Improving health and viability in mitochondrial disease through inhibition of cytosolic translation and autophagy

Peng M. et al.

Supplemental Files

Fig S1. Effects of RC inhibition, probucol, and nutrients on AMPK activation.



Table S1. Table of all lifespan results in C. elegans gas-1(fc21) worms treated with
probucol, rapamycin, and cycloheximide

STUDY DRUG	Concentration	Buffer	Worm Stage at Treatment Initiation	Worm # Studied	Experimental Replicate #	Study Date	Lifespan Percent Change Relative to Untreated gas-1 Median	p value vs gas-1	p value vs N2	NOTES
	5 mM	2.7% DMSO	Dev	60	1	Oct-12	NA	NA	NA	TOXIC DMSO
	5 mM	2.7% DMSO	YA	60	1	Oct-12	NA	NA	NA	TOXIC DMSO
	500 uM	Ethanol	Dev	60	1	Dec-12	85	< 0.0001	< 0.0001	
Probucol	500 uM	Ethanol	YA	60	1	Dec-12	85	0.0869	< 0.0001	
TTOBUCCI	50 uM	Ethanol	Dev	60	1	Mar-13	117	0.0034	0.3994	
	50 uM	Ethanol	YA	60	1	Mar-13	108	0.0354	0.0961	
	5 uM	Ethanol	Dev	60	1	Mar-13	133	< 0.0001	0.4285	
	5 uM	Ethanol	YA	60	1	Mar-13	108	0.0003	0.894	
	2.5 uM	Ethanol	Dev	56	1	Dec-12	85	< 0.0001	< 0.0001	
	2.5 uM	Ethanol	YA	60	1	Dec-12	85	0.0025	< 0.0001	
	250 nM	Ethanol	Dev	56	1	Dec-12	85	0.0157	< 0.0001	
	250 nM	Ethanol	YA	56	1	Dec-12	85	0.0313	< 0.0001	
D	25 nM	Ethanol	Dev	56	1	Dec-12	100	0.5081	< 0.0001	
Rapamycin	25 nM	Ethanol	YA	60	1	Dec-12	100	0.648	< 0.0001	
	25 nM	Ethanol	Dev	59	2	Mar-13	100	0.114	0.0419	
	25 nM	Ethanol	YA	58	2	Mar-13	92	0.9537	0.0005	
	2.5 nM	Ethanol	Dev	54	1	Mar-13	117	0.0151	0.133	
	2.5 nM	Ethanol	YA	57	1	Mar-13	107	0.0066	0.1154	
	2.5 nM	Ethanol	Dev	60	2	Aug-14	100	0.512	< 0.0001	
	2.5 nM	Ethanol	YA	60	2	Aug-14	100	0.0689	< 0.0001	
	2.5 nM	Ethanol	YA	60	3	Sep-14	100	0.7236	< 0.0001	
	250 pM	Ethanol	Dev	60	1	Sep-14	82	0.0096	< 0.0001	
	2.5 uM	Water	Dev	60	1	Jul-14	82	0.0006	< 0.0001	
	2.5 uM	Water	YA	60	1	Aug-14	100	0.1294	< 0.0001	
	250 nM	Water	YA	60	1	Aug-14	100	0.8881	< 0.0001	
Cycloheximide	250 nM	Water	YA	60	2	Sep-14	100	0.4995	< 0.0001	
	25 nM	Water	YA	60	1	Aug-14	118	0.3689	< 0.0001	
	25 nM	Water	Dev	60	1	Sep-14	100	0.7099	< 0.0001	

*Dev, Development; YA, young adult day 1

Fig S2. Probucol effects on lifespan of C. elegans gas-1(fc21) CI deficient worms



Fig S3. Rapamycin effects on lifespan of C. elegans gas-1(fc21) CI deficient worms



Fig S4. Cycloheximide effects on *C. elegans* lifespan of *gas-1(fc21)* CI deficient worms



Fig S5. Cytosolic translation activity effects in human podocytes.





Fig S6. Cycloheximide effects in CIII (Antimycin A) or CV (oligomycin) inhibition & in CI-III (*FBXL4*) disease





Fig S7. Cycloheximide effects on mitochondrial physiology in human cells with pharmacologic or genetic based RC deficiencies.



Fig S8. Apoptosis is induced only by high-dose, short-duration rotenone



24 24 6 6 6 24 6 10 100



Human Podocytes 11 mM glucose

Cleaved CASP9 (37 kDa)

Cleaved PARP (89 kDa)



Fig S9. Mitophagy is activated in *FBXL4* deficient patient fibroblasts with RC complex I-III dysfunction.

