

Dataset S1: Drugs from the top-100 best-selling drugs list that target circadian genes.						
Rank	Sales	Trade name	Drug	Indications	Circadian-gene targets	Organs in which targets oscillate
1	\$1.53 b	Abilify	aripiprazole	Bipolar disorder, Major depressive disorder...	<i>Htr2c, Htr1b, Htr2a, Chrm2, Drd4, Adra2b, Adra1b, Adra1a</i>	lung, heart, brainstem, white fat, adrenal gland, liver, brown fat, kidney, skeletal muscle, cerebellum
2	\$1.46 b	Nexium	esomeprazole	Gastritis, GERD, Esophagitis	<i>Atp4a</i>	liver
3	\$1.30 b	Cymbalta	duloxetine	Chronic pain, Fibromyalgia, Diabetic neuropathy...	<i>Slc6a4</i>	adrenal gland, kidney
4	\$1.30 b	Crestor	rosuvastatin	Hyperlipidemia	<i>Hmgcr, Abcc1, Abcc4</i>	lung, heart, hypothalamus, liver, brown fat
5	\$1.28 b	Advair Diskus	fluticasone + salmeterol	Asthma, Chronic obstructive pulmonary disease...	<i>Serpina6, Pgr, Nr3c2, Adrb2, Pla2g4a</i>	lung, heart, liver, kidney, skeletal muscle, aorta
6	\$1.22 b	Humira	adalimumab	Rheumatoid arthritis, Crohn's disease, Ulcerative colitis...	<i>Fcgr2b, Fcgr3</i>	liver, kidney
7	\$1.08 b	Enbrel	etanercept	Rheumatoid arthritis, Psoriasis	<i>Fcgr2b, Tnfrsf1b, Fcgr3</i>	hypothalamus, liver, kidney
10	\$859 m	Neulasta	filgrastim	Acute myeloid leukemia	<i>Csf3r</i>	lung
11	\$794 m	Rituxan	rituximab	Rheumatoid arthritis, Non-Hodgkin's lymphoma...	<i>Fcgr2b, Ms4a1, Fcgr3</i>	liver, kidney, skeletal muscle
12	\$726 m	Spiriva	tiotropium	Chronic obstructive pulmonary disease	<i>Slc22a5, Slc22a4, Chrm2</i>	heart, brainstem, brown fat, kidney, aorta
14	\$701 m	Januvia	sitagliptin	Diabetes mellitus T2	<i>Abcb1a, Dpp4</i>	heart, adrenal gland, liver, kidney
16	\$641 m	Avastin	bevacizumab	Colorectal cancer, Non-small cell lung cancer...	<i>Fcgr2b, Vegfa, Fcgr3</i>	heart, brown fat, liver, kidney, skeletal muscle, aorta
17	\$637 m	Lantus Solostar	insulin glargine	Diabetes mellitus T2	<i>Igf1r</i>	kidney
18	\$592 m	Lantus	insulin glargine	Diabetes mellitus T2	<i>Igf1r</i>	kidney
20	\$538 m	Diovan	valsartan + hydrochlorothiazide	Hypertension, Heart failure	<i>Slc22a6, Agtr1a, Slco1b2, Car4, Kcnma1, Car12, Car2</i>	heart, adrenal gland, liver, kidney, skeletal muscle
22	\$518 m	Celebrex	celecoxib	Osteoarthritis, Rheumatoid arthritis	<i>Ptgs2, Pdpk1, Abcc4</i>	lung, brainstem, brown fat, aorta, cerebellum
24	\$471 m	Herceptin	trastuzumab	Breast cancer	<i>Fcgr2b, Erbb2, Egfr, Fcgr3</i>	heart, liver, kidney
26	\$438 m	Gleevec	Imatinib	Chronic myeloid leukemia	<i>Ptgs1, Kit, Slc22a2, Abcg2, Pdgfra, Pdgfrb, Ddr1, Abca3, Abl1, Ret, Abcb1a</i>	lung, heart, brainstem, white fat, adrenal gland, brown fat, liver, kidney
27	\$431 m	Vyvanse	lisdexamfetamine	Attention deficit hyperactivity disorder	<i>Adra1b</i>	liver
29	\$415 m	Lucentis	ranibizumab	Macular degeneration	<i>Vegfa</i>	heart, brown fat, liver, skeletal muscle, aorta
30	\$413 m	Synagis	palivizumab	Respiratory syncytial virus	<i>Fcgr2b, Fcgr3</i>	liver, kidney
31	\$395 m	Zetia	ezetimibe	Hyperlipidemia	<i>Soat1, Abcc2, Anpep, Abcb1a</i>	lung, heart, brainstem, adrenal gland, liver, kidney
32	\$392 m	Tamiflu	oseltamivir	Influenza	<i>Neu2, Neu1, Ces1g, Slc22a8, Slc15a1, Abcc4</i>	lung, liver, brown fat, kidney, cerebellum
33	\$383 m	Ritalin	methylphenidate	Attention deficit hyperactivity disorder	<i>Slc6a4</i>	adrenal gland, kidney

