ONLINE METHODS

Reagents. The following antibodies were used: goat antibody against human VE-cadherin (AF938; R&D systems); mouse antibody against human ICAM-1 (BBA3; R&D systems); rabbit antibody against human vWF (AB6994, Abcam); sheep antibody against human CD31 (PECAM-1) (AF806; R&D systems); PE mouse antibody against human CD31 (555446; BD Biosciences); FITC mouse antibody against human CD144 (560411; BD Biosciences); κ-FITC mouse IgG1 (555748; BD Biosciences); κ-PE mouse IgG1 (555749; BD Biosciences); Alexa Fluor-594 donkey anti-goat IgG (A11058, Thermo Fisher Scientific); Alexa Fluor-488 donkey anti-rabbit IgG (A21206, Thermo Fisher Scientific); Alexa Fluor-594 donkey anti-sheep IgG (A11016; Thermo Fisher Scientific); Alexa Fluor-488 donkey anti-mouse IgG (A21202; Thermo Fisher Scientific).

Differentiation of iPSC-ECs. To initiate endothelial cell differentiation, the medium was changed to a differentiation medium (RPMI and B-27 supplement minus insulin, Life Technologies) supplemented with 6 μM glycogen synthase kinase 3-β inhibitor, CHIR-99021 (Selleck Chemicals) on day 0 and 2 μM CHIR-99021 on day 2. For days 4-12, cells were cultured in different combinations of differentiation media and EGM-2 medium containing EBM-2 Basal Medium supplemented with the EGM-2 BilletKit from Lonza (100% differentiation medium on day 4, 50% differentiation medium and 50% EGM2 on day 6, 25% differentiation medium and 75% EGM2 medium on day 8, and 100% EGM2 medium on day 10) with growth factors that included 50 ng/ml VEGF, 20 ng/ml FGF2, and 20 ng/ml BMP4 (PeproTech). At day 12 post-differentiation, cells were sorted using the human CD144 (VE-Cadherin) MicroBeads and magnetic cell sorting (MACS) system (Miltenyi Biotech), as directed by the manufacturer, and expanded on 0.2% gelatin coated plates. iPSC-ECs were then cultured in the EGM2 medium at 37 °C and 5% CO_2 in

a humidified incubator with medium changes every other day. Experiments described in this manuscript were performed between passages 1 and 3. Full differentiation protocol and characterization of iPSC-ECs are shown in **Online Figure 1**.

Characterization of iPSC-ECs. Flow cytometry analysis, low-density lipoprotein (LDL) uptake assay, and immunofluorescence staining were performed to assess endothelial-differentiation efficiency and to confirm endothelial cell phenotypes. For flow cytometry, the cells were stained with PE-conjugated CD31 antibody (BD Biosciences) and FITC-conjugated CD144 antibody for 15 minutes in the dark at 4 °C and analyzed using a LSRII flow cytometer (BD Biosciences). Isotype controls (PE-mouse IgG_1,κ and FITC-mouse IgG_1,κ; BD Biosciences) were used to establish gating (data not shown). Data analysis was conducted using the FlowJo software (Three Star). For immunostaining, the cells were fixed in 4% paraformaldehyde (PFA) for 10 minutes, permeabilized in 0.1% triton-X, and blocked with 10% normal donkey serum in PBS for an hour. The cells were then incubated with the primary antibodies in 5% normal donkey serum in PBS overnight at 4 °C. After three washes with PBS, cells were incubated with secondary antibodies and DAPI. Images were acquired with a fluorescence microscope. To determine intercellular adhesion molecule 1 (ICAM-1) expression, cells were either unstimulated or stimulated with 10 mg/ml of tumor necrosis factor-alpha (TNF-α) for 24 hours at 37 °C. For LDL uptake assay, cells were incubated with LDL-DyLight™ 550 (Abcam) in the EGM2 medium at 37 °C for 4 hours. Cell were then washed three times with PBS and fixed with 4% PFA for 10 minutes. Cellular uptake of LDL was visualized with a fluorescence microscope. For gene expression analyses of the endothelial cell markers, total RNA was extracted from iPSC-ECs using the RNeasy Mini kit (Qiagen) and 1 μg of RNA was reverse transcribed using a high capacity cDNA transcription kit

(Life Technologies), followed by quantitative gene expression on the StepOne Plus Real-Time PCR platform (Applied Biosystems). TaqMan Gene Expression Assay Reagents for endothelial cell markers, such as human PECAM-1 (CD31), VE-cadherin (CD144), von Willebrand Factor (vWF), and nitric oxide synthase 3 (NOS3), and 18S (housekeeping gene) were used for specific probes and primers for PCR amplifications and the ΔΔCt method was used to calculate fold-change of gene expression.

Endothelial cell plating and e-liquid treatment. Cells were dissociated using TrypLE Express for 4 minutes at 37 °C, centrifuged at 300 x g for 5 minutes, and then plated onto 0.2% gelatin-coated 96-well black-sided plates (5,000 live cells/well for fluorescence), 96-well white-sided plates (5,000 live cells/well for luminescence), 24-well plates (50,000 live cells/well for tube formation), or 12 mm diameter glass coverslips (5,000 live cells/cover slip for immuno-fluorescence staining) in EGM2 medium. After 48 hours, cells were treated for up to 48 hours with various doses of e-liquids (0.001%. 0.01%, 0.03%, 0.1%, 0.3%, and 1%) diluted in EGM2 in ascending order.

Assays for plate-based cellular viability, reactive oxygen species (ROS), and caspase 3/7 activity. Assays using CellTiter-Glo® 2.0, ROS-Glo™ H_2O_2, and Caspase-Glo® 3/7 (Promega) were performed following the manufacturers' instructions and luminescence signal was recorded on the GloMax®-Multi system (Promega) with an integration time of 0.25 seconds. Following incubation of the cells with various doses of e-cigarette refill solutions and serum treatment, 100 µl of CellTiter-Glo 2.0 (Promega) reagent was added directly to each well of 96-well plates, followed by incubation at room temperature on an orbital shaker to induce cell lysis for 12 minutes.