A RC subunit (complex)	1. Control 2. FBXL4 3. Mother 4. Father	β-actin (loading control)
GRIM19 (Complex I)		
SDHA (Complex II)		
UQCRC2 (Complex III)		
MTCO1 (Complex IV)		
ATP5A (Complex V)		



Fig S10. Chloramphenicol effects on cell viability with RC inhibition and therapies





Fig S11. Long-term (24-48 hours) mitochondrial RC inhibition activates the ER stress response (GRP78 and PERK) in human podocytes and is prevented by cycloheximide.





Fig S12. Short-term mitochondrial RC inhibition induces the ER stress response (PERK and phosphor-EIF2α) in human podocytes.





Fig S13. Gene expression profiling in *C. elegans gas-1(fc21)* adult worms following 24 treatment with (A) 5 uM probucol and (B-C) 2.5 uM cycloheximide



C	
Eukaryotic-type ABC trans	
ABCA Sub family	
ABCA1 ABCA5 ABCA2 ADCA6 ABCA3 ABCA8 ABCA4 ABCA9 ABCA4 ABCA9 ABCA7 ABCA10 ABCA12	0 1
ABCA13	
ABCB Sub family ABCB2 ABCB1 ABCB3 ABCB4 ABCB9 ABCB9 ABCB10 ABCB10	ABCB6 ABCB11 MsbA ABCB7 HlyB ATM RaxB IntA/B AbcA SteA/B
ABCC Sub family	
ABCC1ABCC2ABCC2ABCC9ABCC3ABCC11ABCC5ABCC12ABCC6ABCC13	MdlBABCC4HasDCFTRPrsDABCC10RsaDEexDLapBCydC/D
ABCD Sub family	
ABCD1 PXA1/2 ABCD2 ABCD3 ABCD4 ABCG Sub family	
ABCG1 ABCG2	ABCGS PDRS
ABCG4 ABCG3	ABCG8 SNO2
Macrolide exporters	
MacB TylC	MsrA
Other p utative ABC transpo YojI PvdE SyrD YddA	rters

Fig S14. Pathway-level RNAseq transcriptome effects of treating *C. elegans* gas-1(fc21) mutant adult worms with cycloheximide, probucol or rapamycin.

