1ca3a2,CYBB,IRF8,LYZ,NPPA	
STAT		group				0.000145	IRF1,NPPA,SERPINA3	
lisinopril		biologic drug				0.000145	CYBB,GBP2,Ifi47	
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine		chemical toxicant		1.868		0.000146	CCL5,CYBB,GFAP,PENK	28 (7)
Histone H2b		group				0.000147	Ifi47,IRF1	
PIK3C3	0.216	kinase				0.000147	HLA-A,HLA-DQB1	
tyrphostin AG490		chemical drug		-1.177	bias	0.000151	CCL5,GFAP,IGF1,IRF1	32 (12)
N-cor		group				0.000163	C1QA,CCL5,CTSS,IGF1	
IL13		cytokine		0.521		0.000166	CCL5,C1ca3a1/C1ca3a2,CTSS,CYBB,ERBB4,HLA-DRB5,IGF1	16 (2)
ethanol		chemical - endogenous mammalian		0.342		0.000168	CCL5,Cxcl9,GFAP,HLA-A,Ifi47,NPPA,Nrgn	29 (14)
RNASEH2A	1.63	enzyme				0.000182	GBP2,IFITM3,IRF1	
CYP19A1		enzyme		0.762		0.000183	GBP2,GFAP,HLA-A,IGF1	
sildenafil		chemical drug				0.000196	CYBB,GFAP,NPPA	
ibuprofen		chemical drug				0.000196	CYBB,GFAP,SERPINA3	22 (6)
S-nitrosoglutathione		chemical toxicant				0.000196	CCL5,GFAP,IGF1	
doxorubicin		chemical drug		1.655		0.000196	C4A/C4B,CYBB,IRF1,LGALS3BP,NPPA,RAC2,TAP1	
GSK0660		chemical reagent				0.000196	C1QA,C1QB	
CLTC	-0.008	other				0.000196	CD74,HLA-A	

TAPBP	1.268	transporter				0.000196	HLA-A,TAP1	
dihydrotestosterone		chemical - endogenous mammalian		-0.047		0.000201	B2M,C4A/C4B,CD74,CYBB,GFAP,HLA-A,IGF1,LYZ	32 (9)
ARHGAP21	0.552	other				0.00021	Cxcl9,Igip1,IRF1	
Cdc42	-0.016	enzyme				0.00021	CTSS,GFAP,NPPA	
VIP	-0.691	other		-0.815		0.000211	CCL5,IGF1,IRF1,LYZ	30 (12)
CEBPB	-0.102	transcription regulator		0.277	bias	0.000214	C1QA,CCL5,CD74,GFAP,HLA-A,IFITM3,IGF1,RAC2	29 (7)
SOX4	0.138	transcription regulator		1.342	bias	0.000234	CD74,HLA-DQB1,IGF1,LYZ,TUBB2B	
IL12 (complex)		complex				0.000244	CCL5,Cxcl9,Igip1,IRF1,IRF8	30 (15)
PSMB9	5.28	peptidase				0.000252	HLA-A,TAP1	
RFXAP	0.649	transcription regulator				0.000252	B2M,HLA-DQA1	6 (2)
HA900		chemical reagent				0.000252	CCL5,PTN	
KIT	0.332	transmembrane receptor				0.000259	Cxcl9,Ifi47,Igtp,IRF1	
IFNGR1	0.328	transmembrane receptor				0.000274	CCL5,Cxcl9,IRF1	26 (11)
ZFTA-RELA		fusion gene/product				0.000274	IRF1,TAP1,TAPBP	
RELA	0.457	transcription regulator		1.13	bias	0.000276	B2M,CCL5,CYBB,IGF1,IRF1,TAP1,TAPBP	29 (12)
SMARCA4	-0.088	transcription regulator		1.913	bias	0.000281	CD74,CTSS,IFITM3,IGF1,IRF1,PCDH1,RAC2,TAP1	15 (3)
DMD	-0.099	other				0.000303	C1QB,CTSS,IGF1,LYZ,MPEG1	
B4GALT6	-0.263	enzyme				0.000314	CCL5,GFAP	
ganetespib		chemical drug				0.000314	HLA-A,HLA-DQA1	
cortistatin A		chemical reagent				0.000314	IRF1,IRF8	
salmonella minnesota R595 lipopolysaccharides		chemical - endogenous non-mammalian		1.964	bias	0.000314	CCL5,HLA-DQA1,IRF1,IRF8	27 (9)
mimosine		chemical drug				0.000383	HLA-DQA1,HLA-DQB1	
JUN	0.137	transcription regulator		-0.669	bias	0.000385	C1QB,C1ca3a1/C1ca3a2,Cxcl9,FABP7,IGF1,NPPA,PENK	
BAX	0.341	transporter				0.000391	CCL5,CTSS,HLA-A	
NR1H3	0.841	ligand-dependent nuclear receptor				0.000395	Bst2,C1QA,CCL5,LYZ,TAP1	
epigallocatechin-gallate		chemical drug	Inhibited	-2.204		0.000419	CCL5,Ifi47,IRF1,PTN,TAP1	28 (10)
IL1RN		cytokine	Inhibited	-2	bias	0.000425	CTSS,HLA-DQB1,IGF1,IRF1	21 (4)
MOG	0.554	other				0.000436	CCL5,Cxcl9,IGF1	22 (6)
CDK9	1.441	kinase				0.000436	CCL5,HLA-DQA1,HNRNP1	
FCGR2A	0.857	transmembrane receptor				0.000436	CCL5,GBP2,IFITM3	9 (3)
RAS		group				0.000438	GBP2,Ifi47,IGF1,IRF1	
diaminopimelic acid		chemical - endogenous non-mammalian				0.000459	CCL5,Cxcl9	
15-deoxy-delta-12,14 -PGJ 2		chemical - endogenous mammalian		-0.714		0.000461	CCL5,CYBB,GFAP,IRF1,NPPA	29 (12)
CTCF	0.179	transcription regulator				0.000476	HLA-DQA1,HLA-DQB1,HLA-DRB5,LYZ	
LDLR	0.624	transporter				0.000479	Bst2,C1QA,CCL5,LYZ,TAP1	
Growth hormone		group		0.615		0.000497	CCL5,GFAP,IGF1,IRF1,NPPA	29 (13)
ADAM10	-0.016	peptidase				0.000532	CD74,FABP7,OMP,TUBB2B	
IKBKKG	1.928	kinase		1.934	bias	0.000532	CCL5,GBP2,HLA-A,NPPA	27 (13)
mibolerone		chemical drug	Inhibited	-2		0.000532	C4A/C4B,CD74,HLA-DQA1,IGF1	
cardiotoxin		chemical - other		1	bias	0.000535	B2M,CCL5,Cxcl9,IGF1,PTN	
NCOR2	0.274	transcription regulator				0.000536	C1QA,CTSS,IGF1	5 (2)
Ccl2		cytokine				0.000536	CCL5,CYBB,IGF1	17 (6)
heme		chemical - endogenous mammalian				0.000536	CCL5,Cxcl9,CYBB	22 (7)
CCL3L3	1.626	cytokine				0.000542	CCL5,Cxcl9	
tacrolimus		chemical drug				0.000545	CCL5,CD74,CYBB,NPPA,PENK	33 (13)
ciglitazone		chemical drug		-1		0.000561	CCL5,CYBB,GFAP,NPPA	24 (9)
CSF2		cytokine		1.218	bias	0.000562	C4A/C4B,CD74,Cxcl9,CYBB,HLA-DQB1,IFITM3,IGF1	37 (9)
IL11		cytokine				0.000563	IGF1,IRF1,SERPINA3	4 (2)
IL1A	2.089	cytokine		1.319	bias	0.000565	C4A/C4B,CCL5,IGF1,IRF1,SERPINA3	27 (11)
SOCS1	3.005	other		-1.934	bias	0.000576	Cxcl9,Ifi47,Igip1,IRF1	20 (6)
LY294002		chemical drug		-1.132	bias	0.000587	CCL5,CD74,Cxcl9,GFAP,IGF1,IRF1,PTN	33 (16)
ACOX1	-0.224	enzyme	Inhibited	-2		0.000623	HLA-DQA1,HLA-DRB5,IGF1,LGALS3BP	
HTT	0.224	transcription regulator				0.00063	B2M,CCL5,CD74,FABP7,GFAP,MPEG1,PENK,SERPINA3	
TRPV1		ion channel				0.000631	GFAP,HLA-DQB1	
trichostatin A		chemical drug		1.238		0.000631	B2M,CYBB,HLA-DQB1,IGSF9,IRF1,IRF8,NPPA,PENK,SEZ6L	
TICAM1	-0.623	other		1.943	bias	0.00064	CCL5,Ifi47,Igtp,IRF1	26 (9)
PRDM1	-0.528	transcription regulator		-1.406		0.000651	CD74,HLA-DQA1,IRF8,SERPINA3,TAPBP	
morphine		chemical drug		-0.83		0.000656	CYBB,GFAP,NPPA,PENK	12 (3)

