

**Supplementary Table 1.** GeneAnalytics- Brain Endothelial Cell Pathways in Bulk RNAseq: Young versus Aged -Pooled Hippocampal and Cortical BECs

<b>Results</b>			
<b>Score</b>	<b>SuperPath Name</b>	<b># SuperPath Total Genes</b>	<b># SuperPath Matched Genes</b>
<b>37.75</b>	Metabolism	2543	207
<b>27.91</b>	Phospholipase-C Pathway	498	59
<b>27.19</b>	ERK Signaling	1177	107
<b>27.11</b>	Degradation of The Extracellular Matrix	298	42
<b>26.88</b>	Neuroscience	323	44
<b>24.86</b>	Transport of Glucose and Other Sugars, Bile Salts and Organic Acids, Metal Ions and Amine Compounds	678	70
<b>24.47</b>	Angiogenesis (CST)	87	20
<b>23.66</b>	AGE-RAGE Signaling Pathway in Diabetic Complications	99	21
<b>22.47</b>	Non-integrin Membrane-ECM Interactions	46	14
<b>22.39</b>	Response to Elevated Platelet Cytosolic Ca <sup>2+</sup>	640	65
<b>22.22</b>	RET Signaling	974	88
<b>22.07</b>	Cell Adhesion Endothelial Cell Contacts By Non-junctional Mechanisms	40	13
<b>21.31</b>	Apoptotic Pathways in Synovial Fibroblasts	725	70
<b>19.91</b>	Ras Signaling Pathway	322	39
<b>19.25</b>	Adhesion	110	20
<b>18.89</b>	VEGF Pathway (Qiagen)	122	21
<b>18.3</b>	Mechanisms of CFTR Activation By S-nitrosoglutathione (normal and CF)	43	12
<b>18.24</b>	Diseases of Glycosylation	86	17

Super Pathway Analysis of bulk RNAseq data from young versus aged pooled hippocampal and cortical BECs. Canonical pathways that are differentially regulated in aged BECs were identified by GeneAnalytics (GSEA) software.

<b>18.21</b>	Development VEGF Signaling Via VEGFR2 - Generic Cascades	147	23
<b>17.99</b>	Actin Nucleation By ARP-WASP Complex	341	39
<b>17.8</b>	Photodynamic Therapy-induced HIF-1 Survival Signaling	37	11
<b>17.77</b>	Cell Adhesion_ECM Remodeling	61	14
<b>17.74</b>	MAP Kinase Signaling	108	19
<b>17.19</b>	Signaling By GPCR	2601	181
<b>17.12</b>	P70S6K Signaling	390	42
<b>16.84</b>	NRF2 Pathway	145	22
<b>16.84</b>	EPH-Ephrin Signaling	145	22
<b>16.55</b>	ECM Proteoglycans	57	13
<b>16.44</b>	PAK Pathway	682	62
<b>16.44</b>	Cell Adhesion_Plasmin Signaling	49	12
<b>16.38</b>	Myometrial Relaxation and Contraction Pathways	218	28
<b>16.08</b>	Fluid Shear Stress and Atherosclerosis	139	21
<b>15.71</b>	NFAT and Cardiac Hypertrophy	326	36
<b>15.36</b>	Blood-Brain Barrier and Immune Cell Transmigration: Pathways Overview	71	14
<b>15.31</b>	Integrin Pathway	568	53
<b>15.22</b>	ECM-receptor Interaction	112	18
<b>15.18</b>	Signaling in Gap Junctions	180	24
<b>14.84</b>	Focal Adhesion	283	32
<b>14.78</b>	Sertoli-Sertoli Cell Junction Dynamics	391	40
<b>14.74</b>	Nanog in Mammalian ESC Pluripotency	533	50