Α	Cvcloheximide effects in	gas-1(fc21)
	oyolonickinnac checks in	gus nuer

UPREGULATED	KEGG	#Genes	#Genes	Enrichment	R Value	EDP	KEGG Bathway Namo
by CHX in gas-1	Pathway ID	Total	Measured	Score (ES)	r value	FDR	REGG Pathway Name
1	cel02010	16	16	2.03	7.85E-05	0.71%	ABC transporters
2	cel03010	142	115	1.61	9.49E-04	4.27%	Ribosome
3	cel04350	34	32	1.5	1.86E-03	5.57%	TGF-beta signaling pathway
4	cel04310	58	56	1.26	6.57E-03	14.78%	Wnt signaling pathway
5	cel04141	124	119	0.81	5.56E-02	92.23%	Protein processing in endoplasmic reticulum
6	cel03030	32	30	0.76	6.75E-02	92.23%	DNA replication
7	cel00350	22	21	0.73	7.67E-02	92.23%	Tyrosine metabolism
8	ce103040	106	102	0.65	1.05E-01	92.23%	Spliceosome
9	ce103060	21	20	0.63	1.12E-01	92.23%	Protein export
10	ce103008	79	58	0.61	1.17E-01	92.23%	Ribosome biogenesis in eukaryotes
11	cel03018	44	43	0.54	1.48E-01	92.23%	RNA degradation
12	cel00970	113	32	0.48	1.76E-01	92.23%	Aminoacyl-tRNA biosynthesis
13	ce100590	13	13	0.45	1.90E-01	92.23%	Arachidonic acid metabolism
						02 220/	ALC 811
14	ce100600	25	24	0.44	1.96E-01	92.23%	Sphingolipid metabolism
14 15	cel00600 cel04145	25 56	24 55	0.44	1.96E-01 2.28E-01	92.23% 92.23%	Sphingolipid metabolism Phagosome
14 15 DOWNREGULATED	cel00600 cel04145 KEGG	25 56 #Genes	24 55 #Genes	0.44 0.38 Enrichment	1.96E-01 2.28E-01	92.23%	SpringOlipid metabolism Phagosome
14 15 DOWNREGULATED by CHX in gas-1	cel00600 cel04145 KEGG Pathway ID	25 56 # Genes Total	24 55 #Genes Measured	0.44 0.38 Enrichment Score (ES)	1.96E-01 2.28E-01 P Value	92.23% 92.23% FDR	Springolipid metabolism Phagosome KEGG Pathway Name
14 15 DOWNREGULATED by CHX in gas-1 1	cel00600 cel04145 KEGG Pathway ID cel01040	25 56 # Genes Total 15	24 55 #Genes Measured 14	0.44 0.38 Enrichment Score (ES) -1.78	1.96E-01 2.28E-01 P Value 4.03E-04	92.23% 92.23% FDR 3.62%	Spningolipid metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids
14 15 DOWNREGULATED by CHX in gas-1 1 2	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190	25 56 # Genes Total 15 111	24 55 #Genes Measured 14 98	0.44 0.38 Enrichment Score (ES) -1.78 -1.14	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02	92.23% 92.23% FDR 3.62% 59.02%	Sphingolipia metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation
14 15 DOWNREGULATED by CHX in gas-1 1 2 3	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520	25 56 # Genes Total 15 111 32	24 55 #Genes Measured 14 98 30	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66%	Springolipic metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism
14 15 DOWNREGULATED by CHX in gas-1 2 3 4	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel04146	25 56 # Genes Total 15 111 32 60	24 55 #Genes Measured 14 98 30 59	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66%	Springolipio metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism Peroxisome
14 15 DOWNREGULATED by CHX in gas-1 2 3 4 5	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel04146 cel00450	25 56 #Genes Total 15 111 32 60 11	24 55 #Genes Measured 14 98 30 59 10	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 3.96E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66%	Springoupio metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nudeotide sugar metabolism Peroxisome Selenocompound metabolism
14 15 DOWNREGULATED by CHX in gas-1 2 3 4 5 6	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel00520 cel04146 cel00450 cel00051	25 56 # Genes Total 15 111 32 60 11 23	24 55 #Genes Measured 14 98 30 59 10 22	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93 -0.87	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 3.96E-02 4.28E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66%	Springolipic metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism Peroxisome Selenocompound metabolism Fructose and mannose metabolism
14 15 DOWNREGULATED by CHX in gas-1 1 2 3 4 5 6 6 7	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel004146 cel00450 cel00051 cel00500	25 56 # Genes Total 15 111 32 60 11 23 26	24 55 #Genes Measured 14 98 30 59 10 22 25	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93 -0.93 -0.87 -0.87	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 4.28E-02 4.64E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66% 59.66%	Springoujo metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism Peroxisome Selenocompound metabolism Fructose and mannose metabolism Starch and sucrose metabolism
14 15 DOWNREGULATED by CHX in gas-1 1 2 3 4 5 6 7 7 8	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel04146 cel00450 cel00051 cel00050 cel00380	25 56 #Genes Total 15 111 32 60 11 23 26 29	24 55 Measured 14 98 30 59 10 22 25 25 27	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93 -0.93 -0.87 -0.87 -0.87 -0.79	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 4.28E-02 4.28E-02 6.19E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66% 59.66% 59.66% 62.71%	Springoujojo metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nudeotide sugar metabolism Peroxisome Selenocompound metabolism Fructose and mannose metabolism Trytophan metabolism
14 15 DOWNREGULATED by CHX in gos-1 1 2 3 4 5 6 6 7 7 8 9	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel04146 cel00450 cel00051 cel00051 cel00050 cel00380 cel04140	25 56 # Genes Total 15 111 32 60 111 23 26 29 15	24 55 Measured 14 98 30 59 10 22 25 27 15	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93 -0.87 -0.8	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 4.28E-02 4.28E-02 6.19E-02 6.27E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66% 59.66% 59.66% 62.71% 62.71%	Springioupio metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism Peroxisome Selencocompound metabolism Fructose and mannose metabolism Starch and sucrose metabolism Tryptophan metabolism Regulation of autophagy
14 15 DOWNREGULATED by CHX in gas-1 2 3 4 5 6 6 7 8 9 10	cel00600 cel04145 KEGG Pathway ID cel01040 cel00190 cel00520 cel004051 cel00050 cel00300 cel00300 cel00310 cel00300	25 56 # Genes Total 15 111 32 60 11 23 26 29 15 15	24 55 #Genes Measured 14 98 30 59 10 22 25 27 15 14	0.44 0.38 Enrichment Score (ES) -1.78 -1.14 -0.95 -0.93 -0.87 -0.8 -0.72	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 3.96E-02 4.28E-02 4.28E-02 6.19E-02 6.27E-02 8.20E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66% 59.66% 62.71% 62.71% 70.21%	Springoujo metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nucleotide sugar metabolism Peroxisome Selenocompound metabolism Fructose and mannose metabolism Starch and sucrose metabolism Tryptophan metabolism Regulation of autophagy Fatty acid elongation
14 15 DOWNREGULATED by CHX in gos-1 2 3 4 5 6 7 7 8 9 10 11	ce100600 ce10145 KEGG Pathway ID ce101040 ce100190 ce100520 ce100450 ce100450 ce100450 ce100520 ce100450 ce100450 ce100450 ce100450 ce100450 ce100450 ce100450 ce100450 ce100450 ce1004555 ce1004555 ce1004555 ce1004555 ce10045555	25 56 # Genes Total 15 111 32 60 11 23 26 29 15 15 37	24 55 #Genes Measured 14 98 30 59 10 22 25 27 15 14 37	0.44 Enrichment Score (ES) -1.78 -1.14 -1.06 -0.95 -0.93 -0.87 -0.87 -0.8 -0.72 -0.68	1.96E-01 2.28E-01 P Value 4.03E-04 1.31E-02 1.99E-02 3.09E-02 4.28E-02 4.28E-02 4.64E-02 6.19E-02 6.27E-02 8.20E-02 9.09E-02	92.23% 92.23% FDR 3.62% 59.02% 59.66% 59.66% 59.66% 59.66% 62.71% 62.71% 70.21%	Springoujo metabolism Phagosome KEGG Pathway Name Biosynthesis of unsaturated fatty acids Oxidative phosphorylation Amino sugar and nudeotide sugar metabolism Peroxisome Selenocompound metabolism Fructose and mannose metabolism Fructose and mannose metabolism Trytopohan metabolism Trytopohan metabolism Regulation of autophagy Fatty acid elongation Calcium signaling pathway

