

Supplementary Information

Genomice and Transcriptomic Analysis for Identification of Genes and Interlinked Pathways Mediating Artemisinin Resistance in *Leishmania donovani*

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Supplementary Figures and Tables:

Figure S1.

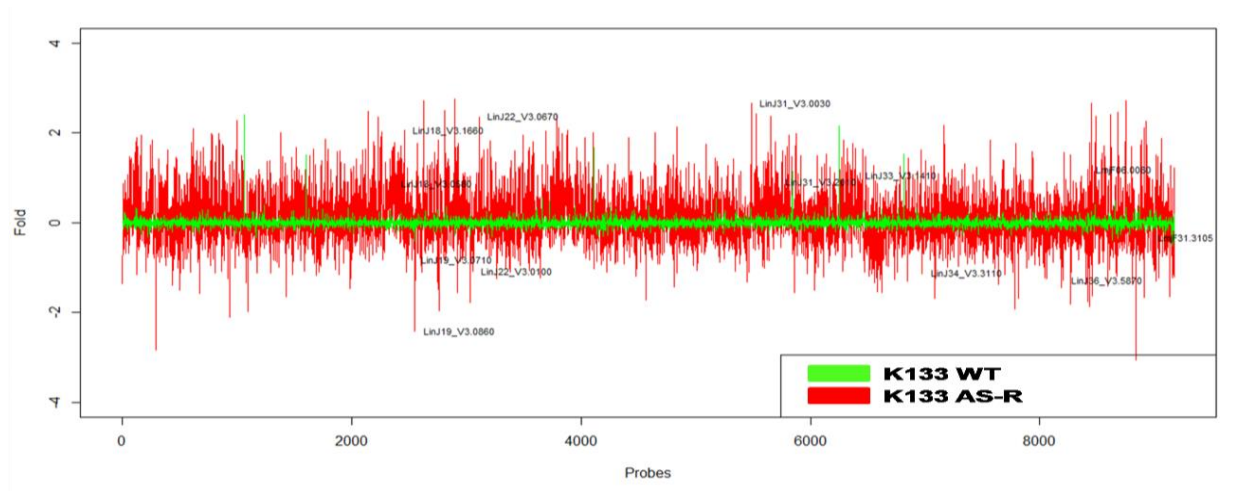


Figure S1: Comparative transcriptional responses following ART adaptation in *L. donovani*. Overlap of log2 transformed K133 AS-R and K133 WT expression ratio plotted as a function of chromosomal location of probes representing the full genome microarray. The plot represents the average values of three independent hybridizations for each isolate.

Table S1: List of genes validated for their modulated expression by Quantitative real time-PCR

S.N o.	Primer Name	Gene Name/ Gene ID	Function/relevance	Primer Sequence
1	AQP1	Aquaglyceroporin (LinJ.31.0030)	Metal ion transmembrane transporter activity, integral to membrane; transmembrane transport; transporter activity; water transport.	F- 5'CAGGGACAGCTCGAGGGTAA AA3' R- 5'GTTACCGGCGTGAAAGACAG TG3'

2	A2	A2 protein (LinJ.22.0670)	Cellular response to stress	F- 5'GTTGGCCCGCTTTCTGTTGG3' R- 5'ACCAACGTCAACAGAGAGAGGG3'
3	ABCG1	ATP-binding cassette protein subfamily G, member 1 (LmjF.06.0080)	ATP binding, ATPase activity, coupled to transmembrane movement of substances, phosphopantetheine binding	F- 5'GATCTTCTTGAATGTGCGGGC C3' R- 5'CCACCAGCACTGCAAGAATC TG3'
4	GATase	Glutamine aminotransferase (LinJ.33.1410)	Putative cysteine conjugate beta-lyase, aminotransferase - like protein biosynthetic process	F- 5'GCAGGCTCTCAACGCCATATT C3' R- 5'AGCTTCCAGTTCTCAGCGGAT T3'
5	PECH	peroxisomal enoyl-co hydratase (LinJ.18.0580)	Putative enoyl-CoA hydratase activity, Fatty acid metabolism	F- 5'AGATTATCCAGCGCTCCTCAC C3' R- 5' TTGATGGCAGCTTGGTACTCGA 3'
6	ATPP	autophagocytosis protein (LinJ.33.0320)	autophagy; cytoplasm; protein transport	F- 5'CCCTGAGAGCGTGCAAGACT 3' R- 5'CGCCAGAGTCATCGTCGTCT 3'
7	Tpx	Tryparedoxin-like protein (LinJ.31.2010)	Hypothetical protein, involved in redox metabolism in trypanosomatids	F- 5'CTCATCTGCTTCTCCGCCCA 3' R- 5'CAGTCTCGGCCGATCGTCTG3

