

### **Supplementary material to:**

Gene Regulatory Control of Myocardial Energy Metabolism Predicts Postoperative Cardiac Function in Patients Undergoing Off-pump Coronary Artery Bypass Graft Surgery: Role of Anesthetic Choice

by E. Lucchinetti, C. Hofer, L. Bestmann, M. Hersberger, J. Feng, M. Zhu, L. Furrer, M.C. Schaub, R. Tavakoli, M. Genoni, A. Zollinger, and M. Zaugg

including:

- Supplementary Information
- Three supplementary tables (Table S1 to Table S3)
- Three supplementary figures (Figure S1 to Figure S3)

### **Supplementary information**

Gene Set Enrichment Analysis (GSEA) is designed to identify genes with co-ordinate transcriptional regulation within functionally related groups of genes, which are called gene sets in GSEA. Signaling pathways are examples of gene sets. Pathway information was curated using knowledge from online databases and from peer-reviewed literature sources. For further details about gene sets and statistical procedures, please see the online supplementary material to the original publication (Subramanian et al. PNAS 2005;102:15545-50), which is freely available under:

<http://www.pnas.org/cgi/data/0506580102/DC2/1>

Public online pathway sources are: Biocarta (<http://www.biocarta.com>), Human Protein Reference Database ([www.hprd.org](http://www.hprd.org)), Gene Ontology ([www.geneontology.org](http://www.geneontology.org)), Signal Transduction Knowledge Environment STKE: (<http://stke.sciencemag.org/cm/>), GenMAPP (<http://www.genmapp.org>), Signaling Pathway Database SPAD (<http://www.grt.kyushu-u.ac.jp/spad/menu.html>), Kyoto Encyclopedia of Genes and Genomes (<http://www.genome.jp/kegg/kegg2.html>), the AfCS-Nature Signaling Gateway ([www.signaling-gateway.org](http://www.signaling-gateway.org)), the Cancer Genome Anatomy Project (<http://cgap.nci.nih.gov/Pathways>). The G-CSF pathway was curated by the authors according to the following peer-reviewed publications:

1. Harada et al. G-CSF prevents cardiac remodeling after myocardial infarction by

activating the Jak-Stat pathway in cardiomyocytes. Nat Med 2005; 11: 305-11

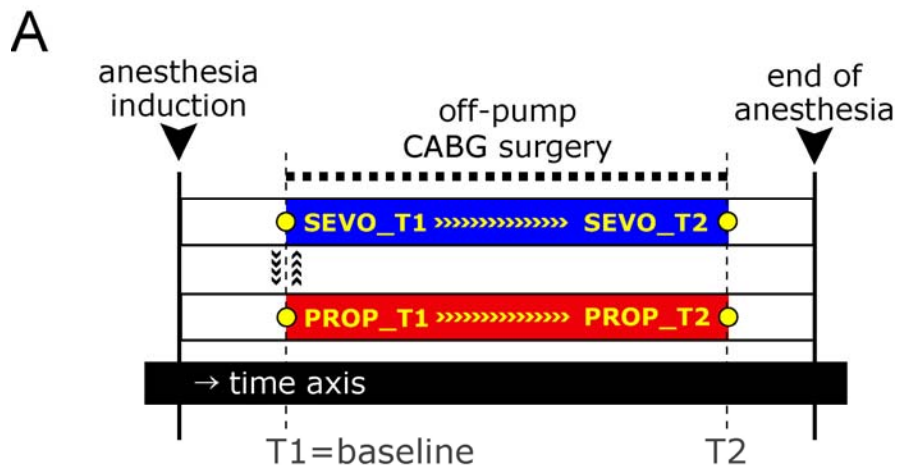
2. Takano et al. Effects of G-CSF on left ventricular remodeling and heart failure after acute myocardial infarction. J Mol Med 2006; 84: 185-93

GSEA was selected to achieve the following analysis goals:

Goal 1: to identify pathways that are altered from time T1 (baseline; before off-pump CABG surgery) to time T2 (end of CABG surgery) in both the SEVO and the PROP groups. This resulted in the list of pathways given in Table 4. These pathways appear to be mainly regulated by the surgical stimulus per se with no detectable modulation by the two anesthetics used.

Goal 2: to identify pathways that are differentially altered between SEVO and PROP from time T1 to time T2, which would illustrate the differential transcriptional responses to SEVO and PROP.