For assessing intracellular ROS generation, six hours prior to the completion of treatment the H_2O_2 substrate was added and incubated for the final 6 hours of the experiment. 50 µl of media samples were transferred to a separate 96-well white-sided plate and 50 µl of ROS-Glo™ Detection Solution was added to each well, followed by incubation at room temperature for 20 minutes before detecting luminescence signal. Cells in the original sample plate were kept for measuring total cell number by Calcein AM (Invitrogen) to allow normalization. In addition, the activity of caspase 3/7 was assessed after adding 100 µl of Caspase-Glo 3/7 reagent to each well for an hour and total luminescence was measured.

Measurement of endothelial function. For *in vitro* migration assays, cells were treated with e-liquids for 48 hours before seeded in 24-well plate (5×10^4 cells/well). When the confluence reaches 80% (approximately 48 hours after seeding the cells), the culture medium was replaced with EGM-2 + 2% FBS for overnight -serum starvation. The next morning, cells were scratched with a sterile 200 µl pipette tips to generate a cell-free zone and cultured in complete EGM-2 medium, imaged at 0, 4 and 10 hours after scratch, and analyzed the scratch area and width with ImageJ. In addition, concentrations of free fatty acids were quantified using a free fatty acid quantification kit according to the manufacturer's instruction (BioVision).

In vitro endothelial cell tube formation was carried out following the manufacturer's instructions. Briefly, after coating the 24-well plate or 15-well µ-Slide Angiogenesis (ibidi, Germany) with Corning® Matrigel® Basement Membrane Matrix (Corning), iPSC-ECs were seeded at 50,000 cells/well (24-well plate) or 10,000 cells/well (15-well µ-slides) in e-liquid solutions or serum diluted in EGM2 medium. After 16 hours incubation, capillary network images were taken using a Revolve microscope and quantitation was made using ImageJ.

Cross-talk between endothelial cells and macrophage. To prepare the conditioned medium, human iPSC-ECs were seeded at 5×10^5 live cells/dish in a 10 cm petri dish and treated with e-liquid solutions diluted in EGM2 medium. After 48 hours of incubation, medium from each treatment group was collected and then concentrated using Amicon® Ultra-15 Centrifugal Filter Unit with Ultracel-10 membrane (Millipore) before being stored at -20 °C for further experiments. Human monocyte SC (ATCC® CRL-9855™) were seeded at 10^6 live cells/well on 6-well plate with SC complete growth medium containing 10 ng/ml phorbol myristate acetate (PMA) for adherent macrophage-like cells differentiation. After 48 hours, medium was replaced, and the adherent macrophage-like cells were cultured in SC complete growth medium for another 24 hours. Concentrated conditioned medium were diluted 1:20 in SC complete growth medium and applied to the adherent macrophage-like cells for 48 hours. Following the treatment, the cells were collected and labeled with APC-conjugated CD14, BV510-conjugated CD40 and BV421-conjugated CD163 (all from BD Biosciences) for flow cytometry. Data analysis was conducted using the FlowJo software (Three Star).

For gene expression analyses of macrophage phenotype-related cytokines, macrophages were treated with conditioned medium for 48 hours and mRNA levels of IL-6, IL-1β, and IL-10 were determined by real-time RT-PCR. In order to measure intracellular ROS levels of macrophages, macrophages were first treated with EC conditioned medium. After 48 hours, conditioned medium was removed and SC complete growth medium was added for 16 hours. Assay using ROS-Glo™ H_2O_2, was performed following the manufacturers' instructions.

Blood analysis. Peripheral venous blood was obtained by venipuncture before (-1 hour) and after tobacco product use (immediately after smoking (0 hour), 1 hour, and 3 hours). Blood samples for

serum were allowed to clot at room temperature for 30 minutes before centrifugation at 1000 x g, and serum samples were aliquoted and immediately stored at -80 °C until analysis. The bioanalysis of nicotine and cotinine were conducted by the Benowitz Laboratory at the University of California, and the blood lipid profile, C-reactive protein (CRP), and total and sub-population of leukocyte counts were conducted by Zuckerberg San Francisco General Hospital Clinical Laboratory, using standard laboratory methods.

Luminex (magnetic bead kits). Serum samples were added to a 96-well plate containing the mixed antibody-linked beads and incubated at room temperature for an hour, followed by overnight incubation at 4 °C on an orbital shaker at 500-700 rpm. After washing plates in a Biotek ELx405 washer, a biotinylated detection antibody was added for 75 minutes at room temperature with shaking. The plate was washed as described above and streptavidin-PE was added for 30 minutes. Another wash was performed before adding the reading buffer. All standards and samples were measured in duplicate. Plates were read using a Luminex 200 instrument with a lower bound of 50 beads per sample per cytokine. For quality control, custom assay control beads (Radix Biosolutions) were added to all of wells.

RNA-seq library preparation and data procedure. Total RNA was extracted from iPSC-ECs using the Qiagen RNeasy kit according to the manufacturer's instruction, and 100 ng RNA was used to construct sequencing libraries. The raw 150 bp paired-end RNA-seq reads (27 million reads per sample on average) sequenced by Illumina HiSeq 2000 were trimmed for quality control by TrimGalore version 0.4.2 (https://www.bioinformatics.babraham.ac.uk/ projects/trim_galore/) to exclude adapter sequences and bases with Phred scores of less than 20, producing a low probability of base-calling errors ($p < 1\%$) equivalent to >99% accuracy. On average, 98.51% bases

passed the filtering. The trimmed RNA-seq reads were then mapped to hg38 using STAR software (1) with ENCODE options. The bam files containing reads mapped to GENCODE (2) (hg38, version 25) and annotated transcriptome regions were used for estimating gene expression by DESeq2 (3) in R (4).

Detection of differentially expressed genes. We used DESeq2 in R to detect differentially expressed genes between groups. To control the effects cell lines differences, we set full model as full = ~treatment + line and the reduced model as reduce = ~line. Genes with adjusted p-value (false discovery rate, FDR) < 5% and expressed higher/lower in MAR0 and MAR18 samples compared to controls are defined as up-regulated/down-regulated genes in MAR.