Rank	Sales	Trade name	Drug	Indications	Circadian-gene targets	Organs in which targets oscillate
83	\$201 m	Synthroid	levothyroxine	Hypothyroidism	<i>Slc16a2, Serpina7, Thrb, Thra, Abcb1a</i>	lung, heart, white fat, adrenal gland, brown fat, liver, kidney, aorta, skeletal muscle, cerebellum
84	\$198 m	Evista	raloxifene	Osteoporosis	<i>Ncoa2, Cyp2b10, Esr1, Esr2</i>	lung, white fat, brown fat, liver, kidney, aorta
87	\$196 m	Betaseron	Interferon beta-1b	Multiple sclerosis	<i>Ifnar2</i>	skeletal muscle
88	\$193 m	Lipitor	atorvastatin	Hyperlipidemia	<i>Hmgcr, Cyp2b10, Ahr, Abcc5, Abcc1, Abcb1a, Abcc4, Dpp4</i>	lung, heart, brainstem, white fat, adrenal gland, hypothalamus, brown fat, liver, kidney, aorta, cerebellum
90	\$189 m	Lunesta	eszopiclone	Insomnia	<i>Ptgs1, Tspo, Gabra3</i>	lung, heart, adrenal gland, kidney
97	\$175 m	Xeloda	capecitabine	Breast cancer, colorectal cancer	<i>Cda, Tymp, Tyms, Ces1g, Dpyd</i>	lung, adrenal gland, liver, brown fat, kidney, aorta
98	\$173 m	Prilosec	omeprazole	Gastritis, GERD, Esophagitis	<i>Cyp1a1, Atp4a, Abcg2, Cyp1b1, Abcb1a</i>	lung, heart, brainstem, white fat, adrenal gland, brown fat, liver, kidney
99	\$171 m	Focalin XR	dexmethylphenidate	Attention deficit hyperactivity disorder	<i>Slc6a4</i>	adrenal gland, kidney

Primary antibodies used were as follows: anti-PTGS1 (160110; Cayman Chemical) and anti-GAPDH (sc-25778; Santa Cruz). Membranes were then rinsed twice each with TBS-0.05% Tween and blocking solution. Following rinses, membranes were probed with secondary antibody at room temperature for 70 min. Those membranes treated with anti-PTGS1 were incubated with anti-mouse IgG HRP-linked secondary antibodies (NA931V; GE Healthcare), whereas membranes treated with anti-GAPDH were incubated with anti-rabbit IgG HRP-linked secondary antibodies (NA934-1ML; GE Healthcare). Membranes were then rinsed five times for 10 min in TBS-0.05% Tween, and then imaged by using standard autoradiograph techniques after the application of Western Lightning Plus ECL (PerkinElmer) Western blotting detection reagent.

RNA extraction and quantitative PCR. RNA was extracted from cells by using TRIzol reagent (Life Technologies) with Direct-zol RNA MiniPrep kit (Zymo Research), according to manufacturer's protocol, cDNA was generated from 500 ng of RNA by using the qScript cDNA Synthesis Kit (Quanta Biosciences), and qPCR was performed on the ViiA 7 Real-Time PCR System (Life Technologies) using the Perfecta FastMix II, Low ROX reagent (Quanta Biosciences), according to the manufacturer's protocols. Relative expression quantification of the qPCR data were performed by using the $\Delta\Delta CT$ method with the ViiA 7 analysis software v1.2 (Life Technologies). *Ptgs1* (Mm00477214_m1; Life Technologies) was quantified by using *Gapdh* (4352661; Life Technologies) as the endogenous reference.

- Dobin A, et al. (2013) STAR: Ultrafast universal RNA-seq aligner. *Bioinformatics* 29(1): 15–21.
- HTSeq (2013) Analysing high-throughput sequencing data with Python. Version 0.5.4p1.
- Flicek P, et al. (2012) Ensembl 2012. *Nucleic Acids Res* 40(Database issue):D84–D90.
- Bu D, et al. (2012) NONCODE v3.0: Integrative annotation of long noncoding RNAs. *Nucleic Acids Res* 40(Database issue):D210–D215.
- Anders S, Huber W (2010) Differential expression analysis for sequence count data. *Genome Biol* 11(10):R106.
- Quinlan AR, Hall IM (2010) BEDTools: A flexible suite of utilities for comparing genomic features. *Bioinformatics* 25(6):841–842.
- Meyer LR, et al. (2013) The UCSC Genome Browser database: Extensions and updates 2013. *Nucleic Acids Res* 41(Database issue):D64–D69.
- Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ (1990) Basic local alignment search tool. *J Mol Biol* 215(3):403–410.
- Washietl S, Kellis M, Garber M (2014) Evolutionary dynamics and tissue specificity of human long noncoding RNAs in six mammals. *Genome Res* 24(4):616–628.
- Pruitt KD, Tatusova T, Klimke W, Maglott DR (2009) NCBI Reference Sequences: Current status, policy and new initiatives. *Nucleic Acids Res* 37(Database issue): D32–D36.
- Harrow J, et al. (2012) GENCODE: The reference human genome annotation for The ENCODE Project. *Genome Res* 22(9):1760–1774.
- Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA (2005) Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res* 33(Database issue):D514–D517.
- UniProt Consortium (2013) Update on activities at the Universal Protein Resource (UniProt) in 2013. *Nucleic Acids Res* 41:D43–7.
- Davis AP, et al. (2013) The Comparative Toxicogenomics Database: Update 2013. *Nucleic Acids Res* 41(Database issue):D1104–D1114.
- Whirl-Carrillo M, et al. (2012) Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther* 92(4):414–417.
- Bundschuh M, DeJori M, Stetter M, Tresp V, Kriegel H-P (2008) Extraction of semantic biomedical relations from text using conditional random fields. *BMC Bioinformatics* 9:207.
- Law V, et al. (2014) DrugBank 4.0: Shedding new light on drug metabolism. *Nucleic Acids Res* 42(Database issue):D1091–D1097.
- WHO (2013) WHO Model Lists of Essential Medicines WHO. Available at www.who.int/medicines/publications/essentialmedicines/en/.
- NIH (2013) Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC). Available at report.nih.gov/categorical_spending.aspx. Accessed July 9, 2013.
- Lewis BP, Burge CB, Bartel DP (2005) Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* 120(1): 15–20.