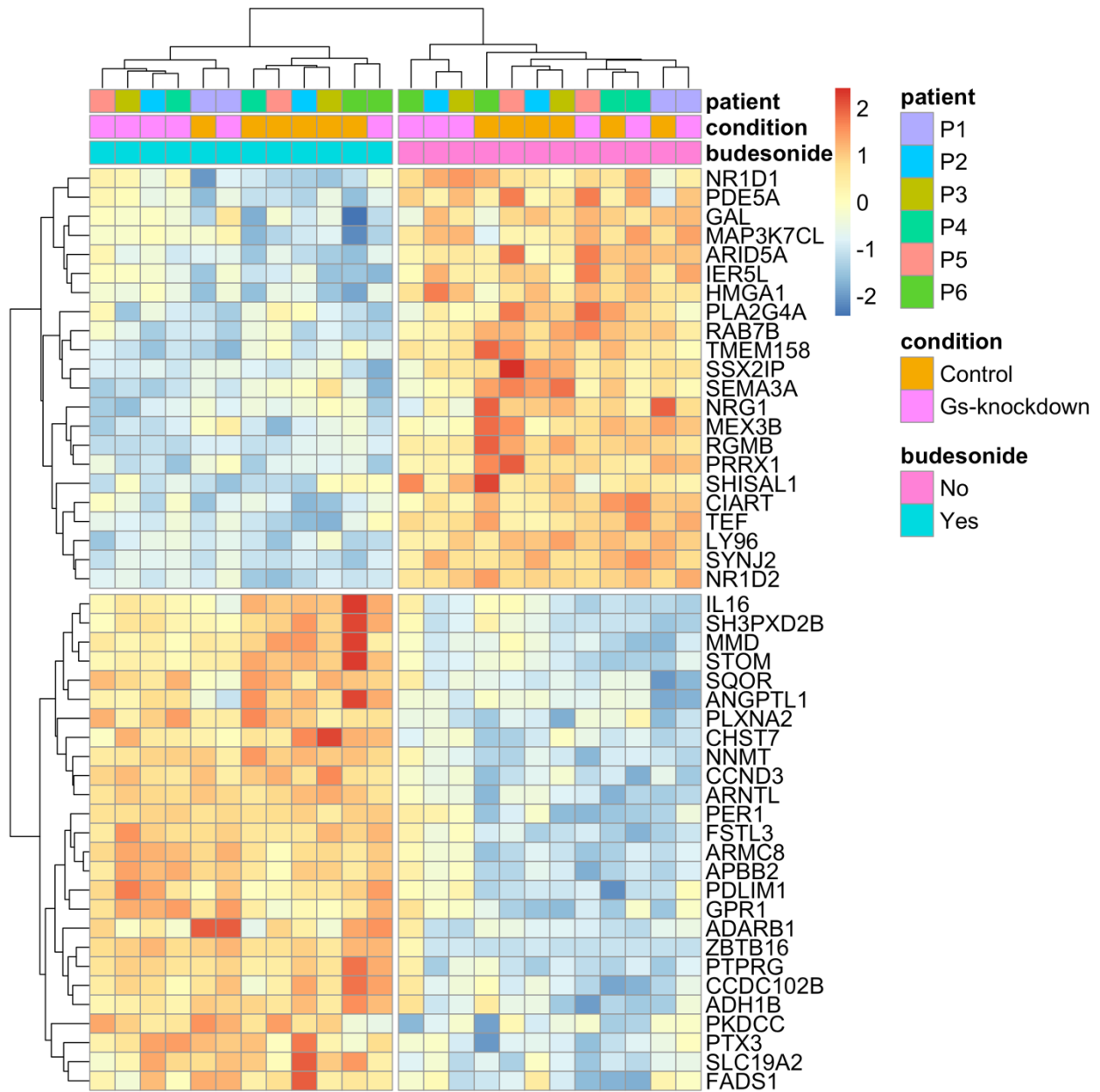
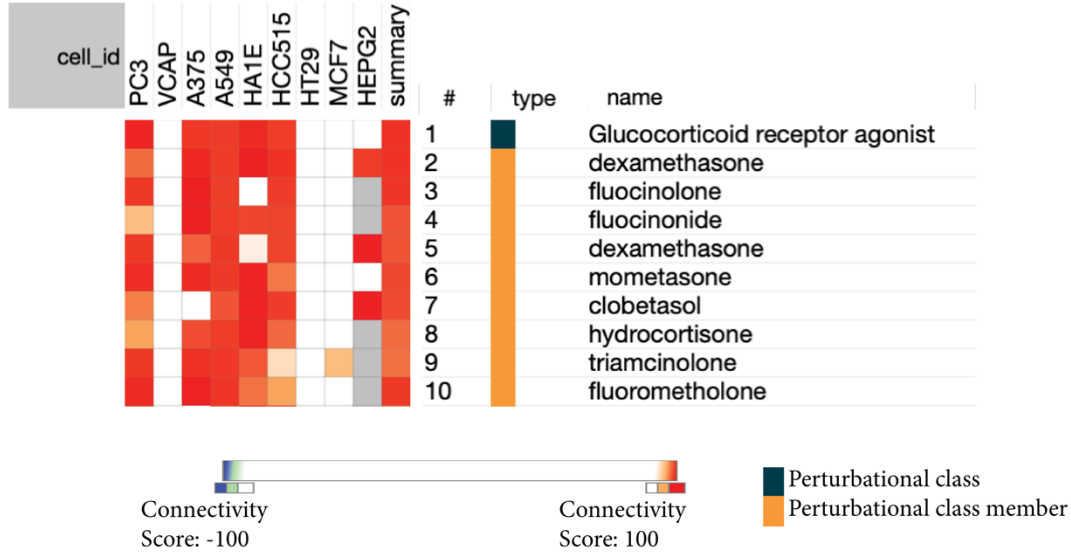