				,
8	VPS	vacuolar protein sorting-like protein (LinJ.25.2280)	vesicle docking involved in exocytosis vesicle-mediated transport	F- 5'GTTCTTAGCAGGGTGTACGA G3' R- 5' GGAAAGCAAGTGAACGACAA C3'
9	HDH	haloacid dehalogenase-like hydrolase (LinJ.28.1480)	Hydrolase activity	F- 5'TGACCAGAATGCCCATCAAG 3' R- 5'GCTGGTGATAATGTAGTCCGG 3'
10	AUT	Autophagy-related protein (LinJ.19.0860)	Autophagy-related protein ATG8/AUT7/APG8/PA Z2, putative (ATG8B.3)	F- 5'CCTCTCCAGACCACCAATGT CC3' R- 5'GGCGAGCGTCACCTTCTTGA3 ,
11	gMDH	glycosomal malate dehydrogenase (LinJ.19.0710)	glycolysis, malate metabolic process	F- 5'GCGTGGATGTGTTTGTGATGG T3' R- 5'TTCGTCACAATGCAGAACAC CG3'
12	ItRS	Isoleucyl-tRNA synthetase (LinJ.36.5870)	isoleucyl-tRNA aminoacylation, tRNA aminoacylation for protein translation, translation	F- 5'CCGCTGGATCGACTTTGACA AC 3' R- 5'AGGAAGTATGTGTTGGGGTC GG3'
13	AC	Adenylate cyclase-like protein	cyclic nucleotide biosynthetic process, intracellular signaling	F- 5'CGGTATGGAAAGGTGTACGA AG3'

		(LinJ.28.0090)	pathway, transport Purine metabolism	R- 5'TCGATGTATGACTGCAAGAC G3'
14	CYPs	Cytochrome p450-like protein (LinJ.34.3110)	Electron carrier activity, heme binding, monooxygenase activity	F- 5'TACATCCCCTTCAGCTGCGG3' R- 5'CGCTCGTAAACCTCGCCAAC3 ,
15	CBS	cystathionine beta-synthase (LinJ.17.0300)	Endogenous control gene	F- 5'GAAGTACACGGTGGAGGCTG 3' R- 5'CGCTGATCACGACCTTCTTC3'
16	GAPDH	Glyceraldehyde s-3 Phosphatedehy drogenase (LinJ.30.2990)	Endogenous control gene	F- 5'CGCCGATGTCAACTGGATG3' R- 5'GCTCCTTCTTCAGCGTGTGCG3'

Table S2: Pattern of up-regulated and down-regulated gene expression in K133 AS-R parasite:

Fold changes	AS-R, Up-regulated	AS-R, Down regulated
>2.0-3.0	70	85
>3.0 – 4.0	20	16
>4.0	12	5
Total genes	102	106
Percent of modulated genes	1.11%	1.15%

Footnote: The percent modulated genes calculated from the total 9,170 genes obtained in QC after filter

Table S3: Genes differentially modulated with their functional categories in K133 AS-R *L. donovani* parasites.

