CHAPTER III

Result

3.1 Characteristics of circulating endogenous stem cells (CESs)

3.1.1 Effect of chemical environments

CESs derived from healthy donors were characterized using high resolution inverted microscope as shown in figure 3.1. After resuspension the PBMCs in condition medium RPMI 1640 (without phenol red) in the presence and in the absence of 10 % fetal bovine serum (FBS), at day 1, majority of cells were round and oval shapes. The typical colonies of HSCs were also found. It should be noted that at day 7 after culture, the typical morphology of MSCs were appeared at the bottom of the culture flask. At day 12, both HSCs and MSCs were differentiated into mature cells and still found colonies that are bigger in size.Indeed, an increase in cell numbers and changed morphology were similar done in both series of culture. However, in the series of culture in the presence of 10% FBS were found increase cell numbers and the more stem cell colonies.

Two series of experiments were performed in order to investigate the influence of cytokines derived from their own donors' serum and the enrich source of cytokines like FBS. The PBMCs (10^6 cell/ml) were cultured in RPMI 1640 without phenol red in the presence of 10% donors' serum (figure 3.2) and 10% FBS (figure 3.3) for 24 days. It was clearly found that only few colonies were developed even after day 24, while the aggregation of cells was bigger proportionally to the incubation time. The attached cells at day 24 were majorly foam like cells in the series of experiments using donor's serum (Figure 3.2). Contrary, the series using fetal bovine serum, a

variety of cell types were observed including, adipocytes, osteocytes, chondrocytes, neurons, leucocytes, stromal cells, etc., (Figure 3.3).

3.1.2 Effect of gender and age on the potency of CESs culture

In order to compare the behavior of CESs obtained from male and female of adult and elder groups, the cells were cultured using the RPMI 1640 medium completed with 10% fetal bovine serum. Figure 3.4 at day 1 the CESs have oval shape, when the cells were in culture until Day 6 the colonies of stem cells were observe in all sample. And the cells can similarly undergo differentiation in 24 days. Showed that CESs grew and underwent differentiation similarly in all donors independently neither gender nor age.

3.1.3 Analysis of cellular kinetic of CESs by flow cytometry

On the microscopic analysis point of view, CESs composed of two subpopulations; one was adherent cell and the other is suspension cell. Both of cell types were able to originate the colony forming units of stem cells in the culture system but it was difficult to enumeration of the cells. The study rigorously isolated only the suspension cells then the cells were analyzed by measuring their DNA content as a function of time. Figure 3.5a shows that these cells were found in different cell phases including G0/G1, S, G2/M and sub G0/G1 that corresponding to the apoptotic cells. The results of this study allow writing the diagram (Figure 3.5b), explaining the homeostasis which is the characteristic of normal stem cells. The parameters of cell kinetics including the mean rate of cell to re-entering to the cell cycle, move from S to G2/M (k2), move from G2/M to G0/G1 (k1) undergone apoptosis (β) and differentiation (α) were determined as indicated in Table 3.1

3.2 Ex vivo reconstitution of tissue using circulating endogenous stem cells (CESs).

3.2.1 Reconstitution of tissue using CESs in 3D-nanofibous

The potency of CESs growth and differentiation in the presence of biocompatible 3D-nanofibrous PVDF scaffold was studied. In the series of experiments, the 3D-nanofibous scaffolds were mixed-morphology of non-woven and woven designs(figure 3.6). The CESs of all donors able to grow and undergo differentiation yielding complex tissues when they were cultured using the scaffolds. The results of this study also demonstrated that CESs can originate communities of cells and tissue as revealed by SEM micrographs after 10 days (figure 3.7, 3.8 and 3.9). CESs obtained in this study exhibited similar efficiency to yield communities of cells and tissues when were cultured 3D-nanofibrous PVDF scaffolds. Almost the attached cells on the alignment zone were to be differentiated in a variety of cellular morphologies. The cells found in the non-woven zone were irregular in shape and sites.

3.2.2 Comparison of proteomics by 2D gel electrophoresis

The whole cell proteins and secretory proteins profiling of CESs that culture in absence and in the presence of 10% FBS were analyzed by 2D-gel electrophoresis using the pH 3-10 IPG strip condition 1mg/gel (figure 3.11).Figure 3.11 clearly shows that both whole cell and secretory proteins in the two conditioned-media have similar migration pattern. However, the quantities of protein of each spot of the 10% FBS series were abundantly found compared with those of non-FBS series.

The proposed protein-protein interaction diagram, the so-called "repair and regeneration diagram" can be drawn as indicated in figure 3.10. CESs should have eight principle processes that involve into repair and regenerations. The

major phenomenon in repair and regeneration process are cell kinetics and metabolism, cell-cell communications, immunity system and neurovascular genesis.

The proteins corresponding to genes that govern the repair and regeneration processes was obtained by spot gel excision following elution and digestion then analyzed by LC-MS.It was found that at least 42 proteins were found to play role in repair and regeneration processes (Table 3.2).

The similar conditions of experiments of secretory protein profiling were performed but this time using plasma proteins of 15 healthy donors (children n=5; adult n = 5; elder n= 5). With the certitude of detection, all 2D-gel of the 15 donors similarly presented their specific migration pattern of children, adult and elder group. Table 3.3 indicated the proteins that found 100%, 80% and 50% similarity when compared among the three groups. There are 5 proteins that found 100% similarity in all groups including protein number 5.Q8N6Y2 (Leucine-rich repeat-containing protein), 16.Q9UBD9 (cardiotrophin-like cytokine factor 1), 30.Q60687 (sushi repeat-containing protein precursor), 37.P04179 (superoxide dismutase [Mn]) and 38.Q8IW75 (serpin A12).

The semi-quantitative measurements of proteins were performed by densitometric scanner for child, adult and elder groups (figure 3.12).