С	Rapamycin effects	in gas-1(fc21
---	-------------------	---------------

	UPREGULATED	REGG	# Genes	#Genes	Enrichment	D Value	Value FDR	KEGG Bathway Namo
	by RAPA in gas-1	Pathway ID	Total	Measured	Score (ES)	r value	FDR	REGG Pathway Name
	1	cel04145	56	55	0.93	3.33E-02	97.55%	Phagosome
	2	cel03050	38	37	0.72	7.87E-02	97.55%	Proteasome
	3	cel00590	13	13	0.71	8.40E-02	97.55%	Arachidonic acid metabolism
Ē								
I	DOWNREGULATED	KEGG	#Genes	#Genes	Enrichment	P Value	EDP	KEGG Pathway Name
L	by RAPA in gas-1	Pathway ID	Total	Measured	Score (ES)	P value	FUK	REGG Pathway Name
I	1	cel00982	36	35	-1.29	6.27E-03	56.39%	Drug metabolism - cytochrome P450
I	2	cel03020	24	23	-0.93	3.54E-02	61.93%	RNA polymerase
I	3	cel03010	142	115	-0.87	4.31E-02	61.93%	Ribosome
I	4	cel04120	77	73	-0.87	4.45E-02	61.93%	Ubiquitin mediated proteolysis
I	5	cel04080	24	24	-0.83	5.13E-02	61.93%	Neuroactive ligand-receptor interaction
I	6	cel04140	15	15	-0.81	6.13E-02	61.93%	Regulation of autophagy
I	7	cel00040	20	19	-0.78	6.48E-02	61.93%	Pentose and glucuronate interconversions
I	8	cel00450	11	10	-0.78	6.83E-02	61.93%	Selenocompound metabolism
I	9	cel04310	58	56	-0.75	7.38E-02	61.93%	Wnt signaling pathway
I	10	cel04020	37	37	-0.73	7.56E-02	61.93%	Calcium signaling pathway
	11	cel00980	32	31	-0.7	8.71E-02	61.93%	Metabolism of xenobiotics by cytochrome P450
L	12	cel03040	106	102	-0.67	9.35E-02	61.93%	Spliceosome

D Consistent pathway-level effects in gas-1(fc21) by all 3 drugs (depicted for Probucol)

Probucol effects in gas-1(fc21)