<b>14.65</b>	HIV Life Cycle	865	72
<b>14.62</b>	HIF-1-alpha Transcription Factor Network	65	13
<b>14.58</b>	Cell Adhesion_Cell- matrix Glycoconjugates	39	10
<b>14.36</b>	Amoebiasis	96	16
<b>14.15</b>	FMLP Pathway	317	34
<b>13.85</b>	Akt Signaling	681	59
<b>13.62</b>	Neurotransmitter Release Cycle	51	11
<b>13.57</b>	Drug Metabolism - Cytochrome P450	134	19
<b>13.36</b>	L1CAM Interactions	102	16
<b>13.2</b>	GPCR Pathway	708	60
<b>13.09</b>	VEGF Signaling Pathway	93	15
<b>12.8</b>	Developmental Biology	1079	83
<b>12.78</b>	Primary Focal Segmental Glomerulosclerosis FSGS	74	13
<b>12.67</b>	Metabolism of Water-soluble Vitamins and Cofactors	177	22
<b>12.63</b>	Beta-Adrenergic Signaling	308	32
<b>12.52</b>	Tyrosine Kinases / Adaptors	142	19
<b>12.48</b>	BMAL1- CLOCK,NPAS2 Activates Circadian Gene Expression	86	14
<b>12.43</b>	Metabolic States and Circadian Oscillators	10	5
<b>12.43</b>	Prostaglandin Synthesis and Regulation	30	8
<b>12.39</b>	Cell Surface Interactions at The Vascular Wall	143	19
<b>12.39</b>	Pathways in Cancer	395	38
<b>12.25</b>	Neuropathic Pain- Signaling in Dorsal Horn Neurons	232	26
<b>12.16</b>	S1P3 Pathway	48	10

<b>12.13</b>	HIF-1 Signaling Pathway	99	15
<b>12.11</b>	Circadian Rhythm	31	8
<b>11.81</b>	Ca, CAMP and Lipid Signaling	124	17
<b>11.7</b>	Arginine and Proline Metabolism	50	10
<b>11.65</b>	MAPK Signaling Pathway	279	29
<b>11.48</b>	Platelet Aggregation Inhibitor Pathway, Pharmacodynamics	51	10
<b>11.47</b>	Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways	163	20
<b>11.42</b>	NOTCH1 Regulation of Human Endothelial Cell Calcification	18	6
<b>11.33</b>	Thyroid Hormone Signaling Pathway	116	16
<b>11.32</b>	Apoptosis Pathway	152	19
<b>11.28</b>	PPAR Signaling Pathway	72	12
<b>11.1</b>	PI3K-Akt Signaling Pathway	342	33
<b>10.96</b>	Prion Diseases	35	8
<b>10.91</b>	RhoGDI Pathway	181	21
<b>10.71</b>	Angiopoietin Like Protein 8 Regulatory Pathway	196	22
<b>10.52</b>	Phospholipase D Signaling Pathway	185	21
<b>10.48</b>	Regulation of Lipid Metabolism By Peroxisome Proliferator-activated Receptor Alpha (PPARalpha)	280	28
<b>10.33</b>	Glycosaminoglycan Metabolism	296	29
<b>10.33</b>	ADP Signalling Through P2Y Purinoceptor 1	67	11
<b>10.1</b>	P75 NTR Receptor-mediated Signalling	216	23

**Supplementary Table 2: Proteomics List of differentially regulated proteins with human aging (see reference for Source Proteomics Data)**