3.3 Up and down regulation of the biomarkers of repair and regeneration in degenerative disease groups

The similar conditions of experiments of plasma protein analysis was performed in degenerative disease groups including head injury, retinal detachment, stroke and CA colon. The plasma protein profiling was constructed in parallel with the CESs culture. The migration pattern of proteins of all degenerative disease group was similar to those of healthy donors (figure 3.17). Table 3.4 indicated that the 5 proteins including protein

number 5 Q8N6Y2 (Leucine-rich repeat-containing protein), 16Q9UBD9 (cardiotrophinlike cytokine factor 1), 30Q60687 (sushi repeat-containing protein precursor), 37P04179 (superoxide dismutase [Mn]) and 38Q8IW75 (serpin A12) were found as 100% common protein as healthy donors.

As can be seen, the 5 proteins were down regulated in case of head injury and retinal detachment, while upregulated in case of stoke and mixed of stroke, hypertension and CA-colon.

28181

In parallel with plasma protein analysis, the PBMCs were isolated and cultured in RPMI 1640 completed with 10% FBS and 1% penicilin-streptomycin. The cells were monitored under high resolution inverted microscope. Figure 3.13a, 3.14a, 3.15a and 3.16a show that the PBMCs obtained from all degenerative volunteers presented the residual bodies, granules, droplets and vacuole. The particular observation was for retinal detachment, the cell changed their morphology from round to irregular shape consist of fibrous like. The common types of cells obtained from degenerative groups can be classified as stress-cell, transformed cell and undergo death cells. It should be noted that there were not colonies of stem cells found in the culture system.

3.4 Effects of Siamois polyphenols on repair and regeneration volunteer with degenerative disease

After 1 month of treatment using Siamois polyphenols, the PBMCs were isolated and cultured. It was clear that the microenvironment of the culture was improved, the cells were found as round shape, neither residual bodies or granules/droplets were found inside of cells. In all case, the colony forming units of stem cells was clearly seen in particular neurovascular bundles (Figure 3.13b, 3.14b, 3.15b and 3.16b).

The semi-quantitative measurement of plasma proteins after treatment using Siamois polyphenols for one month was indicated in figure 3.18. As can be seen that in head injury, retinal detachment, the 5 proteins were upregulated while stroke including hypertension and CA-colon down regulation, however higher amount than those of control group.

3.5 Role of circulating endogenous stem cells (CESs) in neurogenesis in PD and MS

3.5.1 Determination of biomarkers for PD and MS

The similar conditions of experiments of plasma protein analysis was performed for PD and MS volunteers. The plasma protein profiling was constructed in parallel with the CESs culture. The migration pattern of proteins of PD and MS volunteers was similar to those of healthy donors (figure 3.21). Table 3.5 indicated 2 proteins including Leucine-rich repeat-containing protein (LRRC 17) and superoxide dismutase (Mn-SOD), while the 2 proteins name Leucine-rich repeat-containing protein (LRRC 17) and Serpin A12 as 100% similarity for PD and MS, respectively.

Live imaging of PBMCs derived from PD and MS volunteer was indicated in figure 3.19a and 3.20a. In both cases of pre-treatment, the PBMCs presented the residual bodies, granules, droplets and vacuoles. The common types of cells can be classified as stress-cell, transformed cell and undergo death cells. It should be noted that there were not colonies of stem cells found in the culture system.

3.5.2 Effects of Siamois polyphenols on CESs repair and regeneration of neurovascular bundles in PD and MS

Figure 3.19 and 3.20 show micrographs of CESs isolated from PD and MS volunteer, respectively. After 3, 11 and 22 weeks of treatments, the stress-cells and transformed cells were disappeared, while there were increased number of monocytes and the colonies of CESs. The monocytes and colonies of CESs become high number and bigger in size. Particularly at 22 week we observe the neurovascular bundle formation.

Then quantitative measurements of Leucine-rich repeat-containing protein (LRRC 17) and superoxide dismutase (Mn-SOD) for PD and Leucine-rich

repeat-containing protein (LRRC 17) and Serpin A12 for MS volunteer at different time interval as 1, 5, 7, 9 and 11 months, respectively. As shown in figure 3.22 and 3.23, after treatment of Siamois polyphenols show an up regulation of Leucine-rich repeat-containing protein (LRRC 17) and superoxide dismutase (Mn-SOD) for PD and Leucine-rich repeat-containing protein (LRRC 17) and Serpin A12 for MS volunteer.

3.5.3 Clinical symptom in PD and MS.

An improvement of motor symptoms can be evaluated using average scores as indicated in Figure 3.26 a (for PD) and b (for MS). As can be seen, the score of rigidity, bradykinesia, postural instability and dystonia decreased within 22 weeks for PD. Similar results were found for MS, the score of sensory disturbance, weakness, visual loss, ataxia, fatigue and bladder dysfunction progressively decreased. The sum score of pre-post treatment show decrease of symptom in 30weeks.

3.5.4 MRI in PD and MS.

It was clearly demonstrated that Siamois polyphenols efficiently trigger repair and regeneration processes by increasingin Leucine-rich repeatcontaining protein (RRC 17) and superoxide dismutase (Mn-SOD) in PD and increasing in Leucine-rich repeat-containing protein (RRC 17) and serpin A12 in MS. The Siamois polyphenols should regulate CESs to do repair and regeneration of neurovascular bundles. These events resulted in repair the damaged tissues then improves motor symptoms in PD and MS, can clearly confirm by MRI images as indicated in Figure 3.24 and 3.25 for PD and MS, respectively.

For Parkinson's disease we cannot perform MRI before treatment because of our subject is too much shake. After 3 month of treatment the patient can control movement of body and considerable improve clinical tremor allow performing MRI brain. MRI images show old infarction lesion in Midbrain of substantial nigra (figure 3.24a and b) and found degeneration of basal ganglia in figure 3.24 c and d.