B

by Probucol in gas-1 Pathway ID Total Measured Score (5) Fuller Form Record rativity name 1 cel40145 56 55 1.56 1.366-03 1.223k Phagesome 2 cel60302 33 32 0.44 51.236-02 97.95% Bast Transcription factors 3 cel60303 32 30 0.79 6.166-02 97.95% SNARE interactions in vesicular transport 5 cel60303 44 43 0.71 8.356-02 97.95% Arachiootic aid metabolism 6 cel03018 44 43 0.71 8.356-02 97.95% Nucleotide excision repair 7 cel0302 33 33 0.69 8.252-02 97.95% Nucleotide excision repair 8 cel0070 11 17 1.348-02 97.95% Nucleotide excision repair 9 cel00071 44 1.158 3.866-04 Atfr. Fatty acid degradation 1 cel00072 44 1.	UPREGULATED	KEGG	#Genes	#Genes	Enrichment	R Value	EDP	KEGG Bathway Namo
1 cel0302 33 55 1.56-03 1.23% Phageone 2 cel0302 33 32 0.84 5.13-02 9.79% Basal transcription factors 3 cel0303 22 30 0.79 6.10-22 9.79% DNA epilication 4 cel04030 23 23 0.74 7.61-02 9.79% SNA& interactions in vesical arransport 5 cel00505 13 13 0.74 8.156-02 9.79% SNA& factification 6 cel00301 33 0.69 8.256-02 9.79% Nucleotide excision repair 7 cel0302 33 33 0.69 8.256-02 9.79% Nucleotide excision repair 8 cel00770 11 10 7.17 9.186-03 9.79% Partochenate and CoA biosynthesis DDWNREGULATED KEGG #Genes #Genes Enforment Purale FDR KEGG Pathway Name 9 cel00071 14 -1.58 9.86-03 <	by Probucol in gas-1	Pathway ID	Total	Measured	Score (ES)	r value	FDK	KEGG Pathway Name
2 cel3032 33 32 0.44 5.13-02 97.95% Bast transcription factors 3 cel3030 32 30 0.79 6.105-02 97.95% DNA replication 4 cel40130 32 30 0.74 7.61E-02 97.95% SNARE interactions invasiular transport 5 cel0030 13 13 0.74 8.15E-02 97.95% Arachidonic acid metabolism 6 cel03018 44 43 0.71 8.35E-02 97.95% Machidonic acid metabolism 7 cel03020 33 33 0.69 8.25E-02 97.95% Partothenate and CoA biosynthesis DOWNREGULATED KEGG #Genes #Indremetabolism Pratus FOR KEGG Pathway Name 1 cel00082 36 37 -7.15 1.88E-06 0.17% Drug metabolism - cytochrome P450 3 cel00082 15 14 -1.42 4.50E-08 8.11% Metabolism of semobolicis by cytochrome P450 4 cel	1	cel04145	56	55	1.55	1.36E-03	12.23%	Phagosome
3 cel0303 32 30 0.74 6.16-62 97.5% DNA replication 4 cel04130 23 23 0.74 7.61-02 97.5% SNARE interactions in vesicular transport 5 cel0300 34 43 0.74 7.61-02 97.5% SNARE interactions in vesicular transport 6 cel0301 44 43 0.71 8.354-02 97.5% Nucleotide excision repair 7 cel03420 33 33 0.69 8.322-02 97.5% Nucleotide excision repair 8 cel00770 11 0.71 9.184-02 9.75% Partotherate and CoA biosynthesis DOWNREGULATED KEGG #f Genes #fortherat from the source 5.027 5.038-02 1.7% Drag metabolism - optochome P450 2 cel00070 32 31 -1.39 3.945-03 8.11% Metabolism of acenobiotics by cytochrome P450 3 cel00070 13 12 -1.24 6.564-8 8.11% Fetty aid dengation	2	cel03022	33	32	0.84	5.13E-02	97.95%	Basal transcription factors
4 cel0430 23 23 0.74 7.516.02 97.55K SNARE interactions in vesicalar transport 5 cel00500 13 13 0.74 8.166-02 97.55K SNARE interactions in vesicalar transport 6 cel00500 33 13 0.74 8.166-02 97.55K Nucleotide excision repair 7 cel0070 11 11 0.71 9.186-02 97.55K Nucleotide excision repair 8 cel00770 11 11 0.71 9.186-02 97.55K Nucleotide excision repair 9 rebotorin 27 55K Fathemate Pathemate Pathemate <t< td=""><td>3</td><td>cel03030</td><td>32</td><td>30</td><td>0.79</td><td>6.10E-02</td><td>97.95%</td><td>DNA replication</td></t<>	3	cel03030	32	30	0.79	6.10E-02	97.95%	DNA replication