S.N O	GENE ID	FOLD CHANG E K133AS- R/ K133WT	REGULA -TION	DESCRIPTION
NUCLEIC ACID METABOLISM				
1.	LmjF23.snRNA.01	5.49	UP	small nuclear RNA, U1 snRNA
2.	LinJ.32.2210	2.81	UP	Hypothetical protein , conserved catalytic activity, hydrolase activity, zinc ion binding
3.	LinJ.35.2650	2.49	UP	Hypothetical protein , unknown function DNA binding
4.	LmjF23.snRNA.02	2.36	UP	small nuclear RNA, U3 snRNA
5.	LinJ.06.0750	2.30	UP	Hypothetical protein , conserved Regulation of transcription , DNA binding
6.	LinJ.15.0140	2.27	UP	hypothetical protein, conserved nucleic acid binding, zinc ion binding
7.	LinJ.05.0830	2.12	UP	Methylthioadenosinephosphorylase, putative transferase activity, transferring pentosyl groups
8.	LinJ.33.0580	2.09	UP	Hypothetical protein , conserved RNA ligase activity
9.	LinJ.25.1350	2.03	UP	DNA-directed RNA polymerase ii Transcription
10.	LmjF31.snRNA.01	2.01	UP	small nuclear RNA, U2 snRNA
11.	LinJ.36.1680	3.79	DOWN	Universal minicircle sequence binding protein, putative; nucleic acid binding, zinc ion binding
12.	LmjF27.rRNA.25	3.76	DOWN	28S ribosomal RNA (LSU-beta)
13.	LinJ.28.1000	3.30	DOWN	Endonuclease/exonuclease/phosphatase-like protein; endonuclease & exonuclease activity
14.	LinJ.36.2040	3.20	DOWN	Nucleoside transporter 1, putative nucleoside transmembrane transporter activity;

				guanosine salvage; inosine salvage.
15.	LinJ.33.3390	2.93	DOWN	h1 histone-like protein
16.	LinJ.29.0260	2.67	DOWN	Thymine-7-hydroxylase, putative Iron ion binding; oxidoreductase activity.
17.	LinJ.36.1710	2.29	DOWN	Poly-zinc finger protein 2, putative Nucleic acid binding ; Zinc ion binding
18.	LinJ.33.3340	2.22	DOWN	Small nuclear ribonucleoprotein SmD2 RNA splicing
19.	LinJ.36.0800	2.22	DOWN	Uncharacterized protein Metal ion binding
20	LinJ.30.3630	2.12	DOWN	Zinc finger-domain protein, putative nucleic acid binding ; zinc ion binding
PROTEIN , AMINO ACID METABOLISM				
21.	LinJ.33.0320	3.57	UP	Autophagy-related protein 3 autophagy ; protein transport
22.	LinJ.18.1130	2.95	UP	Hypothetical protein, conserved zinc ion binding
23.	LinJ.32.3080	2.91	UP	Tubulin-tyrosine ligase-like protein tubulin-tyrosine ligase activity protein modification process
24.	LinJ.36.3230	2.72	UP	Putative lipoate protein ligase ligase activity ; octanoyltransferase activity ; cellular protein modification process ; lipoate biosynthetic process
25.	LinJ.36.0590	2.66	UP	Ubiquitin-like protein, putative damaged DNA binding nucleotide-excision repair, proteasomal ubiquitin-dependent protein catabolic process
26.	LinJ.27.0310	2.45	UP	Methylmalonyl-coenzyme a mutase, putative
27.	LinJ.19.1560	2.34	UP	Peptidylprolylisomerase-like protein isomerase activity ; protein folding
28.	LinJ.31.0290	2.16	UP	Hypothetical protein, L-ascorbic acid binding, iron ion binding, oxidoreductase activity
29.	LinJ.33.1410	2.07	UP	Cysteine conjugate beta-lyase, aminotransferase- like protein