Figure 3.25a, b and c demonstrated the MRI Brain of pre-treatment and posttreatment at 2 and 8 month of MS revealed small enhancement at left cerebral peduncle, size about 4mm. While decrease plaque in lateral ventricle. As well as the decrease lesion at C-spine in figure 3.25d, e and f.



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Figure 3.1 Morphology of circulating endogenous stem cells in RPMI 1640 (w/o phenol red) presence and in the absence FBS under inverted microscope (20x). gh t 11

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Figure 3.2 Micrographs of H&E staining cell in human serum; (a, f) keratinocytes, (b, c,d,) foam cells and (e) dendritic with the objective lens 20x



Figure 3.3 Micrographs of H&E staining cell in bovine serum; (a) Adipocyte, (b) Osteocyte, (c) Chondrocytes, (d) Leukocyte, (e) Neuron, (f) Stromal cell at 24 day with the objective lens 20x



Figure 3.4 Micrograph of peripheral blood stem cells at day 1, day 6, and day 24 after seeded. Serum of their own donor compared with the series using fetal bovine serum (10x).



Figure 3.5 Number of proliferating cells as a function of culture time were found in different cell phases including G0/G1, S, G2/M and sub G0/G1 (a), Diagram explaining the homeostasis (b)



Figure 3.6 Mix morphology of 3D-nanofibrous scaffold of nonwoven and aligned nanofibrous



Figure 3.7 SEM demonstrated that the tubular like structure of cell organizations



Figure 3.8 The circulating endogenous stem cells can preserve their own properties such as self renew and differentiation.



Figure 3.9 SEM demonstrated that the irregular forms of cell organizations and the cells used the fibers as support for hanging themselves in the space



Figure 3.10 The analysis of protein-protein interactions network



Figure 3.11 2D-gel electrophoresis, protein samples were processed using the pH 3-10 IPG strip condition 1mg/gel



Figure 3.12 Histogram of proteomic in normal group. (Adult/Child p value=0.009, Elderly /Child p value=0.017, Adult/Elderly p value=0.007)



(a) Pre-treatment

(b) Post-treatment (1month)

Figure 3.13 Micrographs of circulating endogenous stem cells pre and post-treatment with Siamois polyphenols (Retinal detachment)



(a) Pre-treatment

(b) Post-treatment (1month)

Figure 3.14 Micrographs of circulating endogenous stem cells pre and post-treatment with Siamois polyphenols (Stroke)



Figure 3.15 Micrographs of circulating endogenous stem cells pre and post-treatment with Siamois polyphenols (Head injury)



Figure 3.16 Micrographs of circulating endogenous stem cells pre and post treatment with Siamois polyphenols (Stroke, HT, CA colon)



Figure 3.17 2D-gel electrophoresis show protein map of Head injury, retinal detachment, CA colon and stroke in (a) pre-treatment and (b) post-treatment



Figure 3.18 Histogram of proteomic in normal group (Child,Adult,Old) compare with degenerative patients

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Post-treatment



Figure 3.19 Morphology of circulating endogenous stem cells, pre post-treatment of Parkinson's disease under inverted microscope; pre-treatment (a), 1month (b), 3month (c), 6month (d) and angiogenesis of culture (e)



Post-treatment

Figure 3.20 Morphology of circulating endogenous stem cells, pre post-treatment of Multiple sclerosis under inverted microscope; pre-treatment (a), 1month (b), 3month (c), 6month (d) and angiogenesis of culture (e)



Figure 3.21 2D-gel electrophoresis show protein map (a) Parkinson's disease (b) Multiple sclerosis.



Figure 3.22 Histogram of proteomic in Parkinson's disease, post: 1month, post: 5month, post: 7month, post: 9month and post: 11month



Figure 3.23 Histogram of proteomic in Multiple sclerosis, post: 1month, post: 5month, post: 7month, post: 9month and post: 11month



Figure 3.24 MRI imaging: Midbrain of substantial nigra (a,b), T1 and T2 : Degeneration of parts of the basal ganglia (c,d)



Figure 3.25 MRI Brain Pre-treatment (a) and Post -treatment (b and c) (4 month). MRI cspine Pre-treatment (d) and Post -treatment (e and f) (4 month)



Figure 3.26 Clinical symptom evaluation pre and post treatment with Siamois polyphenol in (a) Parkinson's disease and (b) Multiple sclerosis.

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Table 3.1 The determined parameters of cell kinetics including the mean rate of cell to re-entering to the cell cycle (\Box), move from S to G2/M (k2), move from G2/M to G0/G1 (k1) undergone apoptosis (β) and differentiation (α).

Donor	Kinetic parameter of Homeostasis						
	k2(s)	k1(G2/M)	$\beta(SubG0)$	a(Diff)	$\gamma(G0/G1)$		
AM1	2.1	4.9	0.8	1.25	4.95		
AM2	24.8	8.16	0.61	24.35	8		
AM3	3.32	7.7	0.45	21.82	32.4		
AF1	1.1	4.2	0.8	18.9	23.4		
AF2	8.8	0.002	5.4	1.702	1.7		
AF3	0.175	0.084	0.2	37.541	37.6		
EM1	1.2	1.04	1.518	19.678	20.4		
EM2	2.36	0.35	0.72	26.81	28.8		
EM3	1.72	0.51	0.18	16	18.05		
EF1	2.2	6.87	0.6	0.37	8.1		
EF2	0.182	0.12	2.42	3.038	0.92		
EF3	3.84	0.735	3.9	15.525	16.2		
Mean	4.3±6.8 cell/day (0.17±0.28 cell/hr)	2.8±3.2 cell/day (0.11±0.13 cell/hr)	1.4±1.6 cell/day (0.05±0.06 cell/hr)	15.58±11.82 cell/day (0.64±0.49 cell/hr)	16.71±12.25cell/day (0.69±0.51 cell/hr)		