5 cel00590 13 13 0.74 8.16E-02 97.95% Arachidonic acid metabolism 6 cel00510 44 43 0.71 8.35E-02 97.95% RNA degradation 7 cel0320 33 0.69 8.25C-02 97.95% Nucleotide exision repair 8 cel00770 11 11 0.71 9.18E-02 97.95% Pantorthenate and CoA biosynthesis DOWNREGULATED KEGG #Genes #Genes Enrichment P.Value FDR KEGG Pathway Name 1 cel00582 36 35 -2.15 1.88E-65 0.17% Drug metabolism - cytochrome P450 2 cel00581 32 31 -1.38 3.86E-04 4.44% Fathy acid degradation 3 cel00582 32 31 -1.34 3.86E-08 8.11% Metabolism - cytochrome P450 4 cel00062 15 14 -1.42 4.56E-08 8.11% Fathy acid degradation 3 cel00062 15	4	cel04130	23	23	0.74	7.61E-02	97.95%	SNARE interactions in vesicular transport
6 cel03018 44 43 0.71 8.386-02 97.95% RNA degradation 7 cel03201 33 0.69 8.325-02 97.95% Nucleotide excision repair 8 cel0070 11 11 0.71 9.156-02 97.95% Nucleotide excision repair DOWNREGULATED by Probucol in gar-1 REGG If Genes If Genes If Genes File Pata File REGG Pathway Name 1 cel00782 36 35 -2.15 1.886-05 0.17% Drag metabolism -cytochrome P450 2 cel00071 44 41 -1.58 9.866-04 4.4% Faity add degradation 3 cel00580 32 31 -1.39 3.946-03 8.11% Metabolism of zenobiotics by cytochrome P450 4 cel00050 15 14 -1.42 4.506-38 8.11% Faity add biosynthesis of unsaturated faity acids 6 cel00050 15 13 -1.23 6.866-38 7.5% Peroxisome <td< td=""><td>5</td><td>cel00590</td><td>13</td><td>13</td><td>0.74</td><td>8.16E-02</td><td>97.95%</td><td>Arachidonic acid metabolism</td></td<>	5	cel00590	13	13	0.74	8.16E-02	97.95%	Arachidonic acid metabolism
7 cel03420 33 33 0.69 8.52E-02 97.55K Nucleotide excision repair 8 cel0070 11 11 0.71 9.18E-02 97.95K Pantohenate and CoA biosynthesis DOWNREGULATED KEGG FGemes RGenes Enrinhmet Pulate FDR KEGG Pathway IN 1 cel0052 36 35 -2.15 1.88E-95 0.17% Dumetabolism -ytochrome P450 2 cel00581 32 31 -1.38 9.86E-04 4.44% Fatty acid degradation 3 cel00582 35 -2.15 9.86E-04 4.44% Fatty acid degradation 3 cel00580 12 -1.12 9.86E-04 4.44% Fatty acid degradation 4 cel00502 15 14 -1.42 4.56E-03 8.11% Metabolism of semobiotics by cytochrome P450 6 cel00104 15 14 -1.42 4.56E-03 8.11% Metabolism of semobiotics by cytochrome P450 6 cel00050 13<	6	cel03018	44	43	0.71	8.39E-02	97.95%	RNA degradation
8 cel00770 11 11 0.71 9.18-02 97.95% Pantothenate and CoA biosynthesis DOWNREGULATED by Probucol in gos-1 KEGG cel00582 # Genes Total KeGenes Score (12) Fundomental Score (12) Palaue Fundomental Fundomental Score (12) Fundomental Fundomental Score (12) Fundomental Fun	7	cel03420	33	33	0.69	8.92E-02	97.95%	Nucleotide excision repair
DOWNREGULATED by Probucol in gas-1 REGG P tabusy Potal # Genes Total # Genes Measured Enrichment Score (5) P Value P Value FDR KEGG Pathway Name 1 cel0092 36 35 -2.15 1.88-65 0.17% Drag metabolism - cytochrome P450 2 cel00091 32 31 -1.39 3.946-08 8.11% Fatty acid degradation 3 cel00092 32 31 -1.39 3.946-08 8.11% Metabolism of xenobiotics by cytochrome P450 4 cel00020 37 37 -1.34 3.986-08 8.11% Metabolism of xenobiotics by cytochrome P450 5 cel00020 15 14 -1.42 4.506-38 8.31% Fatty acid beingstrons 6 cel00040 15 13 -1.23 6.607-48 5.35% Fatty acid biosynthesis 10 cel00500 15 13 -1.24 2.026% Petrois and glucuronate metabolism 11 cel00501 18 -1.16 1.362-02 1.20% Terpenoid backhone biosynthesis	8	cel00770	11	11	0.71	9.18E-02	97.95%	Pantothenate and CoA biosynthesis
DOWNROUGHZU KEGG Pathwayi N Defines indefines Proluce FOR KEGG Pathwayi Name 1 cell0082 36 35 -2.15 1.88-55 0.17% Drumetabolismcytochrome P400 2 cell00971 44 -1.58 9.86-04 4.44% Fatty acid degradation 3 cell00971 44 -1.58 9.86-04 4.44% Fatty acid degradation 3 cell00980 32 31 -1.39 9.86-04 4.44% Metabolism of renobiotics by cytochrome P400 4 cell0040 37 37 -1.44 4.86-08 8.11% Metabolism of renobiotics by cytochrome P400 6 cell01040 15 14 -1.42 4.86-08 8.11% Fatty acid dengration 6 cell01040 15 13 -1.23 1.86-08 5.78% Peroxisome 9 cell00446 60 59 -1.23 8.62-03 1.78% Retiro inmetabolism 10 cell0050 12 12	DOWINDECULIATED	KECC	#C	#C	Fasishment			