				lyase activity ; pyridoxal phosphate binding ; transaminase activity ; biosynthetic process
30.	LinJ.04.0160	7.11	DOWN	Cell adhesion ; metalloendopeptidase activity
31.	LinJ.19.0860	5.32	DOWN	Autophagy-related protein autophagy
32.	LinJ.09.0180	4.28	DOWN	Autophagy-related protein autophagy
33.	LinJ.20.1320	3.86	DOWN	calpain-like cysteine peptidase, putative,calpain-like cysteine peptidase, Clan CA, family C2
34.	LinJ.19.0820	3.83	DOWN	Autophagy-related protein Autophagy
35.	LinJ.20.1220	2.47	DOWN	Putative calpain-like cysteine peptidase calcium-dependent cysteine-type endopeptidase activity ;proteolysis.
36.	LinJ.20.1210	2.37	DOWN	Putative calpain-like cysteine peptidase calcium-dependent cysteine-type endopeptidase activity ; proteolysis.
37.	LinJ.11.0640	2.18	DOWN	Putative aminopeptidase aminopeptidase activity ; manganese ion binding ; metalloexopeptidase activity ; proteolysis.
38.	LinJ.36.6600	2.13	DOWN	Ubiquitin-protein ligase, putative acid-amino acid ligase activity ; protein modification process ; ubiquitin-protein transferase activity
39.	LinJ.33.2670	2.03	DOWN	Putative carboxypeptidase metallocarboxypeptidase activity ;proteolysis.
40.	LinJ.31.1140	2.01	DOWN	Putative N-acyl-L-amino acid amidohydrolase metallopeptidase activity ;protein dimerization activity;proteolysis ;aminoacylase activity
TRANSLATION				
41.	LmjF21.0960	3.18	UP	Hypothetical protein, conserved ATP binding ; aminoacyl-tRNA ligase activity
42.	LmjF27.rRNA. 32	8.27	DOWN	28S ribosomal RNA (LSU-delta, M2)

43.	LinJ.33.2880	2.54	DOWN	Translation initiation factor IF-2, putative GTP binding ;translation initiation factor activity; GTPase activity.
44.	LinJ.36.5870	2.43	DOWN	Isoleucyl-tRNA synthetase, putative ATP binding ;aminoacyl-tRNA ligase activity ; isoleucine-tRNA ligase activity ; nucleotide binding; zinc ion binding.
45.	LinJ.36.1490	2.14	DOWN	Translation elongation factor 1-beta, putative translation elongation factor activity
LIPID METABOLISM				
46.	LinJ.14.1450	2.59	UP	Myo-inositol-1-phosphate synthase, inositol-3-phosphate synthase, putative (INO1) Inositol biosynthetic process, metabolic process, phospholipid biosynthetic process
47.	LinJ.13.0200	2.25	UP	Hypothetical protein, triglyceride lipase activity, zinc ion binding hydrolase activity ; lipid metabolic process .
48.	LmjF19.1345	2.64	DOWN	Glycerol uptake protein, putative integral component of membrane [GO:0016021]
49.	LinJ.14.0670	2.13	DOWN	Fatty acid elongase, putative fatty acid biosynthetic process, long-chain fatty acid biosynthetic process
50.	LinJ.03.0280	2.13	DOWN	Hypothetical protein, (pseudogene) fatty acid biosynthetic process ; iron ion binding; oxidoreductase activity
CARBOHYDRATE METABOLISM				
51.	LinJ.36.6550	3.48	DOWN	Glucose transporter, lmgT2 fructose transmembrane transporter activity ; galactose transmembrane transporter activity; glucose transmembrane transporter activity ; mannose transmembrane transporter activity ; glucose import
52.	LinJ.22.0002	3.43	DOWN	Hypothetical protein
53.	LmjF06.1290	3.37	DOWN	Hypothetical protein, heme binding, transition metal ion binding

54.	LinJ.34.4290	3.20	DOWN	Lipophosphoglycan biosynthetic protein (lpg2) GDP-mannose transmembrane transporter activity nucleotide-sugar transport
55.	LmjF36.6290	3.15	DOWN	Glucose transporter, lmg2 fructose transmembrane transporter activity ; galactosetransmembrane transporter activity ; glucose transmembrane transporter activity ; mannose transmembrane transporter activity ; carbohydrate transport
56.	LinJ.36.6560	3.10	DOWN	Glucose transporter, lmg1 fructose transmembrane transporter activity ; galactosetransmembrane transporter activity; glucose transmembrane transporter activity; mannose transmembrane transporter activity
57.	LinJ.34.4360	2.38	DOWN	D-isomer specific 2-hydroxyacid dehydrogenase- like protein
58.	LmjF34.1400	2.33	DOWN	D-isomer specific 2-hydroxyacid dehydrogenase- protein
59.	LmjF07.0805	2.01	DOWN	phosphoacetylglucosaminemutase-like protein,acetylglucosaminephosphomutase, putative,N-acetylglucosamine-phosphate mutase, putative
CELL MOVEMENT				
60.	LinJ.25.2050	2.96	UP	Kinesin, putative ATP binding, microtubule motor activity
61.	LinJ.18.0530	2.15	UP	Hypothetical protein, conserved GTPase activator activity ; cell morphogenesis
62.	LinJ.06.1070	2.12	UP	Kinesin, putative ATP binding, microtubule motor activity
63.	LinJ.32.0240	2.93	DOWN	Dynein light chain, flagellar outer arm, putative microtubule-based process
64.	LinJ.05.0290	2.62	DOWN	ARP2/3 complex 16kDa subunit, putative Arp2/3 complex-mediated actin nucleation ; regulation of actin filament polymerization
65.	LmjF05.0285	2.58	DOWN	ARP2/3 complex 16kDa subunit, putative regulation of actin filament polymerization