AGT	-0.795	growth factor		1.379		0.000657	C4A/C4B,CCL5,CTSS,CYBB,IGF1,NPPA,NPTX2,PTN,SERPINA3	29 (14)
CD40LG		cytokine				0.000689	B2M,CCL5,HLA-DQA1,HLA-DQB1,IRF1,TAP1	30 (14)
U0126		chemical drug		-0.025	bias	0.000705	CCL5,CYBB,GFAP,HLA-DQA1,IRF1,NPPA,RAC2	23 (6)
lovastatin		chemical drug		-1		0.000708	CCL5,GFAP,IGF1,IRF1	31 (9)
CUX1		transcription regulator				0.000712	CCL5,CYBB,NPPA	
GF11		transcription regulator				0.000726	Ilgp1,IRF1,LYZ,SERPINA3	
SMC3	0.227	other				0.000727	HLA-DQA1,HLA-DQB1	
CRKL	-0.033	kinase				0.000727	Cxcl9,Ilgp1	
PIAS4	0.196	transcription regulator				0.000727	Cxcl9,IRF1	19 (7)
RFX5		transcription regulator				0.000727	B2M,CD74	
vadimezan		chemical drug				0.000727	CCL5,IRF1	18 (6)
PPARD	-0.121	ligand-dependent nuclear receptor		0.537		0.000734	C1QA,C1QB,FABP7,MPEG1,NPPA	8 (2)
monocrotaline		chemical toxicant				0.000745	CCL5,CYBB,NPPA	16 (5)
Go 6976		chemical drug				0.000778	CCL5,CYBB,NPPA	26 (12)
AZD8055		chemical drug				0.000829	CCL5,Cxcl9	
VIPR1	-0.217	G-protein coupled receptor				0.000829	CCL5,IRF1	13 (4)
pyridostigmine		chemical drug				0.000829	Cxcl9,NPPA	
forskolin		chemical toxicant		-1.281		0.000837	CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK	25 (9)
DOCK8	0.019	other				0.000848	Cxcl9,Ilgp1,IRF1	
STING1	1.402	other				0.000848	CCL5,Cxcl9,IFITM3	28 (8)
TNFSF13B		cytokine				0.000848	CD74,CTSS,HLA-DQA1	4 (2)
CREB1	0.202	transcription regulator		-0.174		0.000867	APOLD1,BRINP2,HLA-A,HLA-DQB1,NPTX2,Nrgn,PENK	
GATA2	1.036	transcription regulator		-0.577		0.000867	C11orf97,CCL5,CYBB,GBP2,NPPA,S100A5	
ERBB2	0.583	kinase		-1.133		0.00088	CCL5,Cxcl9,ERBB4,NPTX2,PCDH1,PENK,SERPINA3,TAP1,TAPBP	15 (4)
SP1	0.563	transcription regulator				0.000893	CCL5,IFITM3,IGF1,IRF1,NPPA,PENK,PTN	
JAK1	0.172	kinase				0.000921	HLA-A,IRF1,TAP1	26 (8)
PLAU		peptidase				0.000921	CCL5,IGF1,PTN	7 (2)
RC3H1	0.575	enzyme				0.00096	CCL5,IFITM3,IRF1	
vorinostat		chemical drug	Inhibited	-2.236		0.000968	CD74,HLA-DQB1,HLA-DRB5,IRF1,LYZ	25 (4)
geldanamycin		chemical drug		-1.342		0.00103	HLA-DQA1,IRF1,NPPA,PCDH1,TAP1	
Endothelin		group				0.00105	CD74,NPPA	
ADORA1	-0.341	G-protein coupled receptor				0.00105	NPPA,PENK	
ATXN7	-0.541	other				0.00105	GNG13,PENK	
TGAL copolymer		biologic drug				0.00105	CCL5,IGF1	
VCAN	1.011	other		1		0.00106	C4A/C4B,IRF8,PARP14,PENK	
levothyroxine		chemical - endogenous mammalian				0.00108	NPPA,Nrgn,PENK	5 (2)
STK40	-0.705	kinase				0.00112	C1QA,C1QB,HLA-DQA1	
NFKB1	-0.398	transcription regulator				0.00116	B2M,CCL5,Cxcl9,CYBB,IRF1	28 (12)
SMURF1	-0.455	enzyme				0.00118	Cxcl9,IRF1	
Cux1	0.209	transcription regulator				0.00118	CCL5,Cxcl9	
triflusal		chemical drug				0.00118	CD74,GFAP	
L-carnitine		chemical - endogenous mammalian				0.00118	GFAP,NPPA	8 (3)
ESR1	2.206	ligand-dependent nuclear receptor	Inhibited	-2.012		0.00121	CD74,CTSS,ERBB4,GFAP,IFITM3,IGF1,Ilgp1,IRF1,KCNH3,LGALS3BP,TAPBP	12 (2)
DDX58	-0.154	enzyme				0.00121	CCL5,IRF1,IRF8	11 (3)
SPI1	2.598	transcription regulator	Activated	2.184		0.00125	CTSS,Cxcl9,CYBB,IFITM3,LYZ	
MAPK9	-0.037	kinase		1.091		0.00125	CCL5,Ilgp1,LGALS3BP,PARP14	25 (6)
enterotoxin B		biologic drug				0.0013	CCL5,Cxcl9,SERPINA3	
prazosin		chemical drug				0.0013	GFAP,NPPA	
AIRE		transcription regulator				0.0014	C4A/C4B,CCL5,PARP14	
RXRA	0.631	ligand-dependent nuclear receptor		-0.277		0.00145	C1QA,CTSS,IGF1,LYZ,NPPA	5 (2)
HOXA10		transcription regulator		-1.964		0.00148	CYBB,HLA-DQA1,HLA-DQB1,LYZ	
CD3		complex		0.928	bias	0.00156	CCL5,CD74,HLA-DQB1,IGF1,IRF1,IRF8,RAC2	38 (12)
probutol		chemical drug				0.00158	CYBB,NPPA	
NKX2-1		transcription regulator				0.0016	CD74,HLA-A,LYZ,RAC2	
sodium chloride		chemical - endogenous mammalian				0.0016	CCL5,CYBB,NPPA	16 (5)
NFYA	0.162	transcription regulator				0.00166	HLA-DQB1,IGF1,IRF1	

NOS2		enzyme		1.387		0.00166	Cxcl9, LGALS3BP, NPPA, SERPINA3	
CG		complex	Activated	2.213	bias	0.00167	B2M, C4A/C4B, HLA-A, HLA-DQA1, IGF1, LGALS3BP	
PPARA	-0.957	ligand-dependent nuclear receptor		-0.577		0.00167	C1QA, C1QB, CYBB, HLA-DQA1, IFITM3, NPPA	
CCK	-0.93	other				0.00173	GFAP, PENK	
lipoarabinomannan		chemical - endogenous non-mammalian				0.00173	HLA-DRB5, IRF1	
ilomastat		chemical drug				0.00173	CCL5, ERBB4	
LCN2	2.773	transporter				0.00177	CCL5, Cxcl9, GFAP	22 (6)
IL18	-0.581	cytokine		-0.33	bias	0.0018	CCL5, IRF1, NPPA, PENK	31 (13)
ZFXH3	-0.416	transcription regulator				0.00183	HLA-A, IFITM3, TUBB2B	
SB203580		chemical drug		-1	bias	0.00184	C4A/C4B, CCL5, GBP2, IRF1, NPPA, PENK	30 (17)
HOXA5		transcription regulator				0.00188	IGF1, PTN	
mifepristone		chemical drug		-1.342		0.00188	C1QB, CD74, CYBB, HLA-DQB1, PTN	27 (7)
SAMSN1	0.001	other				0.00189	Cxcl9, Iigp1, IRF1	
SLC13A1		transporter				0.00195	GBP2, IGF1, Igtp	
IKBKE	0.565	kinase				0.00195	CCL5, Cxcl9, HLA-A	25 (8)
ZFP36	2.028	transcription regulator				0.00201	CTSS, CYBB, IRF1	
PPIF	-0.21	enzyme				0.00201	CCL5, Cxcl9, PTN	
LEP		growth factor		0.93		0.00201	CCL5, CYBB, GFAP, IGF1, IRF1, NPPA	34 (14)
SLPI		other				0.00204	CCL5, CTSS	
imatinib		chemical drug		-1.387		0.00209	Cxcl9, CYBB, Ifi47, Igtp, IRF1	21 (4)
levodopa		chemical - endogenous mammalian		-0.964		0.00213	C1QA, C4A/C4B, GFAP, HLA-A, NPTX2, PENK, RBAK	
daidzein		chemical drug				0.0022	GFAP, HLA-A, HLA-DQA1	
HRAS	-0.02	enzyme				0.0022	B2M, CCL5, CTSS, LYZ, NPPA, SERPINA3, TAP1	22 (7)
PDGF-AA		complex				0.00221	GFAP, IGF1	
CDC73	0.388	other				0.00221	IGF1, IRF1	
TICAM2		other				0.00221	CCL5, IRF1	11 (4)
Saa3	2.556	other				0.00221	CCL5, IGF1	
SPRY1	0.259	other				0.00221	FABP7, IGF1	
Fus	0.315	transcription regulator				0.00221	HNRNP1, KCNIP1	
bee venom		chemical - endogenous non-mammalian				0.00233	CCL5, CYBB, IRF1	27 (10)
NFATC2	-0.024	transcription regulator				0.00236	CCL5, Cxcl9, Iigp1, IRF1	28 (11)
NFIX	0.211	transcription regulator				0.00238	GFAP, SERPINA3	
wortmannin		chemical drug		-0.577		0.00244	CCL5, IGF1, IRF1, IRF8	26 (12)
vancomycin		biologic drug		-0.243		0.00248	C1QA, C1QB, C4A/C4B, SEZ6L	
ZNF503	-1.487	other				0.00256	GFAP, PENK	
dimethyl itaconate		chemical reagent				0.00256	IFITM3, IRF1	
CCR1		G-protein coupled receptor				0.00256	CCL5, CTSS	
IL1		group		1.807	bias	0.00259	CCL5, GFAP, IGF1, IRF1, LYZ	32 (13)
N-nitro-L-arginine methyl ester		chemical drug				0.00261	CYBB, GFAP, NPPA	22 (6)
Gm26504		other				0.00268	IGF1	
CAMTA2	0.218	transcription regulator				0.00268	NPPA	
CAMTA1	0.378	other				0.00268	NPPA	
SNORD21		other				0.00268	HLA-A	
CYTL1		cytokine				0.00268	IGF1	
TPH2		enzyme				0.00268	IGF1	
ENDOG	-0.026	enzyme				0.00268	NPPA	
SGTA	-0.03	other				0.00268	IGF1	
GPLD1	0.739	enzyme				0.00268	LGALS3BP	
CORIN		peptidase				0.00268	NPPA	
PRPF4	0.002	other				0.00268	CCL5	
Raet1d/Raet1e		other				0.00268	HLA-A	
GAN	0.524	other				0.00268	GFAP	
PTS	0.403	enzyme				0.00268	IGF1	
TONSL	-0.132	other				0.00268	CCL5	
ZNF260	0.245	transcription regulator				0.00268	NPPA	
Adora3/LOC100911796		G-protein coupled receptor				0.00268	NPPA	
HSP-990		chemical drug				0.00268	HLA-A	
anthraquinone		chemical toxicant				0.00268	CCL5	