1 cellosts 3 21.5 1.88E-05 0.1% Drug metabolism - cytochrome P450 2 cellosts 3 3 9.86E-04 4.44% Fatury aid degradation 3 cellosts 2 2 1.39 3.94E-04 4.44% Fatty aid degradation 4 cellosts 2 2 1.39 3.94E-08 8.11% Metabolism of senobiotics by cytochrome P450 4 cellosts 2 2 1 -1.39 3.94E-08 8.11% Metabolism of senobiotics by cytochrome P450 5 cellosts 15 1.4 -1.42 4.58E-08 8.11% Fatty aid degradation 6 cellosts 15 1.4 -1.24 4.58E-08 8.33% Biosynthesis of unstrurted fatty aids 7 cellosto 13 12 1.29 6.65E-08 5.3% Peroxisome 9 cellosto 15 13 -1.23 1.65E-02 1.3% Retion lontabone biosynthesis 10 cellosto 2	bullet bu	Redd Rothway ID	# Genes	Moorwood	Enrichment	P Value	FDR	KEGG Pathway Name
1 Clicologie 1-15	1	col00982	36	25	-2 15	1 885.05	0.17%	Drug metabolism - cytochrome P450
1 Cellopsia 2 1.3 3.964 Xeros Metabolism of senobiotics by cytochrome P400 4 Cellopsia 37 -1.34 3.985-03 8.11% Metabolism of senobiotics by cytochrome P400 5 Cellopsia 37 -1.34 3.985-03 8.11% Metabolism of senobiotics by cytochrome P400 6 Cellopsia 15 14 -1.34 6.41E-03 8.33% Biosynthesis of unsaturated fatty acids 7 Cellopsia 13 12 -1.29 6.63E-03 8.53% Fatty acid biosynthesis 9 Cellopsia 18 -1.12 1.126-02 11.20% Terpenoid backbone biosynthesis 10 Cellopsia 18 -1.15 1.386-02 12.38% Retinol metabolism 11 Cellopsia 18 -1.16 1.386-02 2.39% Butanoate metabolism 12 Cellopsia 23 1.21 0.22 2.39% Butanoate metabolism 13 cellopsia 23 2.01 1.30.85-02 2.12.1%	2	cel00071	44	41	-1.58	9.865-04	A AA%	Fatty acid degradation
4 cellood 1.2 -1.24 -3.26 -3.23 -3.26 -3.23 -3.26 -3.23 -3.26 -3.23 -3.26 -3.26 -3.23 -3.26 -3.	2	ce100071	22	21	-1.30	3.945-03	8 11%	Metabolism of venobiotics by cytochrome P450
• Celosical 57 -1.2 <th< td=""><td></td><td>col04020</td><td>27</td><td>27</td><td>1.35</td><td>2 005 02</td><td>0.11%</td><td>Calcium signaling nathway</td></th<>		col04020	27	27	1.35	2 005 02	0.11%	Calcium signaling nathway
5 Cellobol 1.5 1.4 4.14 6.1128 Line in Exception 6 cellobol 1.3 4.1.24 8.358 Biosynthesis of unsuranted fatty acids 7 cellobol 1.3 4.1.24 6.814.48 8.538 Biosynthesis of unsuranted fatty acids 8 cellobal 1.3 1.2 -1.29 6.616.49 7.68* 9 cellobal 1.3 -1.23 1.126.02 11.20% Terpenoid backbone biosynthesis 10 cellobas 1.8 1.16 1.384.22 2.38% Retinol metabolism 11 cellobas 2.2 2.1 1.04 2.256/20 18.7% Yorkine metabolism 12 cellobas 2.0 1.9 -1.01 2.716/22 2.95% Buaranate metabolism 13 cellobas 2.3 2.46/22 2.312% Suffur relay system 14 cellobas 2.3 2.95% Pentose and gluconnet entabolism 15 cellobas 3.3 -0.9 4.466	*	cel00062	15	1/	-1.34	4 50E-03	8 11%	Eatty acid elongation
0 Cellulation 1.3 1.4 1.2.9 6.3.12 Controls of the control of control of controls of the control of controls of the control of control of controls of co	5 C	col01040	15	14	1.42	4.30E-03	0.11/6	Picconthesis of unsaturated fatty aside
A Cellottal Col	7	col00061	12	12	1.34	6 625 02	0.33/6	Eathy acid biocupthoric
a Central Control Source Source Source Formal 9 cellobso 15 13 -1.23 1.124 1.124 1.124 10 cellobso 18 -1.16 1.384.02 12.39K Retinol metabolism 11 cellobso 12 -1.14 2.124.22 11.20K Terpenoid hackbone hissynthesis 12 cellobso 22 21 -1.04 2.254.22 18.70% Tyrosine metabolism 13 cellobso 20 19 -1 3.034.02 20.95% Pentose and glucuronate interconversions 14 cellobs1 23 22 -0.91 3.856.02 23.12K Sulfar relay system 15 celloba1 12 10.9 3.856.02 23.12K Sulfar relay system 16 celloba1 15 15 -0.9 4.66.02 23.65% Begulation of autophagy 18 celloba0 25 25 -0.83 5.906.42 23.65% Storto an	,	col04146	13	50	1.25	0.032-03	0.33/6	Boroxicomo