Functional enrichment analysis Functional enrichment analysis of differentially expressed genes were performed using the Bioconductor package "GeneAnswers"(5) in R (4). Functional annotations were from Gene Ontology (GO) (6). Functional annotated terms with false discovery rate (FDR) <5% were considered as significantly enriched. P-values before multiple test corrections for each functional annotated term was calculated from the hypergeometric test as following:

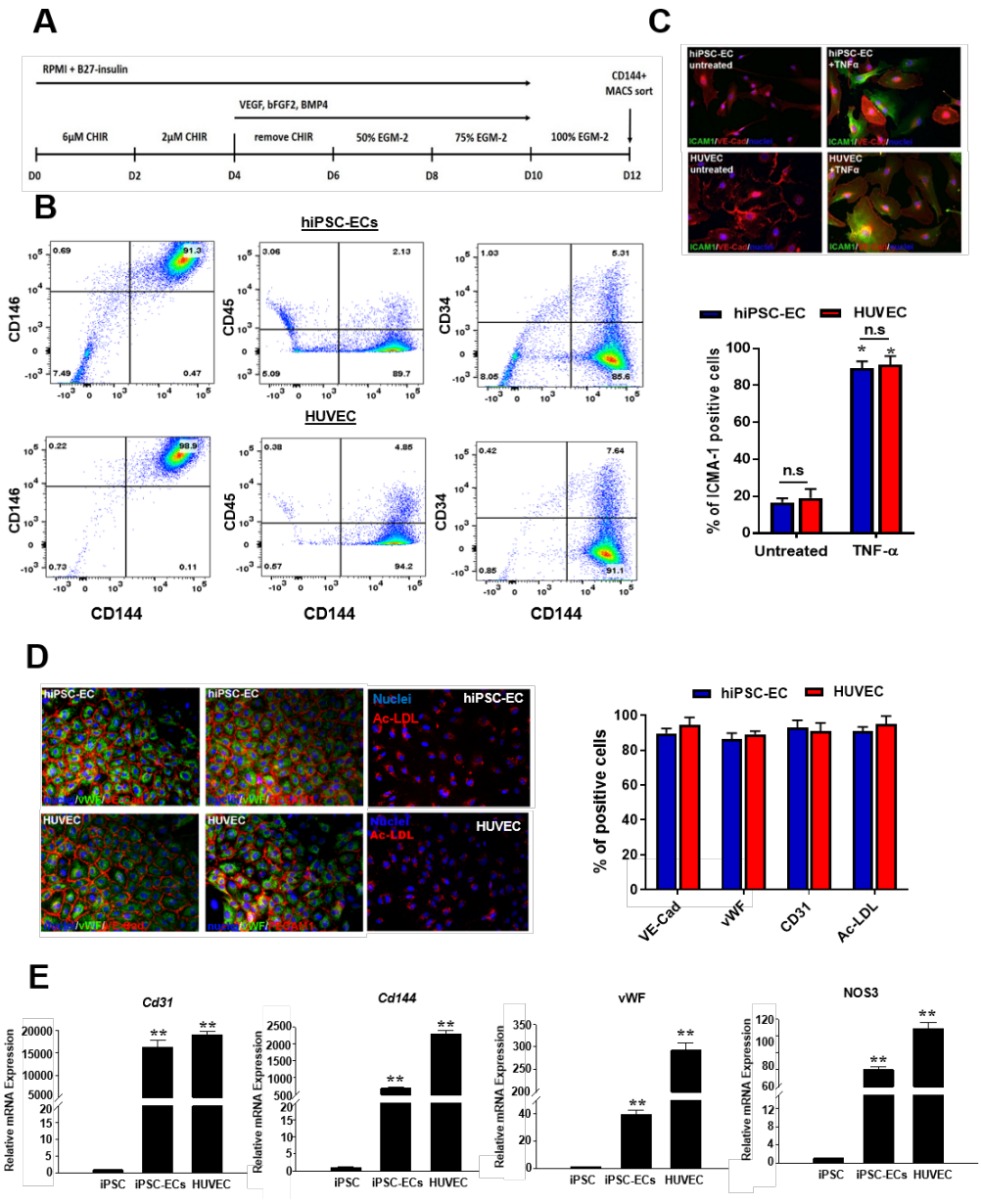
$$p = 1 - \sum_{k=0}^{m-1} \frac{\binom{M}{k}\binom{N-M}{n-k}}{\binom{N}{n}}$$

Where N is the total number of genes with functional annotation across the genome; n is the number of differentially expressed genes in N; M is the number of genes annotated for a particular functional annotated term across the genome; and m is the number of differentially expressed genes annotated for the particular functional annotated term. Bubble plots and chord plots were

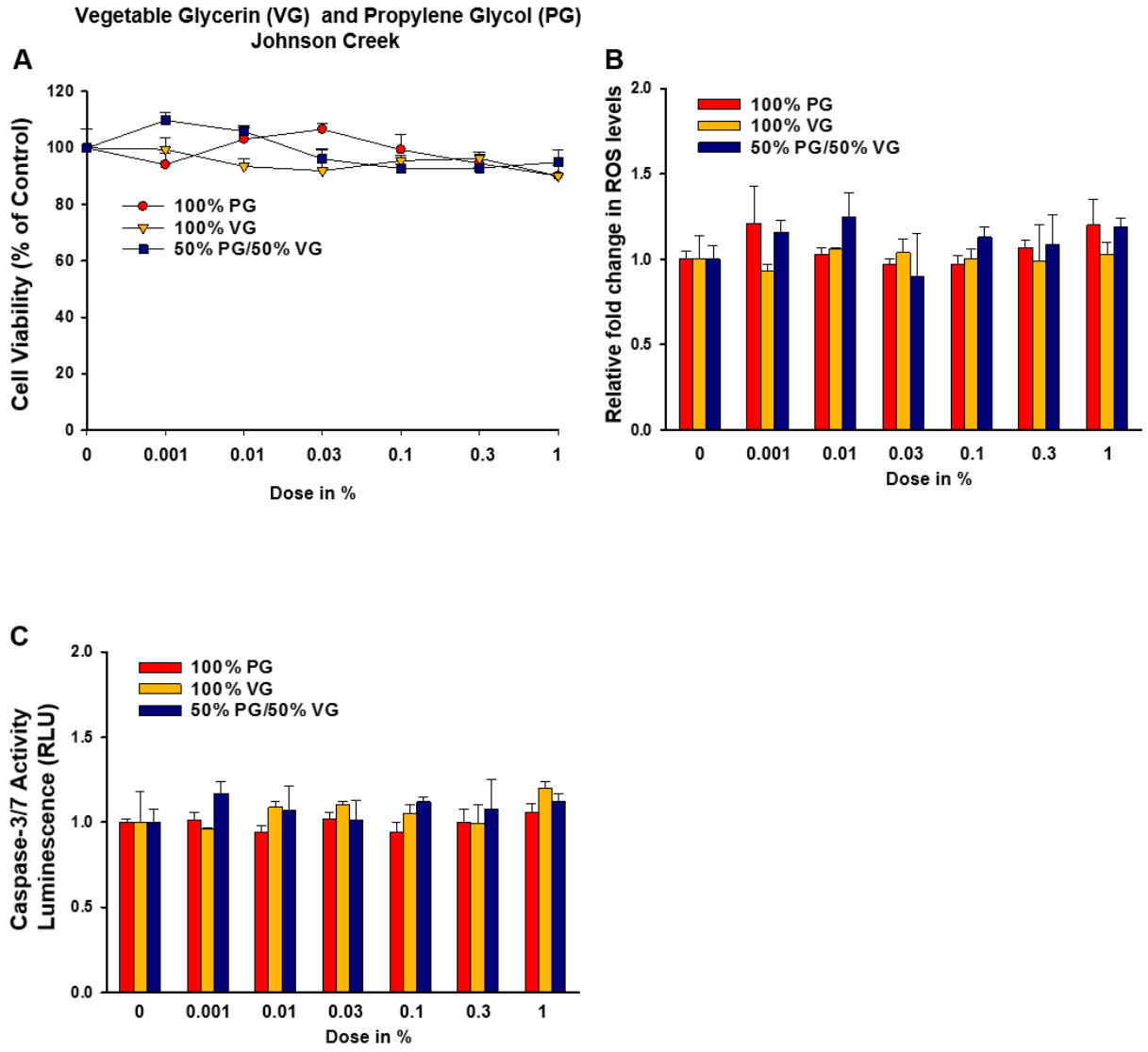
generated using “GOplot” (7) package in R (4) to visualize the functional enrichments. Z scores in bubble plots were calculated as following:

$$zscore = \frac{up - down}{\sqrt{count}}$$

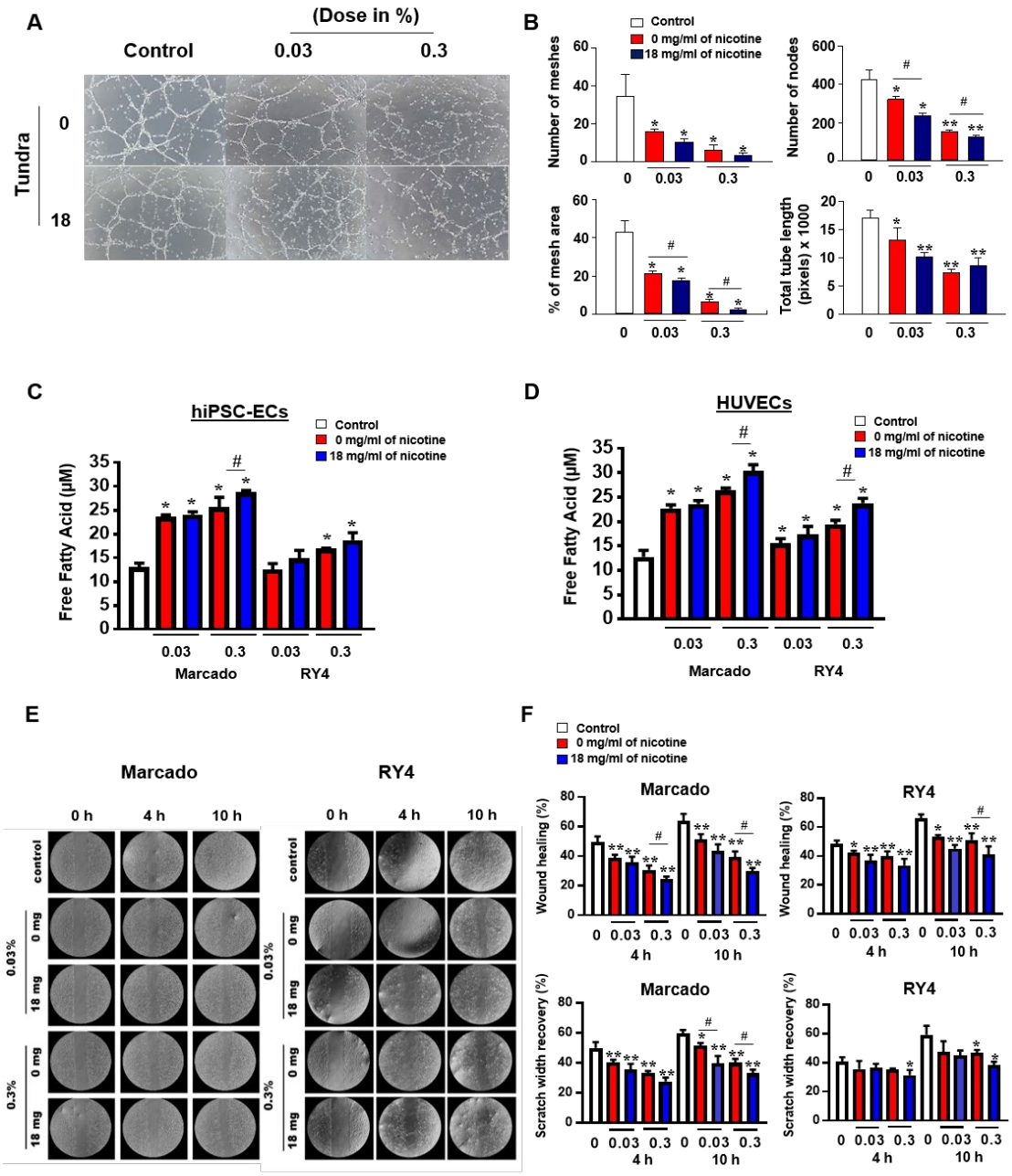
Where count is the total gene number, and up and down are the number of up-regulated or down-regulated differentially expressed genes, respectively.