Protein	Spearman's Correlation Coefficient	P value Spearman	Q value Spearman	Vascular Specific Function? (GeneCards)	Expressed in mouse Brain Endothelial Cells?
VCAM1	0.470281976	7.73E-08	5.72E-06	Yes; Ig superfamily; and encodes a cell surface sialoglycoprotein expressed by cytokine-activated endothelium. Type I membrane protein mediates leukocyte-endothelial cell adhesion and signal transduction, involved in atherosclerosis and rheumatoid arthritis. [provided by RefSeq, Dec 2010]	Yes
Alpha-Fetoprotein	0.416308993	2.75E-06	6.78E-05	No	No
B2M	0.422267485	1.91E-06	6.78E-05	No	Yes
TNFR1	0.409444059	4.15E-06	7.67E-05	No	Yes
MMP2	0.397146169	8.48E-06	0.0001255	Member of the matrix metalloproteinase (MMP) gene family, that are zinc-dependent enzymes capable of cleaving components of the extracellular matrix and molecules involved in signal transduction. Involved in multiple pathways including roles in the nervous system, endometrial menstrual breakdown, regulation of vascularization, and metastasis. Mutations associated with Winchester syndrome and Nodulosis-Arthropathy-Osteolysis (NAO) syndrome. [provided by RefSeq, Oct 2014]	No
Alpha 1 Antitrypsin	0.38028854	2.16E-05	0.0002283		No
FABP3	0.381176337	2.06E-05	0.0002283		No
IL16	0.365038767	4.82E-05	0.0004456		No
CCL3 (MIP1 Alpha)	0.3310868	0.0002502	0.002057		No
TIMP1	0.320871443	0.0003962	0.0029319		No
CCL11 (Eotaxin)	0.306534226	0.0007354	0.0049474		No
Fibrinogen (alpha beta gamma chain)	0.300444625	0.0009476	0.0050087	Blood-borne glycoprotein comprised of three pairs of nonidentical polypeptide chains. Following vascular injury, fibrinogen is cleaved by thrombin to form fibrin. In addition, various cleavage products of fibrinogen and fibrin regulate cell adhesion and spreading, display vasoconstrictor and chemotactic activities, and are mitogens for several cell types. Mutations lead to several disorders, including afibrinogenemia, dysfibrinogenemia, hypodysfibrinogenemia and thrombotic tendency. [provided by RefSeq, Jun 2014]	No
MCSF	0.301081975	0.000923	0.0050087		No
TF	0.301655872	0.0009014	0.0050087	Glycoprotein which binds ferric iron. The function is to transport iron from the intestine, reticuloendothelial system, and liver parenchymal cells to all proliferating cells in the body. This protein may also have a physiologic role as granulocyte/pollen-binding protein (GPBP) involved in the removal of certain organic matter and allergens from serum. [provided by RefSeq, Sep 2009]	No
CEA	0.288317851	0.0015449	0.0076216		No
CA19-9	0.272433137	0.00284	0.013135		No
CD40	0.269243459	0.0031958	0.0139113		Yes
CK-MB	0.266629366	0.0035168	0.0144582		Yes
ICAM1	0.262891835	0.0040261	0.0156807	This gene encodes a cell surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. It binds to integrins of type CD11a / CD18, or CD11b / CD18 and is also exploited by Rhinovirus as a receptor. [provided by RefSeq, Jul 2008]	Yes
Haptoglobin	0.261114706	0.0042907	0.0158756		No
CCL4 (MIP1 Beta)	0.242723911	0.0080894	0.0285055		No
MMP9	0.23607641	0.0100637	0.0338506		No
IL5	-0.228459671	0.0128359	0.039677		No
SHBG	0.228379762	0.0128682	0.039677		No
Myoglobin	0.222396258	0.0154983	0.0458751		No
CCL2 (MCP1)	0.217513373	0.017979	0.0511711		No
CRP	0.212186922	0.0210696	0.0577462		No
IL18	0.209314258	0.0229185	0.0605703		Yes
IL3	0.206647865	0.0247574	0.0631742		No
TNF-beta	0.195707336	0.0336803	0.0830781		No
EN-RAGE	0.187102817	0.0424813	0.101407		No

Highlighted in Blue: Plasma proteins that are correlated with human aging (ages 50-89; Figure 1) and that are also expressed in murine BECs at the transcriptional level (Bulk RNAseq of young and aged BECs; Figure 1, Supplemental Fig. 1)

Proteomics Source Data: Britschgi, M. et al. Modeling of pathological traits in Alzheimer's disease based on systemic extracellular signaling proteome. *Mol. Cell. Proteomics* 10, M111.008862 (2011).

Violin Plot Values for Minimum, Maximum, Percentile, and Median for Figure 2, Extended Data Figure 1, Extended Data Figure 2, BRC, sCRNAseq