66.	LinJ.08.1280	2.38	DOWN	Tubulin beta chain (Fragment) GTP binding, GTPase activity, structural molecule activity ; microtubule-based movement ; microtubule-based process ; protein polymerization
67.	LinJ.29.0520	2.17	DOWN	Actin severing and dynamics regulatory protein actin filament depolymerization
68.	LinJ.23.1570	2.14	DOWN	Putative dynein heavy chain ATP binding, ATPase activity, microtubule motor activity
69.	LinJ.05.0380	2.08	DOWN	Putative microtubule-associated protein
70.	LinJ.20.1340	2.04	DOWN	Calpain-like cysteine peptidase, putative small myristoylated protein-2, putative;(SMP-2) flagellar cell motility ; flagellar pocket membrane.
71.	LinJ.35.5310	2.04	DOWN	Hypothetical protein, conserved
72.	LinJ.33.2770	2.03	DOWN	Dynein intermediate chain, putative
CELL MEMBRANE PROTEIN				
73.	LinJ.17.0020	5.56	UP	integral component of membrane
74.	LinJ.31.0460	5.36	UP	Amastin, putative integral component of membrane
75.	LmjF31.0450	4.36	UP	Amastin, putative
76.	LinJ.31.1900	3.51	UP	Hypothetical protein integral component of membrane
77.	LmjF08.0770	3.44	UP	Amastin-like protein
78.	LinJ.29.3030	3.37	UP	Amastin, putative integral component of membrane
79.	LinJ.08.0690	3.35	UP	Amastin-like protein integral component of membrane
80.	LmjF31.1855	3.35	UP	Hypothetical protein

				integral component of membrane
81.	LinJ.08.0680	3.30	UP	Amastin-like protein integral component of membrane
82.	LinJ.08.0720	3.29	UP	Amastin-like protein integral component of membrane
83.	LinJ.24.1300	3.18	UP	Amastin-like surface protein-like protein integral component of membrane
84.	LinJ.08.0700	2.77	UP	Amastin-like protein integral component of membrane
85.	LinJ.34.3430	2.62	UP	Hypothetical protein (pseudogene) integral component of membrane
86.	LmjF34.0500	2.58	UP	Amastin-like protein
87.	LinJ.26.1440	2.54	UP	Hypothetical protein, integral component of membrane
88.	LinJ.34.1150	2.39	UP	Amastin-like surface protein, putative integral component of membrane
89.	LinJ.29.3000	2.38	UP	Amastin, putative integral component of membrane
90.	LinJ.26.2590	2.08	UP	Hypothetical protein, conserved, ATP binding; D-alanine-D-alanine ligase activity; metal ion binding; methyltransferase activity; peptidoglycan biosynthetic process
91.	LinJ.30.2810	2.07	UP	Hypothetical protein, conserved integral component of membrane
92.	LinJ.25.2390	2.05	UP	Hypothetical protein, conserved protein name -Palmitoyltransferase protein-cysteine S-palmitoyltransferase activity ; zinc ion binding
93.	LmjF31.1165	2.02	UP	Hypothetical protein integral component of membrane ; heme binding
94.	LinJ.34.1690	2.01	UP	Amastin-like surface protein, putative
95.	LinJ.04.0170	4.68	DOWN	Surface antigen-like protein
96.	LinJ.21.1090	2.94	DOWN	integral component of membrane
97.	LinJ.05.0900	2.81	DOWN	Surface antigen-like protein