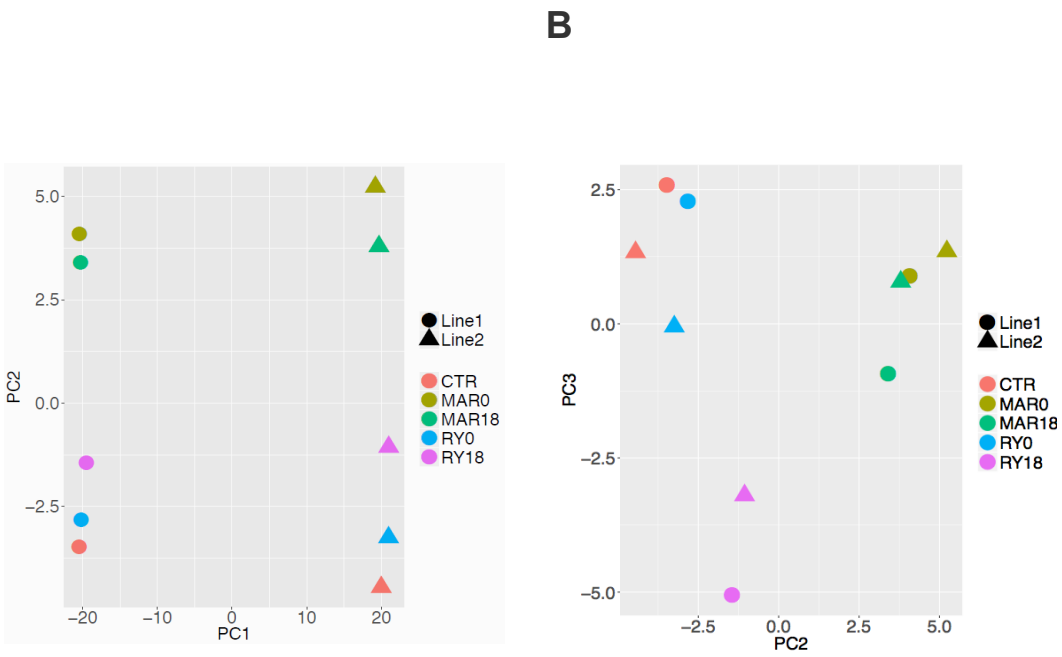
Online Figure 1. *In vitro* characterization of iPSC-ECs. **(A)** Schematic illustration of the EC differentiation protocol for iPSCs. **(B)** Flow cytometry analysis of iPSC-EC differentiation efficiency. iPSC-ECs and human umbilical vein endothelial cells (HUVECs) were stained with the endothelial markers, VE-cadherin (CD144) and CD146, hematopoietic marker (CD45), and progenitor marker (CD34). **(C)** Expression analysis of adhesion molecule intracellular adhesion molecule-1 (ICAM-1) upon TNF-α stimulation. **(D** and **E)** The expression of definitive endothelial markers for VE-cadherin (CD144), von Willebrand Factor (vWF), PECAM1 (CD31), and acetylated-low density lipoprotein (Ac-LDL) in iPSC-ECs and HUVECs were confirmed using immunofluorescence staining and real-time RT-PCR. Data are represented as mean ± SEM. *p<0.05 compared to untreated controls; **p < 0.001 compared to iPSC.



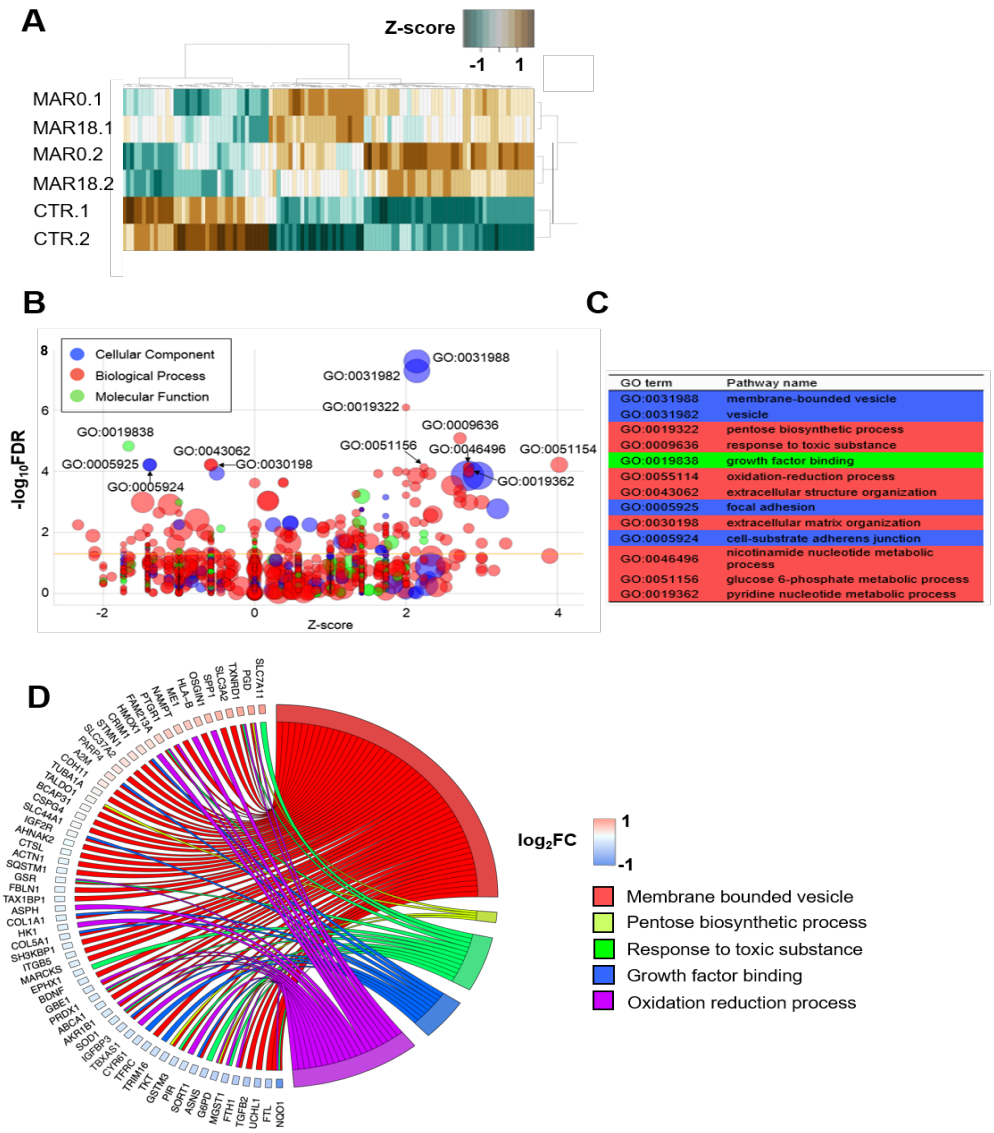
Online Figure 2. Assessment of the humectants used in flavored e-liquids in iPSC-ECs. Effects of two humectants, vegetable glycerin (VG) and propylene glycol (PG), at different dilutions on **(A)** cell viability, **(B)** ROS generation, and **(C)** apoptotic activity of iPSC-ECs were determined after 48-hour treatment. The data were obtained using iPSC-ECs from 3 healthy donors and the assay was repeated twice. Data are represented as mean ± SD.