SCH 39370		chemical - protease inhibitor				0.00268	NPPA	
10-hydroxydecanoic acid		chemical - endogenous non-mammalian				0.00268	IRF1	
thiorphan		chemical - protease inhibitor				0.00268	NPPA	
deoxycorticosterone acetate/potassium chloride/sodium chloride		chemical reagent				0.00274	CCL5,CYBB	
TBK1	0.522	kinase				0.00291	CCL5,Cxcl9,Ilgp1	11 (3)
FTO	0.048	enzyme				0.00293	IGF1,NPPA	
BAK1	0.562	other				0.00293	CCL5,HLA-A	
NKX2-3		transcription regulator	Inhibited	-2		0.00293	GBP2,PARP14,TAP1,UNC93B1	
RARA	0.348	ligand-dependent nuclear receptor		-0.108		0.00295	CTSS,IRF1,LGALS3BP,PENK,TAPBP	
HAVCR1		other				0.00307	B2M,IRF1,TAP1	
STAT4		transcription regulator		1.981	bias	0.00308	Cxcl9,HLA-DQB1,IRF1,TUBB2B	
CARD9		other				0.00313	CCL5,Cxcl9	
CXCL10	2.616	cytokine				0.00313	CCL5,Cxcl9	
PTX3		other				0.00313	CCL5,IGF1	
colistin		biologic drug				0.00315	C1QA,C1QB,SEZ6L	
INSIG1	-0.009	other				0.00315	CCL5,HLA-DQA1,IRF8	
kanamycin A		chemical drug				0.00331	C1QA,C1QB,SEZ6L	
TIRAP	-3.413	other				0.00333	CCL5,IRF1	11 (3)
CFB		peptidase				0.00333	C4A/C4B,NPPA	
mir-23		microRNA				0.00333	IGF1,IRF1	
FAS	1.333	transmembrane receptor				0.00339	CCL5,Cxcl9,GBP2,HLA-DQB1,IRF1	28 (12)
NCF1	1.123	enzyme				0.00354	CCL5,IGF1	22 (7)
CGAS	4.151	enzyme				0.00354	CCL5,Cxcl9	
KDM6B	0.264	enzyme				0.00354	CCL5,Igtp	
C1QA	1.876	other				0.00354	C4A/C4B,SERPINA3	
BECN1	-0.037	other				0.00354	CCL5,NPPA	
NFIC	0.108	transcription regulator				0.00354	FABP7,GFAP	
TAB1	-0.236	enzyme				0.00354	CCL5,GBP2	23 (10)
Rxr		group				0.00357	C1QA,CTSS,IGF1	
SYK	1.298	kinase				0.00366	CCL5,Cxcl9,IRF1	27 (10)
INSR	-0.193	kinase				0.00369	C1QA,IGF1,Ilgp1,LYZ,MPEG1,NPPA	
cholesterol		chemical - endogenous mammalian		1.982		0.00371	CYBB,HLA-DRB5,LYZ,MPEG1	
metronidazole		chemical drug				0.00375	C1QA,C1QB,SEZ6L	
TNFSF14		cytokine				0.00376	CCL5,Cxcl9	20 (4)
SUMO1	0.231	enzyme				0.00376	NPPA,TAP1	
PBX1	0.225	transcription regulator				0.00376	CYBB,FABP7	
Tlr		group				0.00384	CCL5,HLA-A,IRF1	29 (11)
TERC		other				0.00398	CCL5,GFAP	
PTP4A1	-0.523	phosphatase				0.00403	CCL5,HNRNP1,RBAK	
PRDM16	0.568	transcription regulator				0.0042	CCL5,Cxcl9	
CYBB	4.896	enzyme				0.0042	CCL5,CYBB	
HSPG2	0.901	enzyme				0.0042	CTSS,IGF1	
Klrk1		transmembrane receptor				0.0042	CCL5,IRF8	
vinblastine		chemical drug				0.0042	CCL5,HLA-A	22 (7)
Alpha catenin		group				0.00422	IGF1,IRF1,LYZ	
indomethacin		chemical drug		1.91		0.0043	C4A/C4B,IFITM3,IGF1,NPPA	18 (5)
mir-130		microRNA				0.00444	CCL5,IRF8	
UBE2I	0.78	enzyme				0.00444	IRF1,TAP1	
RAD21	0.185	transcription regulator				0.00444	HLA-DQA1,HLA-DQB1	
FOS	-0.184	transcription regulator		-0.581		0.00461	CCL5,Cxcl9,LGALS3BP,NPPA,NPTX2,PENK	23 (8)
tetradecanoylphorbol acetate		chemical drug		0.669		0.00462	CCL5,CYBB,ERBB4,IGF1,IRF1,IRF8,LYZ,NPPA,SERPINA3	33 (13)
PRKCA	0.17	kinase				0.00462	CYBB,GFAP,NPPA	22 (6)
SUMO3	0.464	other				0.00468	Bst2,TAP1	
IGFBP3	-0.084	other				0.00468	CCL5,IGF1	8 (3)
steroid		chemical - endogenous mammalian				0.00468	CCL5,IGF1	5 (2)
genistein		chemical drug		-1.3		0.00468	CCL5,CD74,HLA-A,HLA-DQA1,IGF1	32 (9)

thioacetamide		chemical toxicant			0.00481	C4A/C4B,GFAP,IGF1,LGALS3BP	
bortezomib		chemical drug	0.849		0.00488	CCL5,Cxcl9,IGF1,SERPINA3	29 (9)
SERPINE2	-0.202	other			0.00492	CCL5,Cxcl9	
SMARCA5	0.368	transcription regulator			0.00505	B2M,HLA-A,UNC93B1	
PLAUR		transmembrane receptor			0.00517	CCL5,CYBB	19 (5)
15-keto-13,14-dihydroprostaglandin E2		chemical - endogenous mammalian			0.00536	GFAP	
MEX3C	0.34	enzyme			0.00536	IGF1	
ARL16	-0.099	other			0.00536	CCL5	
ADGRG1	-0.16	G-protein coupled receptor			0.00536	IGF1	
ADH1C	-0.975	enzyme			0.00536	NPPA	
Raet1a		other			0.00536	HLA-A	
CBP-ICSBP-IRF-1-PU.1		complex			0.00536	CYBB	
HLA-B27		complex			0.00536	HLA-DQA1	
SEMA5A	0.079	transmembrane receptor			0.00536	GFAP	
SPR	0.007	enzyme			0.00536	IGF1	
Raet1b		other			0.00536	HLA-A	
AP1M1	0.228	transporter			0.00536	HLA-A	
OAS1		enzyme			0.00536	IRF1	
CELA1	-0.838	peptidase			0.00536	HLA-A	
RIMS2	0.291	other			0.00536	IGF1	
IGFALS		other			0.00536	IGF1	
miR-1195 (miRNAs w/seed GAGUUCG)		mature microRNA			0.00536	IGF1	
H60a		other			0.00536	HLA-A	
apilmod		chemical drug			0.00536	RAC2	
LTK	2.91	kinase			0.00536	NPPA	
DCTN4	0.202	other			0.00536	CCL5	
poly-L-glutamic acid-peptoid 1 conjugate QM56		chemical reagent			0.00536	CCL5	
NAGLU	0.77	enzyme			0.00536	LYZ	
SLC25A12	0.033	transporter			0.00536	CCL5	
TNNT2	-1.685	other			0.00536	NPPA	
AGXT		enzyme			0.00536	NPPA	
ST8SIA2	1.466	enzyme			0.00536	GFAP	
CDO1	0.159	enzyme			0.00536	IGF1	
GBP2	5.235	enzyme			0.00536	HLA-A	
Kcnp2		ion channel			0.00536	KCNIP1	
1,5-bis-(diethyl-N-nitrosoamino)-2,4-dinitrobenzene		chemical reagent			0.00536	CYBB	
GTPL714		chemical reagent			0.00536	NPPA	
RPS19	0.362	other			0.00536	CD74	
selonsertib		chemical drug			0.00536	NPPA	
paraoxon		chemical toxicant			0.00536	GFAP	
fenfluramine		chemical drug			0.00536	PENK	
mavacamten		chemical drug			0.00536	NPPA	
fascaplysin		chemical drug			0.00536	PTN	
lanreotide		biologic drug			0.00536	IGF1	
5-aminovaleric acid		chemical - endogenous mammalian			0.00536	GFAP	
fluorocitric acid		chemical reagent			0.00536	GFAP	
barium		chemical reagent			0.00536	PENK	
NONO	0.256	transcription regulator			0.00538	CCL5,LGALS3BP,PARP14	
memantine		chemical drug			0.00543	GFAP,TAP1	
DRD2		G-protein coupled receptor			0.00569	IGF1,PENK	
IL17F		cytokine			0.00569	Cxcl9,IGF1	22 (6)
CGS 21680		chemical reagent			0.00569	CCL5,NPPA	11 (3)
pentoxifylline		chemical drug			0.00569	CCL5,CYBB	
ribavirin		chemical drug			0.00569	Cxcl9,IRF1	20 (4)
camptothecin		chemical drug			0.00573	GBP2,HLA-A,HLA-DQA1,HLA-DQB1,IRF1,TAP1	26 (5)
semaxinib		chemical drug			0.00584	C1QA,C1QB,Cxcl9	5 (2)
NOTCH1	0.099	transcription regulator	-1		0.00589	FABP7,GFAP,IRF1,IRF8	