	Vcam1	Tfr1a	Irf1	Irf4	Irf8	Hita	Kamt1	Lgt1	H2-K1	B2m	Tpo	Eno2	Bmx	Jag1	Eph4	Vwf	Nr2f2	Em1	Nectn1	Ntnt1	Vegf	Hey1	Ras
25th percent Cap	-4.57E-06	-3.23E-06	-3.79E-06	-2.77E-06	-2.06E-06	-3.29E-06	-4.19E-06	-4.74E-06	0.0036552	2.70362138	3.73E-06	-4.19E-06	-3.79E-06	3.34E-06	-3.79E-06	3.64E-07	-3.89E-06	-3.58E-06	-1.99E-07	-4.21E-06	-4.80E-06	-3.89E-06	3.90E-06
Art	1.19E-05	-4.58E-06	-5.39E-06	-7.95E-06	-2.90E-06	-4.41E-06	-7.93E-06	-8.69E-06	2.52294701	3.28243547	1.99165929	-3.29E-06	0.30812766	1.55947662	-7.93E-06	0.29244885	-8.69E-06	9.09E-06	1.13E-05	-5.76E-07	-2.25E-06	-2.39E-07	0.45692958
Cap	6.71E-07	-3.32E-06	0.0969987	-2.28E-06	9.38E-06	8.32E-06	-4.08E-06	-4.51E-06	2.27264154	3.19546071	1.15E-06	-7.92E-06	-7.92E-06	3.71E-06	-4.89E-06	2.04380758	1.78E-05	-6.24E-06	-1.82E-06	-5.57E-06	-8.63E-06	-8.71E-06	-2.72E-06
Median	1.95E-06	5.77E-06	3.08E-06	3.95E-06	7.95E-06	5.00E-06	2.05E-06	-2.51E-07	-9.47E-07	3.15242799	3.67986156	3.39E-06	2.55E-06	0.05899888	4.16E-06	8.80E-06	2.55E-06	-4.44E-06	1.81E-05	4.44E-06	1.13E-06	3.95E-06	0.60448956
Art	2.2301209	3.74E-06	-4.07E-07	-4.07E-07	6.97E-06	6.29E-10	-2.51E-07	-9.47E-07	3.15242799	3.67986156	2.41489279	6.33E-06	1.50976027	1.99318965	-7.76E-08	1.87597372	-9.47E-07	1.24448992	0.6177776	1.02E-05	8.13E-06	2.29E-05	1.4240732
Cap	0.00994087	0.01670281	1.175899761	1.25E-05	0.07231807	0.10716672	1.17E-05	-1.38E-05	3.27333479	3.5509314	1.44005953	-8.61E-07	8.61E-07	0.50670807	1.21E-05	2.27232876	0.65057783	1.09E-06	1.38E-05	1.90E-06	6.40E-06	-1.22E-06	1.55982864
75th percent Art	8.54E-06	1.59E-05	9.89E-06	1.39E-05	0.07232095	0.01722701	7.65E-06	6.54E-06	3.01283013	3.60046189	1.9287849	1.04E-05	9.14E-06	1.0982896	1.47E-05	0.7078979	1.02E-05	2.54E-06	0.98226274	0.02589218	6.40E-06	1.37E-05	1.55982864
Cap	2.84793416	1.14144934	9.09E-06	7.38E-06	0.3471296	1.33E-05	9.93E-06	6.43E-06	3.1595799	3.94448161	2.38819938	1.08796448	2.50447292	2.72802944	1.33E-05	2.5793999	6.43E-06	2.55099108	1.61693976	1.17630978	1.5570959	1.9900728	1.7870793
Art	2.46931011	1.89348237	2.41726878	1.41776448	2.01379859	2.04702263	1.5724231	2.65471994	3.54797507	3.84515843	2.08346425	9.59E-06	1.18E-05	1.24676149	1.55869873	3.45824645	1.28626519	1.31E-05	0.85037418	1.12308206	1.18E-05	7.89E-06	1.42108927
Min	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05
Cap	-2.66E-05	-2.66E-05	-2.66E-05	-2.70E-05	-2.70E-05	-2.44E-05	-2.70E-05	-2.70E-05	-1.20E-05	1.179075636	-1.20E-05	-2.66E-05	-2.44E-05	6.29E-10	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05
Art	-1.76E-05	-1.85E-05	-1.85E-05	-1.76E-05	-1.76E-05	-1.85E-05	-2.41E-05	-1.85E-05	0.20050205	2.25710034	-1.85E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-2.41E-05	-1.85E-05
Max	4.18757952	2.88180013	2.09120862	2.72283103	2.84302196	2.76944782	2.1597322	1.26908154	4.54235496	4.59660266	3.10754843	2.02210822	3.24860778	2.29875996	2.47294352	3.66764419	2.15394922	2.870191	2.47359386	2.52144883	3.41994294	3.41994294	2.97480907
Art	4.50912369	2.5195712	2.17293906	1.10738713	3.15935973	2.73758344	2.84316462	3.05837315	4.24754226	4.37680068	3.38976782	2.118506101	3.44450306	3.43902083	2.39575446	3.64598133	0.02770642	4.06735024	3.04356465	2.47555403	2.84307596	3.20996688	2.22031691
Cap	4.68656434	2.90228018	3.883918103	3.09918494	2.67505859	3.92908413	4.63613232	4.29207504	4.63623699	2.8947301	0.70547955	3.57294199	2.04212727	2.78416917	3.30711695	2.37162128	2.06568368	2.89259402	1.92338423	2.66110464			