				protein binding
98.	LinJ.10.0070	2.52	DOWN	Dehydrogenase-like protein integral component of membrane ;binding ; catalytic activity ; oxidoreductase activity.
99.	LinJ.04.0180	2.37	DOWN	Surface antigen-like protein
100.	LinJ.04.0190	2.36	DOWN	Surface antigen-like protein
101.	LinJ.33.2980	2.34	DOWN	integral component of membrane
102.	LinJ.14.0500	2.26	DOWN	integral component of membrane
103.	LinJ.34.1050	2.13	DOWN	Amastin-like protein
104.	LinJ.33.0220	2.12	DOWN	integral component of membrane
105.	LinJ.08.0600	2.10	DOWN	integral component of membrane
106.	LinJ.24.1310	2.08	DOWN	Amastin-like surface protein-like protein integral component of membrane
107.	LinJ.23.1130	2.02	DOWN	integral component of membrane
CELL SIGNALLING				
108.	LinJ.35.0780	3.36	UP	CBS domain protein, conserved
109.	LinJ.33.1930	3.15	UP	Protein kinase, putative,dual-specificity protein kinase, putative ATP binding, protein kinase activity, protein serine/threonine kinase activity, protein tyrosine kinase activity
110.	LinJ.22.1450	3.11	UP	Ser/thr protein phosphatase, putative hydrolase activity
111.	LinJ.25.1410	2.99	UP	Hypothetical protein, conserved regulation of signal transduction
112.	LinJ.17.0440	2.08	UP	Protein kinase, putative ATP binding, protein kinase activity, protein serine/threonine kinase activity, protein

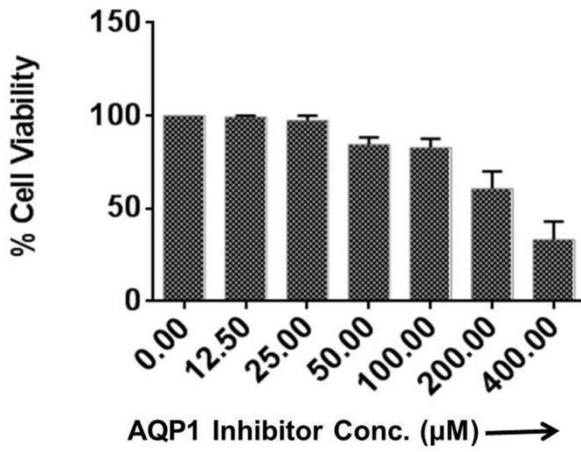
				tyrosine kinase activity
113.	LinJ.34.0840	2.39	DOWN	Serine/threonine-protein phosphatase metal ion binding; phosphoprotein phosphatase activity .
114.	LinJ.16.0240	2.38	DOWN	Protein tyrosine phosphatase-like protein protein tyrosine phosphatase activity, protein tyrosine/serine/threonine phosphatase activity protein dephosphorylation
115.	LinJ.28.0090	2.26	DOWN	Adenylatecyclase-like protein Adenylatecyclase activity ; heme binding ; oxygen binding ; intracellular signal transduction
TRANSPORTER				
116.	LinJ.31.0030	6.33	UP	Aquaglyceroporin (AQP1) metal ion transmembrane transporter activity
117.	LinJ.18.1270	2.70	UP	Hypothetical protein, conserved binding; transport.
118.	LinJ.11.0520	2.60	UP	Nucleobase transporter (NT4) Nucleobase transmembrane transporter activity
119.	LinJ.18.0040	2.54	UP	Transporter, putative,major facilitator superfamily protein (MFS), putativetransporter activity
120.	LinJ.18.0400	2.31	UP	UDP-galactose transporter (LPG5B) sugar: hydrogensymporter activity; nucleotide-sugar transport
121.	LmjF06.0080	2.27	UP	ATP-binding cassette protein subfamily G, member 1, putative (ABCG1), ATP binding, ATPase activity, coupled to transmembrane movement of substances, phosphopantetheine binding
122.	LinJ.10.0900	2.17	DOWN	Nuclear transport factor 2, putative,ntf2-like transport
123.	LinJ.33.3410A	2.16	DOWN	ABC transporter family-like protein ATPase activity ; ATP binding
124.	LinJ.07.1340	2.15	DOWN	Amino acid transporter, putative (AAT19)