JAK		group				0.00595	IFITM3,IGF1	
USP22	0.459	peptidase				0.00595	CCL5,CYBB	
pristane		chemical toxicant				0.00595	CCL5,IRF8	
ATF3	-0.157	transcription regulator				0.00596	CCL5,GBP2,PENK	
IL22		cytokine				0.00621	CCL5,Cxcl9,SERPINA3	
DPP4	-1.215	peptidase				0.00623	CCL5,Cxcl9	
FLT3	0.591	kinase				0.00651	CYBB,LYZ	
HBB	2.726	transporter				0.00651	CCL5,Cxcl9	
SOD1	0.103	enzyme				0.0066	B2M,C1QA,GFAP,IGF1	
Pka		complex				0.00671	IGF1,IRF1,PENK	
SOX11	0.733	transcription regulator				0.00671	CCL5,ERBB4,HLA-DRB5	
PRKACA	-0.138	kinase				0.00679	IGF1,PENK	
temozolomide		chemical drug				0.00679	CCL5,Cxcl9	
fulvestrant		chemical drug		1.869		0.00685	CCL5,CD74,IGF1,IRF1	21 (6)
AHR	0.59	ligand-dependent nuclear receptor	Activated	2.19		0.00704	C1QA,C1QB,CCL5,Cxcl9,IRF1	
SMAD1	-0.628	transcription regulator				0.00708	GFAP,IRF1	4 (2)
C3AR1	2.789	G-protein coupled receptor				0.00708	CCL5,IGF1	
IFIH1	0.687	enzyme				0.00708	Bst2,CCL5	
vincristine		chemical drug				0.00708	CCL5,IGF1	
calcitriol		chemical drug				0.00709	CCL5,Cxcl9,CYBB,IGF1,NPPA,TAP1	28 (13)
quinolinic acid		chemical - endogenous mammalian				0.00737	GFAP,PENK	
N-fomyl-Met-Leu-Phe		chemical reagent				0.00737	CYBB,RAC2	
IL12 (family)		group				0.00751	CCL5,IRF1,IRF8	
NFKB2	1.414	transcription regulator				0.00751	CCL5,CTSS,HLA-DQA1	
resiquimod		chemical drug				0.00755	C4A/C4B,CCL5,Cxcl9,IFITM3	
EBF1	-0.765	transcription regulator				0.00765	CCL5,Cxcl9,IRF1	
PAF1	0.332	other				0.00767	CCL5,IFITM3	
halofuginone		chemical drug				0.00779	C4A/C4B,CTSS,LGALS3BP	
estrogen		chemical drug		0.255	bias	0.00782	CYBB,IGF1,PENK,SERPINA3	29 (11)
IL15	-1.64	cytokine				0.00791	CCL5,CD74,IRF1,NPTX2,RAC2	
KAT2B	0.198	transcription regulator				0.00798	B2M,NPPA	
istradefylline		chemical drug				0.00803	PENK	
HS-243		chemical - kinase inhibitor				0.00803	CCL5	
SXN101959		chemical reagent				0.00803	IGF1	
drotrecogin alfa		biologic drug				0.00803	NPPA	
Ga12/13		group				0.00803	IGF1	
propentofylline		chemical drug				0.00803	GFAP	
SLC4A5		transporter				0.00803	NPPA	
DPP10	0.481	peptidase				0.00803	KCNIP1	
LRRC8E		ion channel				0.00803	CCL5	
AGPAT1	0.102	enzyme				0.00803	IGF1	
HP1BP3	0.348	other				0.00803	IGF1	
ABRA		other				0.00803	NPPA	
SRFBP1	0.915	other				0.00803	NPPA	
PCDH17	-0.209	other				0.00803	NPPA	
Ap1 gamma		group				0.00803	HLA-A	
GLO1	0.222	enzyme				0.00803	GFAP	
GNLY		other				0.00803	CCL5	
INPP1	-1.374	phosphatase				0.00803	NPPA	
Tardbp		transcription regulator				0.00803	ERBB4	
ostarine		chemical drug				0.00803	IGF1	
ZNRD1ASP		other				0.00803	HLA-A	
S100A1	-0.082	other				0.00803	NPPA	
IFNGR2	0.973	transmembrane receptor				0.00803	IRF1	
MBD5	-0.14	other				0.00803	IGF1	
MYOZ2		other				0.00803	NPPA	
DDX4	1.602	enzyme				0.00803	IFITM3	
Lycium barbarum polysaccharides		chemical - endogenous non-mammalian				0.00803	IGF1	
LIFR	-0.03	transmembrane receptor				0.00803	GFAP	

HERC5		enzyme				0.00803	CCL5	
fomepizole		chemical drug				0.00803	CCL5	
dexrazoxane		chemical drug				0.00803	NPPA	
chlorisondamine		chemical drug				0.00803	PENK	
CRTC1-MAML2		fusion gene/product				0.00803	IGF1	
nexinhib20		chemical reagent				0.00803	CYBB	
(-)-gallic acid		chemical - protease inhibitor				0.00803	IRF1	
2',5'-dideoxyadenosine		chemical reagent				0.00803	IGF1	
protamine zinc insulin		biologic drug				0.00803	IGF1	
2R,4R-4-aminopyrrolidine-2,4-dicarboxylic acid		chemical reagent				0.00803	GFAP	
afatoxin B1		chemical - endogenous non-mammalian	1	bias		0.0082	HLA-A,HLA-DQA1,HLA-DQB1,LGALS3BP	
IFNA4		cytokine				0.00829	Bst2,GBP2	
JUNB	1.227	transcription regulator				0.00837	C1QB,Cxcl9,PENK	9 (3)
cytokine		group				0.00837	CCL5,GFAP,IRF1	22 (7)
carrageenan		chemical drug				0.00861	CCL5,GFAP	19 (5)
DIO2	-0.134	enzyme				0.00882	NPPA,PENK,ZNF804A	6 (3)
IRGM	3.578	enzyme				0.00893	B2M,IFITM3	
glucocorticoid		chemical drug	-1.982			0.00908	CCL5,CD74,IRF8,SERPINA3	9 (2)
budesonide		chemical drug	1.732			0.00939	B2M,CCL5,IFITM3,PTN	
TSC2	0.123	other				0.00944	GFAP,Ifi47,IFITM3	
HDL		complex				0.00959	CCL5,GFAP	11 (3)
APLN	0.503	other				0.00959	GFAP,NPPA	17 (6)
DCN	0.422	other				0.00959	HLA-DQA1,HLA-DQB1	
TNFRSF1A	0.505	transmembrane receptor				0.00976	CCL5,GFAP,IGF1	12 (4)
galactosylceramide-alpha		chemical reagent				0.00993	Cxcl9,IRF1	22 (7)
SMPD1	0.103	enzyme				0.00993	CCL5,GFAP	17 (3)
PTPN6	1.712	phosphatase				0.00993	CYBB,IRF1	24 (8)
nitrofurantoin		chemical drug				0.0101	C4A/C4B,CTSS,IGF1	
SP600125		chemical drug	-0.152			0.0101	CCL5,GBP2,IGF1,NPPA	
Insulin		group	-1.732			0.0102	CCL5,CYBB,GFAP,IGF1,LGALS3BP,NPPA	
progesterone		chemical - endogenous mammalian	-1.091			0.0102	CCL5,GFAP,HLA-A,HLA-DQB1,IGF1,PCDH1	
MAP2K7	0.831	kinase				0.0103	CCL5,NPPA	
APOA1		transporter				0.0103	CYBB,GFAP	
MAP2K4	-0.014	kinase				0.0106	CCL5,NPPA	
Ro 25-6760		chemical toxicant				0.0107	NPPA	
sargramostim		biologic drug				0.0107	CYBB	
chitinase		group				0.0107	CCL5	
CACTIN	0.965	other				0.0107	CCL5	
ROBO3	0.191	transmembrane receptor				0.0107	IRF8	
C10orf71	1.224	other				0.0107	NPPA	
SLCO1C1	-0.406	transporter				0.0107	Nrgn	
endothelin receptor		group				0.0107	NPPA	
ITPRID2	-0.074	other				0.0107	IGF1	
LRIG3	-1.051	other				0.0107	ERBB4	
ALX3	-1.162	transcription regulator				0.0107	GFAP	
cathepsin L inhibitor		chemical drug				0.0107	NPPA	
TRIL	0.429	other				0.0107	CCL5	
GALNS	0.755	enzyme				0.0107	GFAP	
KCND3	0.034	ion channel				0.0107	KCNIP1	
PKIA	0.361	other				0.0107	IGF1	
UFD1	0.28	peptidase				0.0107	CCL5	
RGL2	0.523	other				0.0107	NPPA	
mir-384		microRNA				0.0107	NPPA	
K-604		chemical drug				0.0107	CCL5	
TAF12	0.229	transcription regulator				0.0107	IRF1	
NPLOC4	0.195	other				0.0107	CCL5	
A4GALT		enzyme				0.0107	IRF1	
CITED1	-1.565	transcription regulator				0.0107	IGF1	
CSTB	1.037	peptidase				0.0107	GFAP	
SCIN		other				0.0107	RAC2	