In Ageless Young

	Vcam1	Odn	Ddx5	Pnap	Tp1	Bcsl1	Kamt1 (in all BRC)	Kamt1 (in all BRC)
25th percent Old	0.00894768	3.8159554	7.71E-06	5.48E-06	6.15E-06	4.31E-06	-5.53E-06	-3.79E-06
Young	1.90949294	4.13990687	-6.31E-07	0.1210358	9.21E-06	4.32E-06	4.32E-06	4.32E-06
Median	1.75665067	4.02497041	8.73E-07	0.15307051	9.21E-06	3.49E-06	3.49E-06	3.49E-06
75th percent Old	2.61159042	4.3342144	7.30E-06	1.42969994	1.77393989	1.67E-05	9.17E-06	9.17E-06
Young	2.39194428	4.34643131	7.30E-06	1.42969994	1.77393989	1.38E-05	-2.70E-05	-2.70E-05
Min	-1.66E-05	0.6135542	-2.70E-05	-1.66E-05	-2.41E-05	-2.70E-05	-2.70E-05	-2.70E-05
Cap	-2.66E-05	-5.84E-06	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05	-2.99E-05
Art	3.55284016	4.69943113	2.06E-05	3.17366044	3.8216766	3.92908413	3.92908413	3.92908413
Max	4.50912369	3.9150219	4.93704022	4.48627751	3.06574644	3.21521229	3.20821911	3.20821911

Values represent violin plots minima, maxima, centre, and percentile values corresponding to data in Fig. 2, Extended Data Fig. 1, and Extended Data Fig. 2.

Supplementary Table 4. Summary of *In Vivo* Experiments

Mouse Type	Figure #	Plasma type	Treatment paradigm	Neurogenesis			Microglial Activation		VCAM1 at the BBB	Behavior	
<b>Young</b>  3-4-month-old <b>Strains:</b> NSG C57BL6 (WT) Slco1c1 <sup>-/-</sup> ; Vcam1 <sup>fl/fl</sup> (TG) <b>Aged</b>  16-23-month-old		 Aged human plasma >65 yr (AHP)  19-month aged mouse plasma (AMP) Heterochronic Parabiosis	Parabiosis Plasma injections  α-VCAM1 α-VLA-4 Behavior: Barnes Maze, Novel Object, Contextual fear conditioning # Days: # of mice per group	#BrdU+ / Edu+ 	#BrdU+ / Edu+ Sox2+ NPCs 	#DCX+ 	#NeuN+ / Edu+ 	Iba1+ %area 	Iba1+ CD68+ %area 	VCAM1+ Lectin+ BECs 	Barnes Maze (BM) Increase= Improved time to escape hole Novel Object Recognition (NO) Increase= Increased interaction with novel object Contextual fear conditioning (CFC) Increase= Increase in contextual memory
Young WT	1: E11-m	Heterochronic Parabiosis	Parabiosis: 35 days; n=8-13/grp 4 days; n=10-11/grp								
Young WT	3	AMP	Tamoxifen (ip.) 4 days; 6 Cre- and 7 Cre+ mice/grp Tamoxifen: 4 days; plasma; n=7-8/grp α-VCAM1: 4 days; n=10/grp								
Young TG	E4e-i	N/A									
Young TG	4	AMP									
Young NSG	5a-g	AHP									
Young WT	5h-n	AMP									
Aged WT	6a-c; E5k-n; E9a-b	N/A									
Aged TG	6d-f; E7; E8; E9c-d	N/A	Tamoxifen, 16 months aging; n=7-8/grp 21 days; n=5/grp								
Young NSG	E4a-d	AHP									
Young TG	E5a-j	AMP	Tamoxifen; 20 days plasma; n=8/grp								
Young NSG	E6a-j	svVCAM1-depleted AHP									
Young NSG	E6k-p	AHP									
Aged WT	E9k-p	N/A	α-VCAM1; 21 days; n=10/grp α-VLA-4; 21 days; n=7/grp								
Aged WT (17-month-old)	6g-h	N/A									
Aged WT (23-month-old)	6i; E9h-j	N/A	α-VCAM1; one month; Behavior; n=15 mice/group α-VCAM1; one month; Behavior; n=7-13 mice/group α-VCAM1; one month; Behavior; n=11 mice/group								
Aged NSG (13-month-old)	E9e-g	N/A									

\*Changes in Neurogenesis, Microglial Activation and VCAM1 are relative to young mouse plasma-injected genotype-matched control mice. PBS-injected control mice, young genotype-matched isochronic mice, or IgG isotype treated control mice. WT= wildtype (C57BL6) mice; NSG= immunodeficient mice; TG= tamoxifen-treated Vcam1<sup>fl/fl</sup>Slco1c1-Cre<sup>ERT2+</sup> mice