Protein nameUniPort IDSecretion*PATHER Biological Process1 dynkin light chainP8187cCellular component movement2 alpha 1 spectrinP0259cCellular component movement3 Actin, stypedismit 1P0190cIntracellular protein transport, exceptois4 cde21nteracting protein 4Q15642cCellular process, transport5 p37NBQ8N042aCellular process16 Neuroffilment light polypeptideP07196cCellular process17 gamma soluble NSF attachment proteinQ97747cCellular process18 VinculinQ91750cCellular process19 Chouden 18Q90700cCellular process111 pattocatherin alpha C1Q91155cCell communication, cell cell athesian111 pattocatherin alpha C1Q91155cCell communication, cell cell afhesian112 unbihn heta A chainP08776bCell communication, cell cell afhesian113 candold key protein 1P3103cCell communication, cell cell signaling114 collagen, type XNVH, alpha 1Q91726cCell communication, minute system process115 cam PDE 1CQ41423cCell communication, intransport116 cardiorable inductor plateP3204cNervous system development117 clintamae receptor innotropicP3240cNervous system development218 chard albeion molecule 1.1P31434 <td< th=""><th></th><th></th><th></th><th></th><th></th><th></th></td<>						
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4. cdx2 interacting protein 4 Q15642 c Collular process, transport 5. p37NB Q8N012 a Cellular process 6. Neurofilament light polypeptide 197196 c Cellular process 7. gamma soluble NSF attachment protein Q9777 c Cellular process 1 9. Chandin 18 Q0VCN0 c Cellular process 1 9. Chandin 18 Q0VCN0 c Cellular process 1 11. patiekt glycoprotein B alpha P0759 c Cell communication, cell cell adhesion 1 12. Inhibit beta A chain P08476 b Cell communication, interfacton 1 13. Anyold like protein 1 P51693 c Cell communication, interfacton 1 14. collagen, type XXVII, alpha 1 Q812C6 c Cell communication, interfacton 1 14. collagen, type XXVII, alpha 1 Q91122 c Cell communication, interfacton 1 15. Cam PDE IC Q4123 c Cell communication, interfacton 1 15. Cam PDE IC Q41423 c Neurose system development 1 18. neural cell afhesion molecule L1	3. Actin, cytoplasmic 1	P60709	с	Intracellular protein transport, exocytosis	5.3	41.7
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6. Neurofilament light polypeptide P07196 c Cellular process 7. gamma soluble NSF attachment protein Q99747 c Cellular process 9. Chandin JS Q90700 c Cellular process P 9. Chandin JS Q90700 c Cellular process P 10. protocatherin alpha C1 Q911283 c Cell communication, cell-cell adhesion P 11. plattekt gycoprotein D alpha P07359 c Cell communication, cell-cell adhesion P 13. Amyloid like protein 1 P51693 c Cell communication, cell cell adhesion P 14. collagen, type XXVII, alpha 1 Q81ZC6 c Cell communication, lumane system process P 16. cardforphin like cytokine factor 1 Q91B199 b Jimmune system process P 16. cardforphin like cytokine factor 1 Q91B199 b Immune system process P 19. Brevican Q94GV7 b Nervous system development P 19. Brevican Q94GV7 b Nervous system development P 20. nidogen 1 P14543 c Immune resposes, eell edi spanding P <td>5. p37NB</td> <td>Q8N6Y2</td> <td>а</td> <td>Cellular process</td> <td>8.5</td> <td>51.8</td>	5. p37NB	Q8N6Y2	а	Cellular process	8.5	51.8
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8 vinculin P18206 c Cellular process 9. Chaudin-18 Q0VCN0 c Cellular process 10 protocatherin alpha C1 Q9H158 c Cell communication, cell cell athesion 11. platelet glycoprotein 1 alpha P07379 c Cell communication, cell cell athesion 12. Inhibit beta. A chain P08476 b Cell communication, cell profileration 13. Amyloid like protein 1 P51693 c Cell communication, minuite system process 14. collacen, type XXVII, alpha 1 Q8H2C6 c Cell communication, minuite system process 16. cardiotrophin like cytokine factor 1 Q9HB09 b Immune system process, cell cell signaling 17. Ghutamate receptor ionotropic P42261 c Cell communication, innaite instance response 10. Brevican Q94GW7 b Nervous system development 20. nidogen 1 P14543 c Nervous system development 21. brainspecific anglogenesis hiblior O14514 c Immune response, neurotransmitter secretion 22. phrin B1 P98172 c Nervous system development 2 23. plexin_A1 Q94UV2 a Nervous s	7. gamma-soluble NSF attachment protein	Q99747	с	Cellular process	5.3	34.7
9 Chaudin 18 Q0VCN0 c Cellelar process 10 protocalherin alpha C1 Q9H188 c Cell communication, cell cell adhesion 11 platelet glycoprotein Ib alpha P07559 c Cell communication, cell cell adhesion 11 inhib beta A chain P08476 b Cell communication, cell cell adhesion 13 Amyloid like protein 1 P51693 c Cell communication 14 collagen, type XXVI, alpha 1 Q8IZ66 c Cell communication, innate immune response 15 Cam/DFD 1C Q4H23 c Cell communication, innate immune response 16 cardiotrophin like cytokine factor 1 Q91B19 b Immune system process, cell cell signaling 17. Ghtamate receptor ionotropic P42261 c Cell communication, ion transport 18 neural cell adhesion molecule 1.1 P32004 c Nervous system development 20 hidogen 1 P14543 c Nervous system development 21 brain aspecific angiogenesis inhibitor O14514 c Immune response; neurotransmitter secretion 22 ophrin B1 P98172 c Nervous system development; cellular process 23 plexin A1 Q9U1W2 a N	8. vinculin	P18206	с	Cellular process	5.5	123
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11 platelet glycoprotein Ib alpha P07359 c Cell communication, cell cell adhesion 12 inhibin beta A chain P08476 b Cell communication, cell cell adhesion 13 Anyloid-like protein 1 P51693 c Cell communication, cell proliferation 14 collagen, type XXVII, alpha 1 Q81726 c Cell communication, inmate system process 15 Cam.PDE 1C Q41723 c Cell communication, inmate immune response 16 cardiotrophin like cytokine factor 1 Q918D9 b Immune system process, cell cell signaling 17 Ghutamate receptor ionotropic P42261 c Cell communication, ion transport 18 neural cell adhesion molecule 1.1 P32004 c Nervous system development 20 nidogen-1 P14543 c Nervous system development 21 brain specific angiogenesis inhibitor Q14514 c Immune response, neurotransmitter secretion 22 ophrin B1 P98172 c Nervous system development 23 23 plexin-A1 Q9119V2 a Nervous system development 24 24 huntingtin associated protein 1 P54257 c Nervous system development 25 25	10. protocadherin alpha C1	Q9H158	9.09	Cell communication, cell-cell adhesion	5.05	103.9
12 lnhlbin beta.A chain P08476 b Cell communication, cell proliferation 13 Amyloid like protein 1 P51693 c Cell communication, Immune system process 14 collagen, type XXVII, alpha 1 Q81ZC6 c Cell communication, Immune system process 15 Cam PDE 1C QM423 c Cell communication, Immune system process, cell-cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, not transport 18 neural cell adhesion molecule L1 P32004 c Nervous system process, cell-cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, not transport 18 neural cell adhesion molecule L1 P32004 c Nervous system development 20 nidogen 1 P14543 c Nervous system development 21 brain specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22 ephrin B1 P98172 c Nervous system development 22 23 plexin A1 Q91/W2 a Nervous system development, cellular process 26 24 nutringtin associated protein 1 P5257 c Nervous system development, cellular process	11. platelet glycoprotein Ib alpha	P07359	с	Cell communication, cell-cell adhesion	5.87	71.54