Mt3	-0.159	other				0.0107	GFAP	
TXN2	-0.261	enzyme				0.0107	CYBB	
phenylacetic acid		chemical - endogenous mammalian				0.0107	HLA-A	
arzoxifene		chemical drug				0.0107	IGF1	
cilazapril		chemical drug				0.0107	NPPA	
nabumetone		chemical drug				0.0107	NPPA	
cromakalim		chemical drug				0.0107	NPPA	
sodium phosphate		chemical drug				0.0107	NPPA	
AC083837.1		other				0.0107	CCL5	
succinylacetone		chemical - endogenous mammalian				0.0107	CYBB	
CDP-choline		chemical - endogenous mammalian				0.0107	GFAP	
tamoxifen		chemical drug	1.521			0.011	ERBB4,IGF1,IRF1,SERPINA3	
DIO3		enzyme				0.0113	HLA-A,IRF8,Nrgn	
PPP2CA	0.054	phosphatase				0.0113	Cxcl9,IRF1	
PTGES	-0.007	enzyme				0.0113	CYBB,NPPA	
anisomycin		chemical - endogenous non-mammalian				0.0113	CYBB,IRF1	
DNMT3A	0.197	enzyme				0.0114	CYBB,IRF1,IRF8	
STUB1	0.358	enzyme				0.0117	CTSS,NPPA	
Ap1		complex				0.0118	CCL5,GFAP,IGF1	
HIF1A	-0.373	transcription regulator	0.562			0.012	CCL5,Cxcl9,ERBB4,IGF1,NPPA	
DNMT3B	-1.582	enzyme				0.012	CCL5,HLA-DQB1,PTN	
dopamine		chemical - endogenous mammalian				0.012	CCL5,Cxcl9,PENK	
CSHL1		growth factor				0.0121	IGF1,IRF1	
IL6ST	-0.111	transmembrane receptor				0.0124	GFAP,IRF1	
FOXP3		transcription regulator				0.0127	CCL5,GBP2,HLA-A	
rotenone		chemical toxicant				0.0128	CYBB,GFAP	
MAPK8	-0.001	kinase				0.0129	CCL5,CYBB,NPPA	
S100A8		other				0.0131	C1QB,Cxcl9,IGF1	
IL2RG	1.011	transmembrane receptor				0.0132	Cxcl9,HLA-A	
ESR2		ligand-dependent nuclear receptor	-1.964			0.0133	Bst2,GBP2,GFAP,IGF1,LGALS3BP,PARP14	
CF102		chemical drug				0.0133	CYBB	
darusentan		chemical drug				0.0133	NPPA	
teniposide		chemical drug				0.0133	CCL5	
ILX-23-7553		chemical drug				0.0133	NPPA	
RAR-RXR		complex				0.0133	IRF1	
SMPD3	-0.884	enzyme				0.0133	IGF1	
IRF3-IRF7		complex				0.0133	CCL5	
propolis		biologic drug				0.0133	CCL5	
Ftx	0.558	other				0.0133	NPPA	
G6PC3	0.702	phosphatase				0.0133	CYBB	
Gata		group				0.0133	NPPA	
MCOLN2		ion channel				0.0133	CCL5	
TAF9		transcription regulator				0.0133	IRF1	
Nc2		complex				0.0133	HLA-A	
RAP1B	0.134	enzyme				0.0133	CCL5	
KCND2	0.008	ion channel				0.0133	KCNIP1	
NBR1	0.49	other				0.0133	CYBB	
CTSA	0.26	peptidase				0.0133	NPPA	
DCX	0.547	other				0.0133	GFAP	
ADAM8	-0.588	peptidase				0.0133	CCL5	
AQP3		transporter				0.0133	CCL5	
talazoparib		chemical drug				0.0133	CCL5	
RFXANK	0.474	transcription regulator				0.0133	HLA-A	
Z-endoxifen		chemical - endogenous mammalian				0.0133	IGF1	
tideglusib		chemical drug				0.0133	IGF1	
fluticasone		chemical drug				0.0133	CCL5	
H3B-8800		chemical drug				0.0133	CCL5	

gabapentin		chemical drug				0.0133	GFAP	
ranitidine		chemical drug				0.0133	PENK	
fenoldopam		chemical drug				0.0133	CYBB	
nor-binaltorphimine		chemical reagent				0.0133	CYBB	
ceftriaxone		chemical drug				0.0133	GFAP	
5-hydroxydecanoic acid		chemical - endogenous mammalian				0.0133	NPPA	
halofuginol		chemical reagent				0.0133	CCL5	
FLI1	0.185	transcription regulator				0.0136	CCL5,Cxcl9	
MRTFA	0.542	transcription regulator				0.0139	CCL5,HLA-A,NPPA	
cytarabine		chemical drug				0.014	CCL5,HLA-A	
IRF4		transcription regulator				0.0141	B2M,CTSS,IRF1	
SPP1	-0.803	cytokine				0.0143	CCL5,GFAP,IGF1	
topotecan		chemical drug				0.0143	C4A/C4B,ERBB4,HLA-DQA1	
SRF	0.516	transcription regulator				0.0143	APOLD1,CCL5,IGF1,NPPA	
3,3'-diindolylmethane		chemical drug				0.0144	HLA-A,TAP1	
ANXA7	0.299	ion channel				0.0148	Cxcl9,IGF1	
folic acid		chemical - endogenous mammalian				0.0148	CCL5,CYBB	
INHBA	-0.294	growth factor				0.0151	ERBB4,IGF1,IRF1	
USF2	0.293	transcription regulator				0.0152	B2M,LGALS3BP	
PRKD1	0.377	kinase				0.0152	CCL5,Cxcl9	
CD28		transmembrane receptor	Activated	2	bias	0.0153	GBP2,HLA-DQB1,IRF1,IRF8	
MAPK14	0.494	kinase				0.0153	CCL5,Cxcl9,NPPA	
PDX1		transcription regulator				0.0153	GFAP,NPTX2,SEZ6L	
bexarotene		chemical drug				0.0153	ERBB4,FABP7,GFAP	
SHH	0.437	peptidase				0.0155	C1QA,ERBB4,IGF1	
SASH1	-0.78	other				0.0156	Ilgp1,IRF1	
RORA	-0.238	ligand-dependent nuclear receptor				0.0159	CCL5,Cxcl9,IGF1	
MCB-613		chemical reagent				0.016	Cxcl9	
pervanadate		chemical reagent				0.016	IRF1	
Snhg14	0.054	other				0.016	NPPA	
Fcgr2		group				0.016	CCL5	
F Actin		complex				0.016	CTSS	
5R-hydroxytryptolide		chemical drug				0.016	IRF1	
BICC1	-0.012	other				0.016	ERBB4	
PIK3AP1	-0.857	other				0.016	IRF8	
Ampa Receptor		complex				0.016	ERBB4	
PRKACB	0.143	kinase				0.016	PENK	
Msx3		transcription regulator				0.016	IGF1	
ERAP1	0.932	peptidase				0.016	HLA-A	
PPP4C	1.747	phosphatase				0.016	CCL5	
OLIG2	0.311	transcription regulator				0.016	GFAP	
SLC16A1	0.138	transporter				0.016	CYBB	
miR-320b (and other miRNAs w/seed AAAGCUG)		mature microRNA				0.016	IGF1	
obinutuzumab		biologic drug				0.016	CCL5	
MOV10L1		enzyme				0.016	NPPA	
TAF10	0.394	transcription regulator				0.016	IGF1	
LRIG1	-0.627	other				0.016	ERBB4	
RNF17	0.22	other				0.016	SERPINA3	
NOCT	-0.315	transcription regulator				0.016	IGF1	
EPHA4	0.533	kinase				0.016	IGF1	
BAMBI	1.439	other				0.016	PENK	
Npy4r		G-protein coupled receptor				0.016	IGF1	
taselisib		chemical drug				0.016	CCL5	
ERCC3	-0.145	enzyme				0.016	IGF1	
U 50488H		chemical reagent				0.016	CYBB	
lestaurtinib		chemical drug				0.016	LYZ	
ruboxistaurin		chemical drug				0.016	CYBB	
aurintricarboxylic acid		chemical drug				0.016	PTN	
BB-Cl-amidine		chemical reagent				0.016	IGF1	

Z-Leu-Leu-Leu-B(OH)2		chemical reagent				0.016	GFAP	
heroin		chemical drug				0.016	PENK	
zofenopril		chemical drug				0.016	NPPA	
MAVS	2.936	other				0.016	CCL5,IFITM3	
TRAF6	0.071	enzyme				0.016	CYBB,SERPINA3	
GDNF	2.23	growth factor				0.016	GFAP,PENK	
Map3k7	0.34	kinase				0.016	CCL5,Cxcl9	
FLT3LG		cytokine				0.016	CCL5,CYBB	
bleomycin		biologic drug				0.0162	CCL5,CTSS,IGF1	
ID3	0.441	transcription regulator				0.0164	CCL5,IRF8,NPPA	
Calcineurin protein(s)		complex				0.0165	CCL5,NPPA	
HIPK2	-0.03	kinase				0.0165	GNNG13,RAC2	
2-deoxyglucose		chemical drug				0.0165	CCL5,IRF8	
RNF31	0.078	enzyme				0.0169	CCL5,Cxcl9	
ATG5	-0.289	other				0.0169	CCL5,LAMTOR5	
Brd4	0.113	kinase				0.0169	Cxcl9,HNRNP1	
isotretinoin		biologic drug				0.0169	IRF1,SERPINA3	
CTNNB1	0.25	transcription regulator		1.131	bias	0.0173	CCL5,Cxcl9,GFAP,IRF8,MPEG1,SERPINA3,TUBB2B	
BTNL2		transmembrane receptor				0.0173	CD74,IFITM3	
cadmium		chemical toxicant				0.0173	B2M,HLA-DQB1	
IL3		cytokine				0.0178	IGF1,LYZ	
minocycline		chemical drug				0.0178	CYBB,GFAP	
PIAS1	0.198	transcription regulator				0.0182	DOC2A,NPPA	
phosphatidylinositol		chemical - endogenous mammalian				0.0186	NPPA	
phlorizin		chemical - endogenous non-mammalian				0.0186	GFAP	
Stat1 dimer		complex				0.0186	IRF1	
RIOX1	0.231	enzyme				0.0186	IGF1	
SCGB3A2		other				0.0186	CTSS	
ST6GALNAC1		enzyme				0.0186	B2M	
SLC39A14	0.352	transporter				0.0186	IGF1	
CC2D1A	-0.228	transcription regulator				0.0186	CCL5	
NOX5		ion channel				0.0186	NPPA	
SNED1	0.172	other				0.0186	IGF1	
MARCKSL1	0.677	other				0.0186	NPPA	
Org 48762-0		chemical drug				0.0186	CCL5	
DVL1	0.323	other				0.0186	NPPA	
AP2M1	0.333	other				0.0186	CD74	
ST8SIA4	-0.086	enzyme				0.0186	GFAP	
MEFV		other				0.0186	LYZ	
SNTA1	0.636	other				0.0186	IGF1	
IFNGR		complex				0.0186	IRF1	
miR-184 (and other miRNAs w/seed GGACGGA)		mature microRNA				0.0186	NPPA	
CYP4F2		enzyme				0.0186	CYBB	
ERCC1	0.139	enzyme				0.0186	IGF1	
CASQ2	-1.751	other				0.0186	NPPA	
DAB1	0.399	other				0.0186	FABP7	
TRIM8	-0.074	enzyme				0.0186	CCL5	
IGFBP4	-0.583	other				0.0186	IGF1	
CLIC4	0.25	ion channel				0.0186	CCL5	
MRC1	0.923	transmembrane receptor				0.0186	CCL5	
KLRB1		transmembrane receptor				0.0186	CCL5	
CLEC2A		other				0.0186	CCL5	
Muc4		other				0.0186	LYZ	
Clec2d (includes others)		transmembrane receptor				0.0186	CCL5	
NKRF	0.606	transcription regulator				0.0186	CCL5	
benzoquinone		chemical - endogenous mammalian				0.0186	IRF1	
dacarbazine		chemical drug				0.0186	CCL5	
selegiline		chemical drug				0.0186	GFAP	
trimethyltin		chemical reagent				0.0186	GFAP	
BW 245C		chemical reagent				0.0186	GFAP	