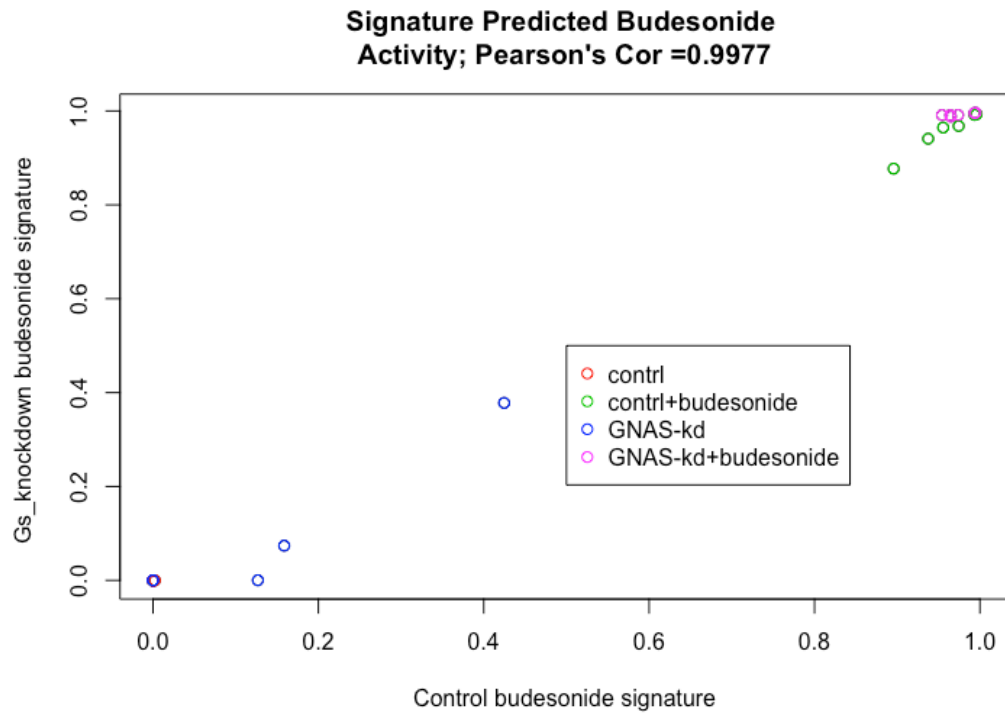
Supplemental Figure 1: Venn diagram showing the overlap of differentially expressed genes due to budesonide 24-hour treatment in (1) control, (2) $G_{\alpha s}$ knockdown (kd) HASM, and (3) dexamethasone 18-hour treatment in control HASM published by Himes et al. 2014.



Supplemental Figure 2: Unsupervised Hierarchical clustering of $\log_2(\text{TPM})$ gene expression of 48 genes unique in budesonide signature compared to G_{α_s} -knockdown budesonide signature captures budesonide-specific transcriptional activity in HASM. Dendrograms represent the hierarchical clustering based on the Euclidean distance between two gene expression values or two samples. 26 of the 48 genes are overexpressed with budesonide treatment. Darker red indicates higher expression, and darker blue indicates lower expression.



Supplemental Figure 3: Top 10 ranked connectivity scores, quantitative scores between a query gene-list and a perturbagen in nine cell lines. Members of glucocorticoid agonists had high connectivity score when 48 genes unique to budesonide’s $G_{\alpha S}$ -dependent gene expression were queried for similarities and dissimilarities against more than a million gene expression signatures in ConnectivityMap (CMap), a publicly available database.