13. Amyloid-like protein 1 P51693 c Cell communication 14. collagen, type XXVII, alpha 1 Q81ZC6 c Cell communication, Immune system process 15. Cam PDE 1C Q14123 c Cell communication, Immune system process, cell cell signaling 16. cardiotrophin like cytokine factor 1 Q9UBD9 b Immune system process, cell cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, Ion transport 18. neural cell adhesion molecule 1.1 P32004 c Neurological system process 19. Brevican Q96GW7 b Nervous system development 20. nidogen-1 P14543 c Immune response, neurotransmitter secretion 22. ephrin B1 P9172 c Nervous system development 23. plexin-A1 Q91WV2 a Nervous system development 24. lumtingtin associated protein 1 P54227 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 29. neogenin Q92839	12. inhibin beta-A chain	P08476	-b ()	Cell communication, cell proliferation	8.3	47.442
14 collagen, type XXVII, alpha 1 Q8IZC6 c Cell communication, Immune system process 15 Cam-PDE 1C Q14123 c Cell communication, Immune system process, cell cell signaling 16 cardiotrophin like cytokine factor 1 Q9UBD9 b Immune system process, cell cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, ion transport 18 neural cell adhesion molecule L1 P32004 c Neurological system process 19. Brevican Q96GW7 b Nervous system development 20. nidogen-1 P14543 c Nervous system development 21. brain specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22. cphrin B1 P98172 c Nervous system development 24 23. plexin-A1 Q9UTV2 a Nervous system development 25 25. growth arrest-specific 2 O43903 c Nervous system development, angiogenesis 27 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 28 29. neogenin Q92859 c Nervous system development, angiogenesis <t< td=""><td>13. Amyloid-like protein 1</td><td>P51693</td><td>c</td><td>Cell communication</td><td>5.54</td><td>72.176</td></t<>	13. Amyloid-like protein 1	P51693	c	Cell communication	5.54	72.176
15. Cam PDE 1C Q14123 c Cell communication, innate immune response 16. cardiotrophin like cytokine factor 1 Q91BD9 b Immune system process, cell cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, ion transport 18. neural cell adhesion molecule L1 P32004 c Netrological system process 19. Brevican Q96GW7 b Nervous system development 20. nidogen 1 P14543 c Nervous system development 21. brain specific anglogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22. ephrin B1 P98172 c Nervous system development 21 23. plexin-A1 Q91IW2 a Nervous system development 21 24. huntingtin-associated protein 1 P54257 c Nervous system development, angiogenesis 26. extracellular lysophosphalipase D Q13822 a Nervous system development, angiogenesis 29. neogenin Q92889 c Nervous system development, angiogenesis 33 30. sushi repeat contalning protein protein Q14766 b Skeletal system development, angiogenesis <	14. collagen, type XXVII, alpha 1	Q8IZC6	c	Cell communication, Immune system process	9.83	186.892
16 cardiotrophin-like cytokine factor 1 Q9UBD9 b Immune system process, cell cell signaling 17. Glutamate receptor ionotropic P42261 c Cell communication, ion transport 18 neural cell adhesion molecule L1 P32004 c Netrological system process 19. Brevican Q96GW7 b Nervous system development 1 20. nidogen 1 P14543 c Nervous system development 1 21. brain specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 1 22. ephrin B1 P98172 c Nervous system development 1 23. plexin-A1 Q9UIW2 a Nervous system development 1 24. huntingtin-associated protein 1 P54257 c Nervous system development, angiogenesis 1 25. growth arrest-specific 2 O43903 c Nervous system development, angiogenesis 1 25. growth arrest-specific 2 O43903 c Nervous system development, angiogenesis 1 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 1 30. sushi repeat containing protein procursor<	15. Cam-PDE 1C	Q14123	c	Cell communication, innate immune response	8.88	80.76
17. Glutamate receptor ionotropic P42261 c Cell communication, ion transport 18. neural cell adhesion molecule L1 P32004 c Neurological system process 19. Brevican Q96GW7 b Nervous system development 20. nidogen-1 P14543 c Nervous system development 21. brain-specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22. cphrin B1 P98172 c Nervous system development, cell communication 23. plexin-A1 Q9UW2 a Nervous system development, cell communication 24. huntingtin associated protein 1 P54257 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat-containing protein precursor Q60687 a Angiogenesis, shelotal system development 31. Tolloid-like protein 1 Q43897 a Immune system process, cell cell signaling 33. SM	16. cardiotrophin-like cytokine factor 1	Q9UBD9	buy	Immune system process, cell-cell signaling	8.68	25.176
18 neural cell adhesion molecule 1.1 P32004 c Neurological system process 19.Brevican Q96GW7 b Nervous system development 20. nidogen.1 P14543 c Nervous system development 21. brain-specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22. cphrin B1 P98172 c Nervous system development, cell communication 23. plexin A1 Q9UW2 a Nervous system development, cell communication 24. huntingtin associated protein 1 P54257 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat containing protein precursor O66687 a Angiogenesis, sholod coagulation 31. Tolloid-like protein 1 Q43897 a Angiogenesis, skeletal system development 33. SMOC 1 Q914478 c Regulation of osteoblast differentiation 34. interleukin-25 isoform 1 pre	17. Glutamate receptor ionotropic	P42261	c	Cell communication, ion transport	7.79	101.506
19. BrevicanQ96GW7bNervous system development20. nidogen-1P14543cNervous system development21. brain-specific angiogenesis inhibitorO14514cImmune response, neurotransmitter secretion22. ephrin-B1P98172cNervous system development, cell communication23. plexin-A1Q9UW2aNervous system development, cell communication24. huntingtin-associated protein 1P54257cNervous system development, cellular process26. extracellular lysophospholipase DQ13822aNervous system development, angiogenesis27. Fibroblast growth factor 4P08620bNervous system development, angiogenesis29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat containing protein precursorO60687aAngiogenesis, skeletal system development31. Tolloid-like protein 1Q41766bSkeletal system development, cell communication33. SMOC 1Q9H293aImmune system process, cell-cell signaling34. interleukin 25 isoform 1 precursorQ9H293aImmune system process35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process37. superoxid dismutase [Mn]P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process39. Calpain 10Q9HC96cMetabolic process39. Calpain 10Q9HC96cLipid metabolism <td< td=""><td>18. neural cell adhesion molecule L1</td><td>P32004</td><td>c</td><td>Neurological system process</td><td>5.84</td><td>140.003</td></td<>	18. neural cell adhesion molecule L1	P32004	c	Neurological system process	5.84	140.003