zimelidine		chemical drug			0.0186	SERPINA3	
lysophosphatidylcholine		chemical - other			0.0186	CCL5,CD74	
IFI16	2.645	transcription regulator			0.0191	CCL5,NPPA	
CCL5	4.542	cytokine			0.0191	CCL5,GFAP	
PLX5622		chemical drug			0.0191	B2M,CCL5	
GATA6		transcription regulator			0.0191	C4A/C4B,IRF8,NPPA	
CHUK	0.192	kinase			0.0196	CCL5,GBP2,HLA-A	
miR-16-5p (and other miRNAs w/seed AGCAGCA)		mature microRNA			0.0196	IGF1,LAMTOR5,NPPA	
curcumin		chemical drug	-0.728		0.0198	CCL5,GFAP,NPPA,PTN	
cisplatin		chemical drug	1.747		0.0199	C4A/C4B,CCL5,CYBB,ERBB4,LYZ,TAP1	
Akt		group			0.02	IGF1,NPPA,PCDH1,PTN	
RETNLB		other			0.02	CCL5,IGF1	
FFAR3		G-protein coupled receptor			0.0205	Cxcl9,GBP2	
TGFA	-0.079	growth factor			0.0205	CCL5,GFAP	
C3		peptidase			0.0205	C1QA,CCL5	
PPP3CA	0.442	phosphatase			0.0205	GFAP,NPPA	
epinephrine		chemical - endogenous mammalian			0.0205	NPPA,PENK	
ANGPT2		growth factor			0.0206	CCL5,CYBB,NPPA	
metformin		chemical drug			0.0206	Ifi47,IGF1,PARP14	
EZH2	-0.086	transcription regulator			0.0208	CCL5,ERBB4,IGF1,PTN	
UCA1		other			0.0213	NPPA	
cyanidin 3-O-glucoside		chemical - endogenous non-mammalian			0.0213	CCL5	
PPT1	-0.08	enzyme			0.0213	GFAP	
ABCC1	0.53	transporter			0.0213	CYBB	
LITAF	0.001	transcription regulator			0.0213	CCL5	
U1 snRNP		complex			0.0213	CCL5	
CD5L		transmembrane receptor			0.0213	CCL5	
ERCC4	0.26	enzyme			0.0213	IGF1	
RLN1		other			0.0213	NPPA	
miR-192-5p (and other miRNAs w/seed UGACCUA)		mature microRNA			0.0213	IGF1	
POU3F3	0.182	transcription regulator			0.0213	FABP7	
SCNN1A		ion channel			0.0213	CYBB	
SMN1/SMN2	0.677	other			0.0213	IGF1	
GRIP1	0.373	transcription regulator			0.0213	IGF1	
HEYL	-2.158	transcription regulator			0.0213	NPPA	
PTPRS	-0.015	phosphatase			0.0213	IGF1	
DSG2	-2.627	other			0.0213	RAC2	
MTPN	0.073	transcription regulator			0.0213	NPPA	
Rfx5	0.013	other			0.0213	HLA-A	
CAPN2	-0.013	peptidase			0.0213	GFAP	
NCR3		transmembrane receptor			0.0213	CCL5	
CCL-34		chemical reagent			0.0213	Cxcl9	
ULBP1		transmembrane receptor			0.0213	HLA-A	
cariporide		chemical drug			0.0213	NPPA	
domoic acid		chemical toxicant			0.0213	GFAP	
ETV6-NTRK3		fusion gene/product			0.0213	Igtp	
epoxyeicosatrienoic acid analog B		chemical reagent			0.0213	CYBB	
epoxyeicosatrienoic acid analog A		chemical reagent			0.0213	CYBB	
tosyllysine chloromethyl ketone		chemical - protease inhibitor			0.0213	IRF1	
USF1	1.174	transcription regulator			0.0214	B2M,CTSS	
TRAF2	2.953	enzyme			0.0214	CCL5,MPEG1	
romidepsin		biologic drug			0.0214	CCL5,Cxcl9	
propylthiouracil		chemical drug			0.0218	C1QB,IGF1,TUBB2B	
ITK		kinase			0.0219	CCL5,HLA-A	
IFNL1		cytokine			0.0224	IFITM3,LGALS3BP	
MAPK3	-0.012	kinase			0.0224	HLA-DQB1,NPTX2	

histamine		chemical - endogenous mammalian			0.0224	CCL5,PENK	
TGM2	0.287	enzyme			0.0228	CD74,PARP14,TAP1	
IRF5	0.462	transcription regulator			0.0234	CCL5,IFITM3	
NCOA3	0.173	transcription regulator			0.0239	IGF1,IRF1	
FGF19		growth factor			0.0239	HLA-DQB1,SERPINA3	
haloperidol		chemical drug			0.0239	GFAP,PENK	
rat pegylated super leptin antagonist (mutant D23L/L39A/D40A/F41A)		chemical reagent			0.0239	IGF1	
Ck2		complex			0.0239	CYBB	
IRF3 dimer		complex			0.0239	CCL5	
BLVRA	-0.232	enzyme			0.0239	CCL5	
ZBED2		transcription regulator			0.0239	HLA-A	
RUBCN	-0.166	other			0.0239	GBP2	
AFF4	0.129	transcription regulator			0.0239	HNRNPH1	
MARCHF2	0.027	enzyme			0.0239	CCL5	
salmonella typhimurium lipopolysaccharide		chemical - endogenous non-mammalian			0.0239	CCL5	
CTDSP1	0.335	phosphatase			0.0239	NPPA	
PHF6	0.301	transcription regulator			0.0239	IGF1	
MHC CLASS I (family)		group			0.0239	CCL5	
Ferritin		complex			0.0239	CCL5	
nicotiflorin		chemical reagent			0.0239	GFAP	
GADD45G	0.362	other			0.0239	NPTX2	
TRG		other			0.0239	HLA-DQB1	
DUSP16	0.676	phosphatase			0.0239	IRF1	
TPM3	0.602	other			0.0239	IGF1	
Ccl6	0.229	cytokine			0.0239	CTSS	
MB		transporter			0.0239	NPPA	
YBX3	0.446	transcription regulator			0.0239	HLA-DQB1	
benazepril		chemical drug			0.0239	NPPA	
ammonium trichloro(dioxoethylene- O,O')tellurate		chemical drug			0.0239	HLA-DQB1	
brimonidine		chemical drug			0.0239	GFAP	
PD 168393		chemical drug			0.0239	CCL5	
SLR14		chemical reagent			0.0239	HLA-A	
3-beta,17-beta-androstanediol		chemical - endogenous mammalian			0.0239	LYZ	
TP73	1.055	transcription regulator		-0.747	0.0243	B2M,LYZ,SERPINA3,TAP1	
ERBB4	1.506	kinase			0.0244	ERBB4,SERPINA3	
ascorbic acid		chemical - endogenous mammalian			0.0244	IGF1,NPPA	
SOCS3	-0.863	phosphatase			0.0254	IRF1,NPPA	
RGS4	-0.64	enzyme			0.0259	IGF1,NPPA	
ATF2	0.132	transcription regulator			0.0259	NPPA,PENK	
TO-901317		chemical reagent			0.0261	IGF1,MPEG1,SERPINA3	
CCL2	2.215	cytokine			0.0264	CCL5,IGF1	
trinitrobenzenesulfonic acid		chemical reagent			0.0264	CCL5,Cxcl9	
Stat1-Stat2		complex			0.0265	IRF1	
RNASEH2B	0.346	other			0.0265	CCL5	
PARP14	2.75	enzyme			0.0265	CCL5	
rhesus theta-defensin 1		chemical - endogenous mammalian			0.0265	CCL5	
DAZ2	2.878	translation regulator			0.0265	IFITM3	
L2HGDH	-0.655	enzyme			0.0265	CYBB	
PHLPP2	0.564	enzyme			0.0265	NPPA	
necrostatin-1		chemical reagent			0.0265	GFAP	
EEF1A2	0.057	translation regulator			0.0265	CYBB	
CD244		transmembrane receptor			0.0265	CCL5	
KCNN4	-0.711	ion channel			0.0265	CCL5	
LGALS8	-0.205	other			0.0265	CCL5	
HLA-DQB1	3.418	other			0.0265	HLA-DQA1	