Supplemental Figure 4: Predicted budesonide activities using both budesonide (genomic + non-genomic) and budesonide $G_{\alpha s}$ knockdown (genomic only) signatures were significantly correlated ($r=0.9977$, p -value < 0.0001).

Supplemental Table 1: Predicted budesonide activity using budesonide (genomic + non-genomic) and budesonide G_{αs} knockdown (genomic only) signatures in 34 Human Airway Smooth Muscle samples from Kan et al.⁴⁰

ID_REF	Sample characteristics disease	Sample characteristics treatment	Budesonide activity signature (genomic + non-genomic)	Budesonide activity signature (genomic only)
GSM2473333	asthma	budesonide	0.98	0.96
GSM2473339	asthma	budesonide	0.86	0.94
GSM2473344	asthma	budesonide	0.97	0.98
GSM2473345	asthma	budesonide	0.97	0.99
GSM2473350	asthma	budesonide	0.96	0.96
GSM2473354	asthma	budesonide	0.98	0.99
GSM2473355	asthma	budesonide	0.97	0.94
GSM2473361	asthma	budesonide	0.98	0.99
GSM2473366	asthma	budesonide	0.98	0.98
GSM2473337	non_asthma	budesonide	0.97	0.96
GSM2473340	non_asthma	budesonide	0.98	0.98
GSM2473341	non_asthma	budesonide	0.98	0.98
GSM2473349	non_asthma	budesonide	0.98	0.98
GSM2473351	non_asthma	budesonide	0.98	0.99
GSM2473359	non_asthma	budesonide	0.94	0.97
GSM2473362	non_asthma	budesonide	0.99	0.99
GSM2473363	non_asthma	budesonide	0.98	0.98
GSM2473334	asthma	vehicle	0	0
GSM2473335	asthma	vehicle	0	0
GSM2473336	asthma	vehicle	0	0
GSM2473346	asthma	vehicle	0	0
GSM2473347	asthma	vehicle	0	0
GSM2473348	asthma	vehicle	0	0
GSM2473356	asthma	vehicle	0	0
GSM2473357	asthma	vehicle	0	0
GSM2473358	asthma	vehicle	0	0
GSM2473338	non_asthma	vehicle	0	0
GSM2473342	non_asthma	vehicle	0	0
GSM2473343	non_asthma	vehicle	0	0
GSM2473352	non_asthma	vehicle	0	0
GSM2473353	non_asthma	vehicle	0	0
GSM2473360	non_asthma	vehicle	0	0
GSM2473364	non_asthma	vehicle	0	0
GSM2473365	non_asthma	vehicle	0	0

Supplemental Table 2: Ranked connectivity scores (CS) for highly similar (>95) and dissimilar (<-95) gene expression against more than 1.7 million perturbation samples in CMAP database filtered for perturbation class and perturbation class members.

Connectivity Score (CS)	Name	Description
98.97	Glucocorticoid receptor agonist	-
98.84	dexamethasone	Glucocorticoid receptor agonist
98.77	fluocinolone	Glucocorticoid receptor agonist
98.59	fluorometholone	Glucocorticoid receptor agonist
98.56	tacrolimus	Calcineurin inhibitor
98.13	halometasone	Glucocorticoid receptor agonist
98.06	mometasone	Glucocorticoid receptor agonist
97.96	clobetasol	Glucocorticoid receptor agonist
97.65	fluocinonide	Glucocorticoid receptor agonist
97.59	betamethasone	Glucocorticoid receptor agonist
97.57	methylprednisolone	Glucocorticoid receptor agonist
97.42	fludroxycortide	Glucocorticoid receptor agonist
97.32	alclometasone	Glucocorticoid receptor agonist
97.29	megestrol	progesterone receptor agonist
97.24	beclometasone	Glucocorticoid receptor agonist
97.08	fluticasone	Glucocorticoid receptor agonist
97.08	L-690330	Inositol monophosphatase inhibitor
97.04	flumetasone	Glucocorticoid receptor agonist
96.97	hydrocortisone	Glucocorticoid receptor agonist
96.97	RHO-kinase-inhibitor-III[rockout]	Rho associated kinase inhibitor
96.9	desoximetasone	Glucocorticoid receptor agonist
96.79	triamcinolone	Glucocorticoid receptor agonist
96.62	tropisetron	Serotonin receptor antagonist
96.62	hydrocortisone	Glucocorticoid receptor agonist
96.58	hydrocortisone	Glucocorticoid receptor agonist
96.09	fluticasone	Glucocorticoid receptor agonist
95.77	budesonide	Glucocorticoid receptor agonist
95.55	halcinonide	Glucocorticoid receptor agonist
95.14	rimexolone	Glucocorticoid receptor agonist
-96.81	PJ-34	PARP inhibitor