Online Figure 3. Effect of flavored e-liquids on endothelial function in iPSC-ECs and HUVECs. Endothelial cells were treated with e-liquid flavors and endothelial function was determined. **(A** and **B)** iPSC-ECs were incubated with e-liquid flavor Tundra for 16 hours to allow tube formation of capillary-like structures on Matrigel. They were then imaged by phase-contrast microscopy (x20) and quantified by ImageJ. Concentration of intracellular free fatty acids in **(C)** iPSC-ECs and **(D)** HUVECs was also determined. (**E** and **F**) After incubation with e-liquid flavors, such as Marcado and RY4, migration of HUVECs was imaged and quantified. Data are represented as mean ± SEM. $^{*}p < 0.05$ and $^{**}p < 0.001$, compared to controls; and $^{\#}p<0.05$, compared to groups treated with 0 mg/ml of nicotine.



Online Figure 4. Principal component analysis (PCA) of gene expression profiles from indicated samples, shown as the scatter plot of (A) PC1 versus PC2 and (B) PC2 versus PC3. Samples were grouped into different groups indicated by different colors and shapes. Samples were grouped by different colors and shapes as indicated. MAR: Marcado flavored e-liquid; RY: RY4 flavored e-liquid. 0 or 18 indicates nicotine concentration (mg/ml).



Online Figure 5. Gene expression changes in iPSC-ECs exposed for 24 hours to e-liquids (with or without nicotine). (A) Hierarchical clustering of the differentially expressed genes (DEGs) between MAR-treated group and control croup. The sample clustering aligns with the experimental factor (treated with e-cigarette flavor MAR containing 18 mg/ml of nicotine (MAR18), no nicotine (MAR0), or no treatment (CTR)) for two cell lines. The brown and green gradients indicate an increase or a decrease in gene expression abundance, respectively, within the -1~1 (Z-score). For details of differential gene expression see **Online Table 4**. **(B)** Bubble plot of pathway enrichment (FDR $<10^{-4}$). The color and size of each bubble indicate the amount of DEGs enriched in the pathway. **(C)** Top enriched pathways (FDR $<10^{-4}$) of DEGs between MAR treatment and controls. The color indicates the GO term category of the pathway, and corresponds to color scheme in **Online Figure 5B**. **(D)** Chord diagram showing top five GO term pathways. Enriched GO terms in different colors are shown on the bottom, and genes contributing to this enrichment are shown on the left. Pathways and genes are connected through ribbons, with the same color as pathways' colors. The color intensity is a function of the Log2 (fold-change).

Online Table 1. List of refill products used for this study.

Flavor	Refill fluid	Company	Nicotine (mg/ml)	Main ingredients
Tobacco	Tennessee Cured	Johnson Creek	0, 6, 18	100% VG
Fruit	Rainier	Johnson Creek	0, 6, 18	100% VG
Tobacco	Marcado	Johnson Creek	0, 6, 18	100% VG
Menthol/Tobacco	Tundra	Johnson Creek	0, 6, 18	100% VG
Sweet	Butter Scotch	Freedom Smoke USA	0, 6, 18	50% PG/50% VG
Sweet	RY-4	E liquid Market (Dekang)	0, 6, 18	80% PG/20% VG
	PG	Freedom Smoke USA		
	VG	Freedom Smoke USA		

Online Table 2. Baseline characteristics of the study participants.

	Non-Smokers (n=5)	E-cig Smokers (n=4)		Cig Smokers (n=5)	
		Before	After	Before	After
Age (yr)	28.4 ± 7.4	29.5 ± 7.9		39.0 ± 6.2	
BMI (kg/m^2)	24.1 ± 1.7	23.3 ± 3.0		23.1 ± 1.7	
Biochemistry					
CRP (mg/l)	3.1 ± 2.1	1.2 ± 0.6	0.8 ± 0.6	1.0 ± 0.2	0.9 ± 0.2
HDL (mg/dl)	-	45.3 ± 6.1	44.8 ± 5.1	55.4 ± 3.4	53.8 ± 3.1
LDL (mg/dl)	-	87.0 ± 24.0	89.0 ± 22.0	78.0 ± 4.7	77.6 ± 5.4
Triglycerides (mg/dl)	-	92.3 ± 33.2	100.0 ± 40.5	72.8 ± 15.2	79.6 ± 18.6
Fasting glucose (mg/dl)	-	92.5 ± 6.8	83.3 ± 11.9	87.8 ± 1.9	98.2 ± 9.5
Smoking variables					
# days of smoking in past 30 days	NA	27.5 ± 5.0		29.8 ± 0.4	
# of cig or e-cig/day	NA	9.8 ± 3.3		10.1 ± 3.4	

Data are presented as mean ± SD. BMI: body mass index, CRP: c-reactive protein, HDL: high-density lipoprotein, LDL: low density lipoprotein.

Online Table 3. Mean cytokine levels after exposing to e-cigarette and cigarette smoking.