SEMA4D	1.399	transmembrane receptor				0.0265	HLA-DQB1	
ITGA4	0.777	transmembrane receptor				0.0265	RAC2	
PKD2	0.278	kinase				0.0265	IRF8	
NCR1		transmembrane receptor				0.0265	CCL5	
RNF41	0.451	enzyme				0.0265	ERBB4	
IGBP1	0.275	phosphatase				0.0265	IRF1	
RELN	-0.151	peptidase				0.0265	FABP7	
CD200R1		transmembrane receptor				0.0265	Cxcl9	
IL18BP	0.875	other				0.0265	Cxcl9	
KCNJ11		ion channel				0.0265	NPPA	
CTTN	1.592	other				0.0265	CCL5	
TDGF1		growth factor				0.0265	NPPA	
diltiazem		chemical drug				0.0265	NPPA	
urea		chemical - endogenous mammalian				0.0265	NPPA	
IC87114		chemical drug				0.0265	CCL5	
clomipramine		chemical drug				0.0265	SERPINA3	
(5-(4-N-methyl-N(2-pyridyl)amino)ethoxy)benzyl thiazolidine-2,4-dione		chemical reagent				0.0265	CTSS	
tyrphostin AG 1024		chemical drug				0.0265	IGF1	
OGA	0.027	enzyme		-0.152		0.0266	C1QA,C1QB,FABP7,IGF1	
TAF4	0.755	transcription regulator				0.0269	PENK,PTN	
TRAF3	0.183	enzyme				0.0275	CCL5,MPEG1	
FOXA2		transcription regulator				0.0275	IGF1,LYZ,NPTX2	
methotrexate		chemical drug				0.0275	C1QB,CCL5,CTSS	
PC-SPES		chemical drug				0.028	B2M,IRF1	
EGF	0.74	growth factor		-0.548	bias	0.0284	FABP7,GFAP,IGF1,NPPA,SERPINA3	
YBX1	0.4	transcription regulator				0.0285	CCL5,HLA-DQB1	
RHOA	0.225	enzyme				0.0285	IRF1,NPPA	
4-phenylbutyric acid		chemical - endogenous mammalian				0.0285	CCL5,HLA-A	
N-acetyl-L-cysteine		chemical drug				0.0287	CCL5,CYBB,NPPA	
ADIPOQ		other				0.029	CCL5,CYBB,NPPA	
EIF2AK2	0.374	kinase				0.0291	IRF1,LGALS3BP	
CTSV	0.49	peptidase				0.0291	PENK	
mGluR		group				0.0291	ERBB4	
tocilizumab		biologic drug				0.0291	CCL5	
APOL1		transporter				0.0291	Cxcl9	
FBXO42	0.731	other				0.0291	CCL5	
YOD1	-0.175	enzyme				0.0291	CCL5	
IRX4		transcription regulator				0.0291	NPPA	
DHTKD1	0.753	enzyme				0.0291	IGF1	
HTR2B		G-protein coupled receptor				0.0291	NPPA	
PRPF19	0.517	enzyme				0.0291	GFAP	
SARM1	1.021	transmembrane receptor				0.0291	CCL5	
Traj18		other				0.0291	CCL5	
Gcn5l		group				0.0291	B2M	
astragalin		chemical - endogenous non-mammalian				0.0291	GFAP	
BMS-754807		chemical drug				0.0291	ERBB4	
TAF5	0.852	transcription regulator				0.0291	IGF1	
IL17RD	1.149	other				0.0291	Cxcl9	
MED14	0.831	transcription regulator				0.0291	IRF8	
miR-193a-3p (and other miRNAs w/seed ACUGGCC)		mature microRNA				0.0291	ERBB4	
mir-320		microRNA				0.0291	IGF1	
docosapentaenoic acid		chemical reagent				0.0291	CCL5	
PLCB1	0.259	enzyme				0.0291	NPPA	
WWP2	0.136	enzyme				0.0291	CCL5	
MMP7		peptidase				0.0291	ERBB4	
LB-205		chemical reagent				0.0291	GFAP	
ISG15	1.698	other				0.0291	IFITM3	

TNNI3	-0.008	transporter				0.0291	CCL5	
AFF1	-0.101	transcription regulator				0.0291	IGF1	
CAMK2G	0.287	kinase				0.0291	NPPA	
OSTM1	-0.379	other				0.0291	IRF8	
GRB10	0.076	other				0.0291	IGF1	
MYZAP		other				0.0291	NPPA	
CYBA	0.416	enzyme				0.0291	CYBB	
Ifnz (includes others)		cytokine				0.0291	IRF1	
emactuzumab		biologic drug				0.0291	IFITM3	
sesame oil		chemical reagent				0.0291	PTN	
pargyline		chemical drug				0.0291	GFAP	
zileuton		chemical drug				0.0291	CCL5	
clonidine		chemical drug				0.0291	NPPA	
SD6		chemical reagent				0.0291	CCL5	
2,2-bis(4-hydroxyphenyl)-1,1,1-trichloroethane		chemical - endogenous mammalian				0.0291	IGF1	
terbutaline		chemical drug				0.0291	GFAP	
phospholipid		chemical - endogenous mammalian				0.0291	CCL5	
CA074-methyl ester		chemical reagent				0.0291	GFAP	
theophylline		chemical drug				0.0291	GFAP	
scopolamine		chemical drug				0.0291	GFAP	
allopregnanolone		chemical - endogenous mammalian				0.0291	PENK	
trestolone		chemical drug				0.0291	IGF1	
erlotinib		chemical drug				0.0307	CCL5,CYBB	
EP300	-0.081	transcription regulator				0.0312	B2M,IGF1,LGALS3BP,NPPA	
THPO		cytokine				0.0313	IRF1,TAP1	
CEBPD	0.263	transcription regulator				0.0313	GFAP,IGF1	
NS-398		chemical reagent				0.0313	CCL5,IGF1	
estrogen receptor		group				0.0314	ERBB4,IGF1,PCDH1	
PPARGC1A	-0.088	transcription regulator		0.106		0.0315	IGF1,NPPA,PTN,SERPINA3	
L-lysine		chemical - endogenous mammalian				0.0317	IGF1	
chlorcyclizine		chemical drug				0.0317	SERPINA3	
ATP6AP2	-0.004	transporter				0.0317	CYBB	
SLC7A2	-0.001	transporter				0.0317	Cxcl9	
BV6		chemical reagent				0.0317	CCL5	
PTGDR2		G-protein coupled receptor				0.0317	CCL5	
DEPTOR	-0.612	other				0.0317	CCL5	
AFAP1-AS1		other				0.0317	RAC2	
PELI1	0.268	enzyme				0.0317	CCL5	
STAR	0.211	transporter				0.0317	CCL5	
CST3	0.431	other				0.0317	IRF8	
AVPR1A	-3.835	G-protein coupled receptor				0.0317	NPPA	
CAV3		enzyme				0.0317	NPPA	
CCR3		G-protein coupled receptor				0.0317	CCL5	
PIAS2	0.277	transcription regulator				0.0317	IRF1	
RB1CC1	-0.092	other				0.0317	CCL5	
DGKZ	0.106	kinase				0.0317	CCL5	
NPY2R		G-protein coupled receptor				0.0317	IGF1	
N4BP1	0.344	enzyme				0.0317	HLA-A	
HSPB8	0.143	kinase				0.0317	NPPA	
ARF6	0.085	transporter				0.0317	CCL5	
GATA5		transcription regulator				0.0317	NPPA	
MAS1		G-protein coupled receptor				0.0317	CYBB	
RASGRF1	0.135	other				0.0317	IGF1	
ITGB8	0.575	other				0.0317	RAC2	
pentylentetrazol		chemical drug				0.0317	PENK	

riluzole		chemical drug				0.0317	GFAP	
trientine		chemical drug				0.0317	IGF1	
Mt		group				0.0317	GFAP	
KITLG	-0.759	growth factor				0.0321	B2M,GFAP,NPPA	
pirinixic acid		chemical toxicant				0.0321	CCL5,HLA-DQA1,IFITM3,IRF8	
GATA4		transcription regulator				0.0324	IRF8,NPPA,SERPINA3	
cyclosporin A		biologic drug	0.152			0.0328	C4A/C4B,CCL5,GFAP,NPPA	
LMNA	0.406	other				0.0333	IRF1,IRF8,NPPA	
Mapk		group				0.0341	CYBB,IGF1	
MYF6		transcription regulator				0.0341	Cxcl9,IGF1	
neomycin		chemical drug				0.0343	Cxcl9	
perhexiline		chemical drug				0.0343	SERPINA3	
ISGF3		complex				0.0343	IRF1	
TRIM38		enzyme				0.0343	CCL5	
hamine		chemical - endogenous non-mammalian				0.0343	NPPA	
ANG	1.432	enzyme				0.0343	CCL5	
PPP3CB	0.226	phosphatase				0.0343	CYBB	
CCL21		cytokine				0.0343	Cxcl9	
GNB3		enzyme				0.0343	GNG13	
PDE4B	0.022	enzyme				0.0343	CCL5	
BGLAP		other				0.0343	CD74	
GHSR		G-protein coupled receptor				0.0343	IGF1	
PLA2G2E		enzyme				0.0343	CCL5	
EDNRB	0.116	G-protein coupled receptor				0.0343	NPPA	
ACO1	0.436	enzyme				0.0343	IGF1	
MIA-602		chemical reagent				0.0343	IGF1	
6-aminopyrazolopyrimidine derivative compound II		chemical drug				0.0343	IFITM3	
RV 538		chemical reagent				0.0343	GFAP	
homone		chemical drug				0.0343	IGF1	
SKF-38393		chemical reagent				0.0343	NPPA	
[D-Ala2,N-Me-Phe4,Gly5-ol]-Enkephalin		chemical reagent				0.0343	CCL5	
bempedoic acid		chemical drug				0.0343	CCL5	
palmitic acid		chemical - endogenous mammalian				0.0346	CCL5,CYBB,IGF1	
puromycin aminonucleoside		chemical reagent				0.0353	C4A/C4B,CYBB	
peptidoglycan		chemical - endogenous non-mammalian				0.0358	CCL5,IRF1	
ciprofloxacin		chemical drug				0.0358	HLA-A,MPEG1	
cyclic AMP		chemical - endogenous mammalian				0.036	IGF1,LGALS3BP,PENK	
TNFSF11		cytokine				0.036	CCL5,IGF1,IRF8	
CDKN1A	0.219	kinase				0.0363	Cxcl9,IFITM3,LGALS3BP	
NFE2L2	0.67	transcription regulator	-0.895	bias		0.0368	CCL5,CYBB,GFAP,SERPINA3	
moxonidine		chemical drug				0.0369	NPPA	
Ginkgo biloba		chemical drug				0.0369	CCL5	
4-nonylphenol		chemical toxicant				0.0369	IGF1	
TRAF3IP3	-1.274	other				0.0369	CCL5	
N(2)-(gamma-D-glutamyl)-meso-2,2'-diaminopimelic acid		chemical reagent				0.0369	CCL5	
SCAVENGER receptor CLASS A		group				0.0369	CCL5	
DNAJC3	0.149	other				0.0369	Nrgn	
mir-302		microRNA				0.0369	CCL5	
PLCE1	0.25	enzyme				0.0369	GFAP	
PTPRE	0.085	phosphatase				0.0369	Cxcl9	
PIAS3	0.289	transcription regulator				0.0369	SERPINA3	
TRAF4	-0.408	other				0.0369	CCL5	
CSF3R	2.887	transmembrane receptor				0.0369	LYZ	
ZBTB32		transcription regulator				0.0369	HLA-DQB1	
RALA	-0.163	enzyme				0.0369	NPPA	