3 Centrol 1.3 1.1.5 1.1.64	8	col00000	15	12	1.23	1 125 02	11 20%	Torponoid backhone biocunthesis
10 Centods 1.4 <th1.4< <="" td=""><td>9 10</td><td>100920</td><td>10</td><td>10</td><td>1.25</td><td>1.120-02</td><td>12.20%</td><td>Patinal matchelism</td></th1.4<>	9 10	100920	10	10	1.25	1.120-02	12.20%	Patinal matchelism
11 Centrols 12 Call -Low Late-value Late-value -Low	10	ce100850	10	21	-1.10	2.305.02	12.36%	Retinol metabolism
12 Centrols 20 13 -Lut 2.1.2+92 2.4.2/37 Duality term relations 13 cell0004 20 19 -1 3.08/20 2.9.6% Pentors and functionate interconversions 14 cell00051 23 22 9.1 3.86/20 2.9.6% Pentors and functionate interconversions 15 cell04122 12 11 0.93 3.86/20 2.3.12% Suffur relay system 16 cell0010 39 33 0.9 4.46/20 2.3.6% Givpolysic / Givconcegenetics 17 cell04140 15 15 0.9 4.46/20 2.3.6% Sepulation of autophapy 18 cell00200 26 25 0.83 5.90/20 3.21.2% Starcia and strateginant 19 cell00200 23 31 0.79 4.56/20 2.3.5% Starcia and strateginant	11	100050	22	21	-1.04	2.295-02	10.70%	Tyrosine metabolism
13 Centore 20 13 -14 Subset of Subset	12	100000	20	19	-1.01	2.710-02	20.29%	Butanoate metabolism
14 Cerrorot 23 24 -0.91 3.86/-92 2.3.12/n Produce and managementationant 15 cell04122 11 -0.93 3.85/-02 23.12/n Froutowe and managementationant 16 cell0010 39 33 -0.9 4.46E-02 23.63% Glycohysis / Gluconeogenesis 17 cell00500 15 15 -0.9 4.46E-02 23.63% Regulation of autophany 18 cell00500 26 25 -0.83 5.96E-02 32.12% Cirtate cycle (TCA cycle) 19 cell00500 23 31 -0.79 6.59E-02 31.21% Cirtate cycle (TCA cycle)	15	100051	20	19	-1	3.035-02	20.90%	Fentose and glucuronate interconversions
13 Central 2 12 11 -0.93 3.65-92 2.3.67 Sature 11-11 16 cell00010 39 33 -0.9 4.466-02 23.63 Glycolysis (Liouxonegenesis) 17 cell04140 15 15 -0.9 4.466-02 23.63% Regulation of autophagy 18 cell00500 26 25 -0.83 5.90-62 23.25% Starch and surces metabolism 19 cell00200 23 31 -0.79 6.55-62 23.12K Cirtate cycle (TCA cycle)	14	104122	25	11	-0.91	3.000-02	23.12%	Fructose and mannose metabolism
10 Cellolul 33 -0.5 -4.46-22 23.65% Cellolular Cellolula	15	100010	20	22	•0.55	3.03E*02	23.12/0	Churchurin / Churchananania
17 Certosta 13 -0.3 4-00 c 25.00% meganatoring 18 cel00500 26 25 -0.83 5-906-02 29.50% Starch and sucrose metabolism 19 cel00020 33 31 -0.79 6.596-02 21.21% Cirtate cycle [TCA cycle]	10	cel0010	39	33	-0.9	4.405-02	23.03%	Bogulation of autonbagy
18 celoudu 20 23 -0.83 5.90E-02 25.30% Starth and Sucrose metadolism	17		20	25	0.02	F. 005.02	20.50%	Charach and autopation matchaliam
15 Leiouzo 35 31 -0.75 0.392-02 31.21% Littale (VLe (TLA CYCLe)	10	col00020	20	25	-0.85	5.502-02	23.30%	Citrate cucle (TCA cucle)
20 col04010 64 62 0.71 8.050 2.6.202/ MADV signaling national	19	col04010	55	51	0.75	0.355-02	31.21/0	MARK cignaling pathway
20 CEIVHOLO 04 02 -0.71 8.00E-02 30.29% WARK Signaling patriway	20	col00290	20	27	-0./1	0.002-02	30.29%	Tomtonbon motobolism
21 CEIVOUR 27 27 "0.00 3.30C*02 30.02/0 ITyptoprian metabolism	21	col00300	40	2/	-0.00	0.205-02	30.02/0 26 029/	Valine loucine and icoloucine degradation
22 colono20 40 30 "0.03 5.30C*02 30.02/0 value, reucine and isoleucine degradation 23 colono20 1/ 1/ 1/ .0.68 0./15.02 36.82% Sulfur matabolism	22	ce100200	14	30	-0.05	9.41F-02	36 82%	Sulfur metabolism

'PHAGOSOME' UPREGULATION



'REGULATION OF AUTOPHAGY' DOWNREGULATION