Target	E-cigarette smoking		*P*-value	Cigarette smoking		*P*-value
	Pre (pg/ml)	Post (pg/ml)		Pre (pg/ml)	Post (pg/ml)	
BDNF	1013.4±416.0	1275.9±513.7	0.13	878.8±107.5	809.0±77.3	1.00
CD40L	148.7±81.9	324.5±208.0	0.26	89.2±25.5	134.7±38.6	0.15
EGF	19.4±7.6	54.6±24.9	0.16	17.2±3.8	30.2±7.6	0.07
ENA78	422.5±181.0	701.2±276.9	0.20	823.5±272.9	1070.5±365.8	0.14
EOTAXIN	26.0±5.0	33.3±8.7	0.34	36.1±8.0	47.6±11.6	0.31
FASL	53.3±35.9	111.6±47.0	0.30	69.8±7.2	127.4±12.6	0.08
FGFB	123.6±87.7	273.4±150.0	0.24	343.4±30.9	540.8±12.9	0.19
GCSF	53.0±10.3	129.1±61.8	0.28	76.4±31.3	125.9±61.5	0.20
GMCSF	25.4±15.9	58.6±30.6	0.23	28.1±11.6	57.4±29.2	0.20
GROA	88.7±39	199.8±9.9	0.36	106.6±7.6	158.0±19.3	0.20
HGF	123.1±18.1	195.8±47.3	0.14	149.4±28.8	261.5±128.4	0.13
ICAM1	**4035.8±2915.9**	**6097.30±3233.1**	**0.03***	**2865.0±617.9**	**6668.3±1473.9**	**0.03***
IFNA	12.7±7.4	25.3±11.8	0.25	12.9±6.4	32.8±13.2	0.18
IFNB	121.4±103.7	960.6±938.1	0.63	21.3±7.8	48.3±29.1	0.30
IFNG	60.2±35.7	123.1±60.2	0.20	51.7±18.1	100.2±47.9	0.21
IL10	60.5±43.7	99.31±54.6	0.18	**38.3±16.8**	**110.7±23.6**	**0.03***
IL12P40	6.8±1.3	9.8±2.3	0.32	7.6±1.9	10.5±4.0	0.26
IL12P70	14.9±5.2	26.4±10.8	0.30	11.4±5.2	25.6±16.3	0.29
IL13	19.5±13.0	37.1±17.9	0.21	12.5±6.7	29.9±13.3	0.20
IL15	49.8±7.5	161.2±47.6	0.30	48.8±29.3	83.4±56.3	0.24
IL17A	37.9±10.2	66.8±26.0	0.27	47.1±10.0	78.9±24.0	0.14
IL17F	12.3±7.7	42.4±36.3	0.13	14.3±7.4	24.5±12.9	0.20
IL18	159.4±76.7	268.9±125.7	0.30	73.1±24.7	108.7±44.1	0.18
IL1A	6.2±3.7	12.4±6.2	0.28	7.7±3.4	11.3±5.5	0.26
IL1B	2.3±0.7	8.6±4.8	0.25	5.9±4.0	13.9±10.2	0.29
IL1RA	111.5±8.2	713.52±30.0	0.19	668.4±409.4	2431.3±1245.9	0.38
IL2	29.9±6.6	51.1±19.2	0.23	26.2±9.8	49.1±25.4	0.24
IL21	49.9±13.3	91.2±53.4	0.28	93.4±4.8	223.2±40.6	0.24
IL22	221.4±65.6	236.3±82.5	0.88	217.4±58.5	326.5±96.9	0.14
IL23	501.2±396.9	912.2±416.7	0.31	339.3±147.8	808.2±101.1	0.20
IL27	1025.4±704.9	1760.6±913.8	0.29	920.1±177.3	1416.9±627.4	0.18
IL31	78.8±51.6	293.4±106.7	0.51	92.9±46.7	345.4±168.3	0.38
IL4	334.4±193.9	586.0±277.1	0.27	208.2±88.9	353.1±181.1	0.22
IL5	67.6±42.3	281.3±117.9	0.22	32.1±18.5	137.3±64.1	0.22
IL6	**121.7±49.6**	**300.7±77.6**	**0.04***	**86.28±18.4**	**150.4±28.6**	**0.01***
IL7	10.8±7.7	15.0±9.0	0.16	6.9±1.5	13.1±5.3	0.23
IL8	57.6±43.6	117.3±66.0	0.25	77.2±4.0	129.2±12.8	0.15
IL9	352.9±265.9	710.2±332.4	0.22	238.7±13.8	541.7±19.1	0.10

Online Table 3. (continued)

Target	E-cigarette smoking		*P*-value	Cigarette smoking		*P*-value
	Pre (pg/ml)	Post (pg/ml)		Pre (pg/ml)	Post (pg/ml)	
IP10	147.6±82.7	231.5±106.3	0.31	100.4±42.5	128.0±61.7	0.28
LEPTIN	793.1±293.6	1040.8±575.6	0.51	3516.0±2004.8	3478.6±2121.0	0.87
LIF	10.2±4.8	17.5±9.3	0.20	10.6±4.8	26.3±16.5	0.27
MCP1	**107.97±48.3**	**306.78±72.6**	**0.04***	**63.4±6.8**	**204.4±34.6**	**0.04***
MCP3	158.4±74.3	244.7±104.5	0.63	131.3±50.1	242.2±118.4	0.20
MCSF	**170.69±57.89**	**328.34±22.17**	**0.02***	**147.4±21.5**	**237.5±28.8**	**0.01***
MIG	189.4±62.0	438.2±231.7	0.27	250.7±130.1	464.6±251.4	0.19
MIP1A	19.9±10.3	59.5±32.2	0.27	48.0±20.2	82.3±33.0	0.17
MIP1B	34.4±13.6	61.9±27.3	0.28	41.4±13.2	55.9±22.5	0.23
NGF	264.0±130.6	449.6±194.5	0.25	305.7±144.7	698.0±280.4	0.18
PAI1	6093.6±1556.8	6897.6±1699.9	0.25	12720.2±1528.0	14239.8±1317.8	0.13
PDGFBB	25850.6±23442.3	43383.4±39597.9	0.25	3167.1±774.8	3753.4±942.0	0.46
RANTES	147.6±85.0	205.8±95.5	0.21	102.6±18.6	115.5±26.4	0.40
RESISTIN	639.1±217.8	866.4±303.2	0.22	1326.2±245.6	1580.2±455.4	0.35
SCF	15.7±8.6	29.5±13.9	0.20	20.9±9.4	39.8±21.2	0.21
SDF1A	966.3±363.3	2028.3±887.4	0.23	1044.4±347.3	1475.7±610.4	0.23
TGFA	8.8±6.5	29.1±11.5	0.20	6.5±3.4	16.5±9.2	0.18
TGFB	55.3±16.9	124.2±61.1	0.27	98.6±41.0	171.5±87.9	0.22
TNFA	61.0±7.4	82.0±18.4	0.26	41.7±7.1	62.6±21.1	0.23
TNFB	152.1±91.3	320.5±172.9	0.26	133.2±76.1	223.3±113.3	0.10
TRAIL	107.3±22.3	192.6±73.3	0.26	157.4±52.0	210.1±87.4	0.28
VCAM1	Undetectable	Undetectable	-	23310.0±5001.9	26505.1±7628.1	0.36
VEGF	204.4±92.7	413.8±198.4	0.26	275.9±148.9	393.3±202.0	0.19
VEGFD	5.2±2.1	18.9±9.4	0.21	11.7±4.3	47.9±29.7	0.26

Data are presented as mean ± SEM. A paired t-test was performed to compare the cytokines between before (Pre) and after (Post) smoking when our data was accorded with normal distribution, otherwise Wilcoxon signed-rank test was used with Bonferroni correction. Unadjusted p values are shown, and an asterisk is noted when comparisons were significant.