20. nidogen 1 P14543 c Nervous system development 21. brain specific angiogenesis inhibitor O14514 c Immune response, neurotransmitter secretion 22. cphrin-B1 P98172 c Nervous system development, cell communication 23. plexin-A1 Q9UW2 a Nervous system development, cell communication 24. huntingtin associated protein 1 P54257 c Nervous system development 25. growth arrest-specific 2 O43903 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat-containing protein precursor O66687 a Angiogenesis, sheletal system development 31. Tolloid-like protein 1 O43897 a Angiogenesis, sheletal system development 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 34. interkeukin 25 isoform 1 precursor Q9H4F8 c Immune system process 35. HLA cla	19. Brevican	Q96GW7	Kber	Nervous system development	4.57	99.118
21. brain-specific angiogenesis inhibitor 014514 c Immune response, neurotransmitter secretion 22. cphrin-B1 P98172 c Nervous system development, cell communication 23. plexin-A1 Q9UW2 a Nervous system development 24. huntingtin associated protein 1 P54257 c Nervous system development 25. growth arrest specific 2 043903 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat containing protein precursor 060687 a Angiogenesis, shold coagulation 31. Tolloid-like protein 1 O43897 a Angiogenesis, shold coagulation 33. SMOC 1 Q9144F8 c Regulation of osteoblast differentiation 34. Interleukin.25 isoform 1 precursor Q914293 a Immune system process 35. HLA class I antigen P01892 c Immune system process 36. cathepsin W P56202	20. nidogen-1	P14543	c	Nervous system development	5.12	136.377
22. ephrin-B1P98172cNervous system development, cell communication23. plexin-A1Q9UIW2aNervous system development24. huntingtin associated protein 1P54257cNervous system development25. growth arrest-specific 2O43903cNervous system development, cellular process26. extracellular lysophospholipase DQ13822aNervous system development, angiogenesis27. Fibroblast growth factor 4P08620bNervous system development, angiogenesis28. semaphorin 3CQ99985aNervous system development, angiogenesis29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat-containing protein precursorO60687aAngiogenesis, skeletal system development33. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development33. SMOC 1Q9H4786cRegulation of osteoblast differentiation34. interleukin-25 isoform 1 precursorQ9H293aImmune system process36. cathepsin WP56202bImmune system process37. superoxide dismutase (Mn)P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process39. Calpain-10Q9HC96cLipid metabolism40. Peroxisomal 2,4 diencyl-CoA reductaseQ9NU11cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 20. like protein 1A8MW92cZing-ion binding	21. brain-specific angiogenesis inhibitor	014514	c	Immune response, neurotransmitter secretion	8.27	173.501
23. plexin-A1 Q9UIW2 a Nervous system development 24. huntingtin-associated protein 1 P54257 c Nervous system development 25. growth arrest-specific 2 O43903 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 28. semaphorin 3C Q99985 a Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat-containing protein precursor O60687 a Angiogenesis, sholod coagulation 31. Tolloid-like protein 1 O43897 a Angiogenesis, skeletal system development, cell communication 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 34. interleukin-25 isoform 1 precursor Q9H293 a Immune system process 36. cathepsin W P56202 b Immune system process 3 37. superoxide dismutase Mn P04179 c Metabolic process 3 39. Calpain-10 <t< td=""><td>22. ephrin-B1</td><td>P98172</td><td>c</td><td>Nervous system development, cell communication</td><td>9.1</td><td>38.007</td></t<>	22. ephrin-B1	P98172	c	Nervous system development, cell communication	9.1	38.007
24. huntingtin-associated protein 1 P54257 c Nervous system development 25. growth arrest-specific 2 O43903 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 28. semaphorin 3C Q99985 a Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat-containing protein precursor O60687 a Angiogenesis, sheletal system development 31. Tolloid-like protein 1 O43897 a Angiogenesis, skeletal system development 32. Latent transforming growth factor-binding protein Q14766 b Skeletal system development, cell communication 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 1 34. interleukin 25 isoform 1 precursor Q9H293 a Immune system process 2 36. cathepsin W P56202 b Immune system process 3 3 38. serpin A12 Q8IW75 a Metabolic p	23. plexin-A1	Q9UIW2	а	Nervous system development	6.49	211.067
25. growth arrest-specific 2 043903 c Nervous system development, cellular process 26. extracellular lysophospholipase D Q13822 a Nervous system development, angiogenesis 27. Fibroblast growth factor 4 P08620 b Nervous system development, angiogenesis 28. semaphorin 3C Q99985 a Nervous system development, angiogenesis 29. neogenin Q92859 c Nervous system development, angiogenesis 30. sushi repeat-containing protein precursor O60687 a Angiogenesis, blood coagulation 31. Tolloid-like protein 1 O43897 a Angiogenesis, skeletal system development, cell communication 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 34. interleukin-25 isoform 1 precursor Q9H293 a Immune system process, cell-cell signaling 35. HLA class I antigen P01892 c Immune system process 3 38. serpin A12 Q8IW75 a Metabolic process 3 39. Calpain-10 Q9HC96 c Metabolic process 4 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 4	24. huntingtin-associated protein 1	P54257	- Con	Nervous system development	4.68	75.506
26. extracellular lysophospholipase DQ13822aNervous system development, angiogenesis27. Fibroblast growth factor 4P08620bNervous system development, angiogenesis28. semaphorin 3CQ99985aNervous system development, angiogenesis29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat containing protein precursorO60687aAngiogenesis, blood coagulation31. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development32. Latent-transforming growth factor-binding proteinQ14766bSkeletal system development, cell communication33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation34. interleukin.25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process38. serpin A12Q8IW75aMetabolic process39. Calpain-10Q9HC96cMetabolic process40. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NUI1cLipid metabolism41. extended synaptotagmin.3A0FGR9cLipid metabolism42. PHD finger protein 10A8HW92cZing ion binding	25. growth arrest-specific 2	O43903	c	Nervous system development, cellular process	8.76	34.945
27. Fibroblast growth factor 4P08620bNervous system development, angiogenesis28. semaphorin 3CQ99985aNervous system development, angiogenesis29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat-containing protein precursorO60687aAngiogenesis, blood coagulation31. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development32. Latent-transforming growth factor-binding proteinQ14766bSkeletal system development, cell communication33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation134. interleukin-25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process336. cathepsin WP56202bImmune system process338. serpin A12Q8IW75aMetabolic process339. Calpain-10Q9HC96cMetabolic process440. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NUI1cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 1A8MW92cZing ion binding	26. extracellular lysophospholipase D	Q13822	a	Nervous system development, angiogenesis	7.14	98.994