125.	LinJ.22.0100	2.11	DOWN	Amino acid permease, putative (AAT22)
STRESS PROTEIN				
126.	LinJ.22.0670	5.13	UP	A2 protein protein binding ;cellular response to stress.
127.	LinJ.18.1660	4.17	UP	Gamma-glutamylcysteinesynthetase (GSH1) glutathione biosynthetic process, response to reactive oxygen species, trypanothione biosynthetic process glutamate-cysteine ligase activity
128.	LinJ.31.0530	2.38	UP	Hypothetical protein, conserved heat shock protein binding ; unfolded protein binding; protein folding .
129.	LinJ.33.0940	2.25	UP	dnaj chaperone-like protein heat shock protein binding ;unfolded protein binding; protein folding.
130.	LinJ.28.1480	2.06	UP	Haloaciddehalogenase-like hydrolase, putative catalytic activity, hydrolase activity
OXIDATION - REDUCTION				
131.	LinJ.31.1190	2.56	UP	Hypothetical protein, heme binding ; transition metal ion binding
132.	LinJ.25.2150	2.40	UP	Hypothetical protein, conserved electron carrier activity, oxidoreductase activity 2 iron, 2 sulfur cluster binding; nitrite reductase [NAD(P)H] activity ; nitrate assimilation
133.	LinJ.34.3110	2.19	DOWN	Cytochrome p450-like protein electron carrier activity ; heme binding; monooxygenase activity
134.	LinJ.19.1490	2.14	DOWN	oxidoreductase-like protein electron carrier activity, oxidoreductase activity
OTHERS				

135.	LinJ.21.0070	5.64	UP	Hypothetical protein, conserved
136.	LinJ.18.0610	3.20	UP	Hypothetical protein, conserved zinc ion binding
137.	LinJ.28.1700	2.52	UP	Hydrolase, alpha/beta fold family, putative hydrolase activity
138.	LinJ.33.0750	2.46	UP	Hypothetical protein, conserved
139.	LinJ.29.3020	2.02	UP	Tuzin like protein, putative
140.	LinJ.06.1350	2.98	DOWN	Hypothetical protein heme binding; transition metal ion binding.
141.	LinJ.01.0010	2.57	DOWN	Hypothetical protein binding
142.	LinJ.36.4270	2.33	DOWN	Phosphoglyceratemutase family member 5, putative protein serine/threonine phosphatase activity.
143.	LinJ.02.0280	2.24	DOWN	Hypothetical protein, conserved binding
144.	LinJ.33.2460	2.07	DOWN	Hypothetical protein, catalytic activity; metabolic process.

Figure S2.

A. AQP1 Inhibitor



B. Verapamil

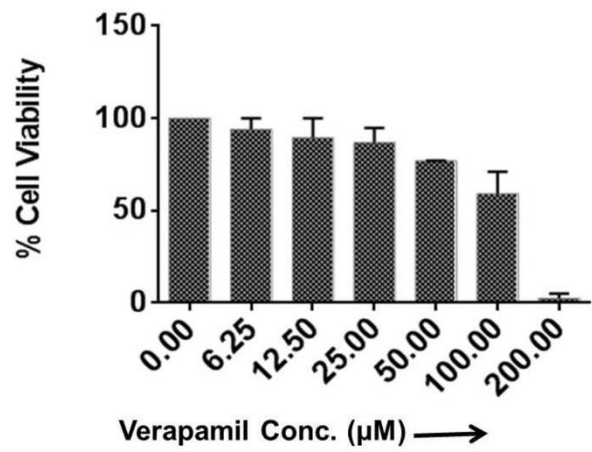


Figure S2: Cytotoxicity of (A) AQP1 inhibitor and (B) Verapamil to host macrophages (mice PECs). % cell viability $\pm$ SD with the increasing drug concentration has been plotted here. The data was obtained from three independent experiments.