ADAM15	-0.139	peptidase			0.0369	CCL5	
SOCS2	-0.165	other			0.0369	IGF1	
picryl chloride		chemical toxicant			0.0369	HLA-DQA1	
metoprolol		chemical drug			0.0369	GFAP	
streptozocin		chemical drug			0.037	GFAP,IGF1,NPPA	
GNA15	3.281	enzyme			0.037	GBP2,SERPINA3	
bisindolylmaleimide I		chemical drug			0.037	IGF1,NPPA	
LDL		complex			0.0373	CCL5,CYBB,IGF1	
hyaluronic acid		chemical - endogenous mammalian			0.0376	CCL5,Cxcl9	
F2		peptidase			0.0376	CYBB,IGF1,RAC2	
5-N-ethylcarboxamido adenosine		chemical reagent			0.0388	HLA-DQA1,HLA-DQB1	
L-glutamic acid		chemical - endogenous mammalian			0.0388	B2M,TAP1	
arsenite		chemical toxicant			0.0388	IGF1,IRF1	
5-hydroxytryptamine		chemical - endogenous mammalian			0.0394	CYBB,IGF1	
estrone		chemical - endogenous mammalian			0.0395	IGF1	
TIFA	0.769	other			0.0395	CCL5	
IFNL2		other			0.0395	Cxcl9	
CLCN5	-1.044	ion channel			0.0395	B2M	
TAP1	2.932	transporter			0.0395	HLA-A	
AIMP1	0.106	cytokine			0.0395	CCL5	
PTBP1	0.057	enzyme			0.0395	SERPINA3	
SPTLC2	0.11	enzyme			0.0395	NPPA	
TBX3	-0.805	transcription regulator			0.0395	NPPA	
MFGE8	0.333	other			0.0395	NPPA	
CAPN3	2.524	peptidase			0.0395	CCL5	
DIRAS3		enzyme			0.0395	HLA-DQA1	
PRKRA	0.381	other			0.0395	IRF1	
CCL19		cytokine			0.0395	Cxcl9	
HNRNPD	0.122	transcription regulator			0.0395	PENK	
Ptgs2os2		other			0.0395	CCL5	
RGS1		enzyme			0.0395	Cxcl9	
SIRPA	0.65	phosphatase			0.0395	CCL5	
intralipid		chemical drug			0.0395	PENK	
FITC		chemical reagent			0.0395	Cxcl9	
hydroxyflutamide		chemical drug			0.0395	IGF1	
N-ethyl-N-nitrosourea		chemical toxicant			0.0395	Cxcl9	
zinc protoporphyrin IX		chemical - endogenous mammalian			0.0395	IGF1	
NUP98-KDM5A		fusion gene/product			0.0395	LYZ	
NUP98-NSD1		fusion gene/product			0.0395	LYZ	
albuterol		chemical drug			0.0395	CCL5	
NAD+		chemical - endogenous mammalian			0.0395	NPPA	
aloxistatin		chemical - protease inhibitor			0.0395	CD74	
cypoterone acetate		chemical drug			0.0395	IGF1	
Histone h3		group			0.0398	B2M,CCL5,IFITM3,IGF1	
diphtheria toxin		chemical - endogenous non-mammalian			0.0401	C1QA,PENK	
THRB	-0.089	ligand-dependent nuclear receptor			0.0404	LYZ,NPPA,PENK	
melatonin		chemical - endogenous mammalian			0.0407	GFAP,IGF1	
STAT5B	0.305	transcription regulator			0.0408	IGF1,IRF1,NPPA	
LDB1	1.284	transcription regulator			0.0419	Ilgp1,TAP1,UNC93B1	
PTEN	0.521	phosphatase			0.0419	CCL5,IGF1,NPPA,PTN,UNC93B1	
prostaglandin A2		chemical - endogenous non-mammalian			0.0421	IGF1	
2-chloroadenosine		chemical reagent			0.0421	NPPA	
salubrial		chemical reagent			0.0421	CCL5	

DPH5	0.157	enzyme				0.0421	IRF1	
Retnla		other				0.0421	NPPA	
CABIN1	0.475	other				0.0421	NPPA	
NTF4		growth factor				0.0421	PENK	
PURA	-0.11	transcription regulator				0.0421	GFAP	
SLC18A3		transporter				0.0421	NPPA	
POU3F2	-0.267	transcription regulator				0.0421	FABP7	
LY96	1.927	transmembrane receptor				0.0421	CCL5	
ZFPM2	-1.135	transcription regulator				0.0421	NPPA	
MIR101		group				0.0421	IGF1	
IGHE		other				0.0421	CCL5	
CSK	-0.269	kinase				0.0421	NPPA	
IGFBP1		other				0.0421	IGF1	
TNFAIP2	2.247	other				0.0421	IRF1	
IFT57	0.283	other				0.0421	PENK	
TNFRSF12A	0.285	transmembrane receptor				0.0421	CCL5	
CXCL2	1.487	cytokine				0.0421	CCL5	
BCL10	0.129	transcription regulator				0.0421	CCL5	
CAMK2D	0.013	kinase				0.0421	NPPA	
DMH1		chemical reagent				0.0421	CCL5	
aroclor 1254		chemical toxicant				0.0421	Nrgn	
tranylcypromine		chemical drug				0.0421	CCL5	
glyburide		chemical drug				0.0421	NPPA	
LMO2	0.206	transcription regulator				0.0422	ligp1,TAP1,UNC93B1	
STAT5A	2.503	transcription regulator				0.0422	IGF1,IRF1,SERPINA3	
FGF2		growth factor				0.0427	GFAP,IGF1,NPPA,PENK	
staurosporine		chemical drug				0.0432	IGF1,SERPINA3	
interferon beta-1a		biologic drug				0.0438	HLA-DRB5,IRF1	
E2f		group				0.0444	IGF1,NPPA	
desoxycorticosterone		chemical - endogenous mammalian				0.0447	CYBB	
picropodophyllin		chemical drug				0.0447	IFITM3	
triclosan		chemical drug				0.0447	CYBB	
VSIR	0.805	other				0.0447	Cxd9	
FZD9	1.961	G-protein coupled receptor				0.0447	CCL5	
CSDE1	-0.085	enzyme				0.0447	FABP7	
IL-17f dimer		complex				0.0447	CCL5	
MYT1	0.94	transcription regulator				0.0447	Bst2	
ARG1		enzyme				0.0447	IGF1	
NRP1	-0.45	transmembrane receptor				0.0447	HLA-DQB1	
DDX3X	0.033	enzyme				0.0447	CCL5	
NBEAL2	0.136	other				0.0447	IRF8	
TOR1A	0.25	enzyme				0.0447	Nrgn	
S1PR3	0.696	G-protein coupled receptor				0.0447	IGF1	
IFIT2	0.788	other				0.0447	CCL5	
premarin		chemical drug				0.0447	IGF1	
7-nitroindazole		chemical reagent				0.0447	GFAP	
phenytoin		chemical drug				0.0447	CCL5	
cerulenin		chemical drug				0.0447	CCL5	
STAT5a/b		group				0.0451	IGF1,IRF1	
LIPE	-0.024	enzyme				0.0451	CD74,HLA-DQA1	
C5		cytokine				0.0451	CCL5,CYBB	
8-bromo-cAMP		chemical reagent	0.469	bias		0.0454	GFAP,IGF1,NPPA,RAC2	
HMOX1	-0.999	enzyme				0.0457	IGF1,NPPA	
PI3K (complex)		complex				0.0463	CYBB,IGF1,NPPA	
AKT1	0.653	kinase				0.0467	CCL5,CD74,NPPA	
mir-155		microRNA				0.047	CCL5,IRF8	
SB-431542		chemical reagent				0.047	GFAP,IGF1	
N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine		chemical drug				0.0472	NPPA	
alpha-amanitin		chemical toxicant				0.0472	GFAP	
Ren2		peptidase				0.0472	CYBB	

c-Src		group				0.0472	GFAP	
NMDA Receptor		complex				0.0472	PENK	
LRBA	0.157	other				0.0472	CCL5	
ghrelin		biologic drug				0.0472	IGF1	
GRK2	-0.008	kinase				0.0472	NPPA	
S100B	-0.631	other				0.0472	GFAP	
TAF1	0.328	transcription regulator				0.0472	IGF1	
mir-322		microRNA				0.0472	NPPA	
mir-208		microRNA				0.0472	NPPA	
SLC6A3	0.726	transporter				0.0472	GFAP	
CD46	1.487	transmembrane receptor				0.0472	LAMTOR5	
PTGFR	2.131	G-protein coupled receptor				0.0472	NPPA	
CXCL3		cytokine				0.0472	CCL5	
PDK4		kinase				0.0472	IRF8	
GAB1	0.592	other				0.0472	CCL5	
PCSK1	-0.564	peptidase				0.0472	IGF1	
pimozide		chemical drug				0.0472	IRF8	
quinpirole		chemical reagent				0.0472	NPPA	
piperine		chemical drug				0.0472	IRF1	
iloprost		chemical drug				0.0472	CCL5	
NR5A2		ligand-dependent nuclear receptor				0.049	C1QB,Cxcl9	
RB1	0.381	transcription regulator				0.0493	CCL5,Cxcl9,IFITM3,IGF1	
Rp-cAMPS		chemical - kinase inhibitor				0.0498	NPPA	
RHOJ	0.302	enzyme				0.0498	PTN	
CBX7	0.713	other				0.0498	CTSS	
XRCC6	0.27	enzyme				0.0498	CCL5	
PTPN2	0.02	phosphatase				0.0498	Cxcl9	
STAT3 inhibitor VI		chemical reagent				0.0498	NPPA	
ITGB4	0.826	transmembrane receptor				0.0498	CCL5	
S1PR2	1.921	G-protein coupled receptor				0.0498	CCL5	
AICDA		enzyme				0.0498	CD74	
KCNIP3	0.105	transcription regulator				0.0498	GFAP	
PAEP		other				0.0498	CCL5	
EMD	1.158	other				0.0498	IRF1	
NRTN	-1.111	growth factor				0.0498	PENK	
KLF13	0.443	transcription regulator				0.0498	CCL5	
CEP-1347		chemical drug				0.0498	CCL5	
thioridazine		chemical drug				0.0498	SERPINA3	