28. semaphorin 3CQ99985aNervous system development, angiogenesis29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat-containing protein precursorO60687aAngiogenesis, blood coagulation31. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development32. Latent-transforming growth factor-binding proteinQ14766bSkeletal system development, cell communication33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation34. interleukin-25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process37. superoxide dismutase Mn P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process39. Calpain-10Q9HC96cMetabolic process40. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NUI1cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 10-like protein 1A8MW92cZing-ion binding	27. Fibroblast growth factor 4	P08620	b	Nervous system development, angiogenesis	9.73	22.048
29. neogeninQ92859cNervous system development, angiogenesis30. sushi repeat-containing protein precursorO60687aAngiogenesis, blood coagulation31. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development32. Latent-transforming growth factor-binding proteinQ14766bSkeletal system development, cell communication33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation34. interleukin-25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process37. superoxide dismutase Mn P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process39. Calpain-10Q9HC96cMetabolic process40. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NU11cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 20-like protein 1A8MW92cZing-ion binding	28. semaphorin 3C	Q99985	a	Nervous system development, angiogenesis	8.96	85.207
30. sushi repeat-containing protein precursorO60687aAngiogenesis, blood coagulation31. Tolloid-like protein 1O43897aAngiogenesis, skeletal system development32. Latent-transforming growth factor-binding proteinQ14766bSkeletal system development, cell communication33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation34. interleukin-25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process37. superoxide dismutase Mn P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process40. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NU11cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 20-like protein 1A8MW92cZing-ion binding	29. neogenin	Q92859	c	Nervous system development, angiogenesis	6.08	160.017
31. Tolloid-like protein 1 O43897 a Angiogenesis, skeletal system development 32. Latent-transforming growth factor-binding protein Q14766 b Skeletal system development, cell communication 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 34. interleukin-25 isoform 1 precursor Q9H293 a Immune system process, cell-cell signaling 35. HLA class I antigen P01892 c Immune system process 1 36. cathepsin W P56202 b Immune system process 1 37. superoxide dismutase Mn P04179 c Metabolic process 1 39. Calpain-10 Q9HC96 c Metabolic process 1 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 1 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 1 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding 1	30. sushi repeat-containing protein precursor	O60687	a	Angiogenesis, blood coagulation	7.05	52.972
32 Latent-transforming growth factor-binding protein Q14766 b Skeletal system development, cell communication 33. SMOC 1 Q9H4F8 c Regulation of osteoblast differentiation 34. interleukin-25 isoform 1 precursor Q9H293 a Immune system process, cell-cell signaling 35. HLA class I antigen P01892 c Immune system process 36. cathepsin W P56202 b Immune system process 37. superoxide dismutase [Mn] P04179 c Metabolic process 38. serpin A12 Q8IW75 a Metabolic process 40. Peroxisomal 2,4 dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	31. Tolloid-like protein 1	O43897	a	Angiogenesis, skeletal system development	5.69	114.709
33. SMOC 1Q9H4F8cRegulation of osteoblast differentiation34. interleukin-25 isoform 1 precursorQ9H293aImmune system process, cell-cell signaling35. HLA class I antigenP01892cImmune system process36. cathepsin WP56202bImmune system process37. superoxide dismutase Mn P04179cMetabolic process38. serpin A12Q8IW75aMetabolic process39. Calpain-10Q9HC96cMetabolic process40. Peroxisomal 2,4-dienoyl-CoA reductaseQ9NU11cLipid metabolism41. extended synaptotagmin-3A0FGR9cLipid transport42. PHD finger protein 20-like protein 1A8MW92cZing-ion binding	32. Latent-transforming growth factor-binding protein	Q14766	b	Skeletal system development, cell communication	5.63	186.796
34. interleukin-25 isoform 1 precursor Q9H293 a Immune system process, cell-cell signaling 35. HLA class I antigen P01892 c Immune system process 36. cathepsin W P56202 b Immune system process 37. superoxide dismutase [Mn] P04179 c Metabolic process 38. serpin A12 Q8IW75 a Metabolic process 39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Zing-ion binding	33. SMOC 1	Q9H4F8	t ^c S	Regulation of osteoblast differentiation	8.59	48.163
35. HLA class I antigen P01892 c Immune system process 36. cathepsin W P56202 b Immune system process 37. superoxide dismutase Mn P04179 c Metabolic process 38. serpin A12 Q8IW75 a Metabolic process 39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	34. interleukin-25 isoform 1 precursor	Q9H293	а	Immune system process, cell-cell signaling	8.73	20.33
36. cathepsin W P56202 b Immune system process 37. superoxide dismutase [Mn] P04179 c Metabolic process 38. serpin A12 Q8IW75 a Metabolic process 39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	35. HLA class I antigen	P01892	c	Immune system process	6.5	40.922
37. superoxide dismutase Mn P04179 c Metabolic process 38. serpin A12 Q8IW75 a Metabolic process 39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NUI1 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	36. cathepsin W	P56202	b	Immune system process	7.14	42.12
38. serpin A12 Q8IW75 a Metabolic process 39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	37. superoxide dismutase [Mn]	P04179	c	Metabolic process	8.35	24.722
39. Calpain-10 Q9HC96 c Metabolic process 40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	38. serpin A12	Q8IW75	а	Metabolic process	9.31	47.175
40. Peroxisomal 2,4-dienoyl-CoA reductase Q9NU11 c Lipid metabolism 41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	39. Calpain-10	Q9HC96	c	Metabolic process	7.97	74.952
41. extended synaptotagmin-3 A0FGR9 c Lipid transport 42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	40. Peroxisomal 2,4-dienoyl-CoA reductase	Q9NUI1	c	Lipid metabolism	9.38	30.778
42. PHD finger protein 20-like protein 1 A8MW92 c Zing-ion binding	41. extended synaptotagmin-3	A0FGR9	c	Lipid transport	8.68	100.035
	42. PHD finger protein 20-like protein 1	A8MW92	с	Zing-ion binding	6.39	115.01