Online Table 4. Differentially expressed genes (DEGs) after exposing to e-liquid MAR flavoring compared to controls.

Gene Name	MAR0.CTR FDR	MAR18.CTR FDR
A2M	6.74E-04	1.22E-03
ABCA1	2.68E-03	1.12E-02
ABLIM3	1.55E-03	8.26E-03
ACTN1	2.34E-03	4.61E-02
AFAP1	3.88E-02	4.23E-01
AHNAK2	2.01E-02	1.00E+00
AKR1B1	1.94E-04	2.76E-02
ALAS1	1.05E-06	8.59E-03
APCDD1L	5.62E-08	2.01E-04
ARSJ	5.71E-06	2.84E-04
ASNS	2.79E-09	6.84E-01
ASPH	4.43E-04	2.75E-01
BCAP31	9.68E-03	4.13E-01
BCYRN1	7.12E-03	3.39E-02
BDNF	9.70E-03	5.72E-02
CDH11	3.84E-04	4.03E-02
CHSY3	3.25E-02	3.27E-01
CNN1	1.13E-02	1.12E-02
COL1A1	4.99E-05	2.73E-03
COL5A1	3.48E-05	1.84E-01
CRIM1	2.76E-02	8.22E-02
CSPG4	1.71E-02	6.47E-02
CTSL	3.50E-18	2.67E-07
CYR61	8.53E-03	1.06E-01
EPHA2	7.08E-04	2.76E-02
EPHX1	1.55E-03	7.80E-02
FAM167A	3.05E-03	6.73E-02
FAM213A	6.74E-03	6.26E-03
FBLN1	4.70E-02	1.02E-01
FBN2	8.45E-05	2.20E-04
FHL1	3.05E-03	1.12E-02
FST	1.66E-06	2.97E-05
FTH1	1.95E-07	7.08E-33
FTL	1.69E-39	1.77E-22
G6PD	1.24E-05	3.28E-18
GBE1	3.63E-02	1.00E+00
GCLM	2.13E-07	1.03E-03

Online Table 4. (Continued).

Gene Name	MAR0.CTR FDR	MAR18.CTR FDR
GNG11	4.41E-02	6.51E-02
GPAT3	1.07E-05	1.01E-04
GPSM1	3.09E-02	7.80E-02
GSR	1.52E-09	5.56E-03
GSTM3	2.34E-03	3.34E-01
HAPLN3	3.78E-02	3.96E-01
HK1	2.76E-02	1.00E+00
HLA-B	2.45E-02	1.36E-01
HMOX1	5.49E-02	6.26E-05
IGF2R	2.03E-02	9.94E-01
IGFBP3	8.71E-04	3.47E-04
IL1RL1	4.54E-04	1.13E-02
ITGA2	1.53E-02	2.57E-02
ITGB5	4.47E-03	6.02E-01
KTN1	2.25E-02	7.07E-01
KYNU	1.34E-02	NA
LACC1	6.25E-05	6.39E-04
MARCKS	1.88E-02	9.81E-01
ME1	7.79E-07	2.54E-03
MGST1	3.90E-14	2.69E-08
MMP1	5.64E-46	7.08E-33
MTATP6P1	3.84E-04	3.59E-02
MTCO1P12	5.54E-03	6.39E-01
MT-ND4L	3.05E-03	9.62E-01
NAMPT	2.65E-03	1.28E-02
NQO1	7.27E-11	8.78E-11
OSGIN1	1.34E-02	7.97E-01
PANX2	3.58E-03	2.04E-01
PARP4	2.76E-02	2.13E-01
PGD	1.06E-18	6.34E-09
PIR	1.13E-02	4.85E-07
POPDC3	1.69E-03	2.02E-01
PRDX1	1.86E-07	4.21E-04
PTGR1	2.60E-06	2.01E-02
RCAN1	4.60E-02	6.73E-02
RNF213	1.88E-02	1.00E+00
SEMA3D	2.25E-02	5.67E-01
SF1	2.52E-02	3.21E-01

Online Table 4. (Continued).

Gene Name	MAR0.CTR FDR	MAR18.CTR FDR
SH3KBP1	5.18E-03	1.12E-01
SLC20A1	3.50E-03	3.34E-01
SLC37A2	6.02E-03	2.04E-02
SLC3A2	1.03E-11	3.33E-05
SLC44A1	6.03E-04	1.22E-03
SLC7A11	2.46E-51	1.85E-25
SOD1	1.34E-02	7.28E-01
SORBS3	3.59E-02	3.34E-01
SORT1	1.57E-04	7.89E-05
SPP1	8.45E-07	7.80E-02
SQSTM1	9.68E-03	1.19E-01
STMN1	4.70E-02	9.48E-01
TAGLN	2.85E-04	6.64E-04
TALDO1	1.89E-09	1.26E-05
TAX1BP1	4.70E-02	5.67E-01
TBC1D8	5.95E-03	3.29E-02
TBXAS1	4.62E-02	1.00E+00
TFPI2	9.99E-01	2.54E-03
TFRC	3.51E-02	4.44E-02
TGFB2	1.43E-07	2.78E-04
TKT	5.15E-14	2.56E-09
TMEM156	1.66E-02	1.24E-01
TNPO2	1.64E-02	2.27E-01
TRIM16	2.05E-04	2.03E-02
TRIM16L	6.61E-12	1.83E-04
TUBA1A	2.22E-03	1.00E+00
TXNRD1	5.70E-36	3.49E-17
UCHL1	5.78E-11	5.08E-06
ZYX	6.10E-03	1.00E+00

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