Table 3.2 List of protein pattern analysis

Groups	100%	80-60%	59-40%	>40%
Adult-Elder	4	2	0	0
Elder	2	5	7	6
Elder-Child	1	0	0	1
Child	1	3	4	10
Child-Adult	0	2219	2	0
Adult	3	8	7	5.
Child-Adult-Elder	5		0	

Table 3.3 2D-gel of the 15 donors similarly presents their specific migration pattern of children, adult and elder group

Table 3.4 5 proteins including protein number 5 Q8N6Y2 (Leucine-rich repeatcontaining protein), 16Q9UBD9 (cardiotrophin-like cytokine factor 1), 30Q60687 (sushi repeat-containing protein precursor), 37P04179 (superoxide dismutase [Mn]) and 38Q8IW75 (serpin A12)

Protein name	UniProt ID	PANTHER Biological Process	pI	kDa
Leucine-rich repeat-	5.Q8N6Y2	Cellular process	8.5	51.8
containing protein	MA	IT THERE'		
Cardiotrophin-like	16.Q9UBD9	Immune system process, cell-cell	8.68	25.176
cytokine factor 1		signaling		
Sushi repeat-containing	30.060687	Angiogenesis, blood coagulation	7.05	52.972
protein precursor	IOUI		OTTR	J
Superoxide dismutase	37.P04179	Metabolic process	8.35	24.722
[Mn]	riak		10	al l
Serpin A12	38.Q8IW75	Metabolic process	9.31	47.175

Table 3.5 2 proteins including Leucine-rich repeat-containing protein (LRRC 17) and superoxide dismutase (Mn-SOD)

	100%	80-60%	59-40%	>40%
Parkinson [,] s disease	2	12	9	19
Multiple sclerosis	2	8	8	24



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