GSEA was first used to screen for regulated pathways using a four-phenotype design, namely (SEVO, T1), (SEVO, T2), (PROP, T1), and (PROP, T2) as illustrated in panel A of the following scheme:



**B**

$$\text{SEVO} = \text{FC}(\text{SEVO}) = \frac{\text{SEVO\_T2}}{\text{SEVO\_T1}}$$

$$\text{PROP} = \text{FC}(\text{PROP}) = \frac{\text{PROP\_T2}}{\text{PROP\_T1}}$$

Of note, all patients received exactly the same anesthetic regimen up to the time of the first biopsy (T1). Thus, the first biopsies represent the background baseline gene expression (phenotypes (SEVO, T1) and (PROP, T1)), while the second biopsies predominantly mirror the transcriptional changes to cardiac surgery modulated by the two anesthetics (phenotypes (SEVO, T2) and (PROP, T2)). The comparison (SEVO, T1) vs. (PROP, T1) of this GSEA analysis revealed an interesting heterogeneous pattern in energy metabolism-related gene activity, reflecting the population variation in patients prior to treatment with a subtle but significant difference between the study groups. This difference in baseline gene activity occurred despite proper randomization and accurate selection of patients (diabetic patients were excluded). Therefore, the activity of the peroxisome proliferator receptor gamma co-activator 1-alpha (PGC-1 $\alpha$ ) pathway was included as one of the relevant variables in our subsequent multivariate analysis. Moreover, this first GSEA analysis also provided a global picture of the pathways regulated during off-pump CABG surgery (comparison (SEVO, T2) vs. (SEVO, T1) and comparison (PROP, T2) vs. (PROP, T1)).

Because of the detected differences in baseline gene activity, which would have clearly biased the results, we did not compare directly SEVO vs. PROP ((SEVO, T2) vs. (PROP, T2)) in this first GSEA analysis. In order to correct for background activity, fold changes were computed, and GSEA analysis was again applied, this time with a two-phenotype design, namely SEVO and PROP (please see panel B in the above scheme). This analysis revealed the reported differentially regulated pathways of fatty acid metabolism, DNA-damage (both enriched in PROP), and G-CSF/Jak2/STAT3 survival (the only pathway significantly enriched in SEVO).

**Table S1:** Primers used for RT-PCR.

Affymetrix ID	representative public ID	gene title	forward primer	reverse primer
203973_s_at	NM_005195	CCAAT/enhancer binding protein (C/EBP), delta	5' - TGC AGT TTG GGA CAT AG - 3'	5' - CTT AGC TGC ATC AAC AGG AG - 3'
206236_at	NM_005282	G protein-coupled receptor 4	5' - ACT CAC CTC CAA GAG GAA CA - 3'	5' - AGA CCA GGA GAG AAG GGA CT- 3'
234103_at	AU145191	Sodium- and chloride-activated ATP-sensitive potassium channel SLICK	5' - CAG AAC AAT GGC AGA AGA TG - 3'	5' - CCC TCC TAA CAC CAA TCA AG - 3'
202484_s_at	AF072242	methyl-CpG binding domain protein 2	5' -AAC AAC CGG TAA CCA AAG TC - 3'	5' - ATT GCT ACC TGG ACC AAC TC- 3'
202458_at	NM_007173	protease, serine, 23	5' - CCA GAG AAC AAT GGA AGC A - 3'	5' - ATA GCT CCC AGA AAG CAC AC - 3'
203619_s_at	NM_012306	Fas apoptotic inhibitory molecule 2	5' - GAA GCC TAG CAG GAT TTC AG- 3'	5' - ACC TGG ATG AGA AAG ACA GG - 3'
210501_x_at	AF119846	eukaryotic translation initiation factor 3, subunit 12	5' - CTA AAG GTG TGG ATG AGC AA - 3'	5' - CCT GAA GTT ACT GGG AGG AG - 3'
243582_at	AW082633	SH3 domain containing ring finger 2	5' - GAC GTT ATC CAC CTC CTC TG - 3'	5' -TTA GGA CAA GGG TCT CTT CG - 3'
n.a.	NG_002801	18S ribosomal RNA	5' - TGG TTG CAA AGC TGA AAC TTA AAG - 3'	5' - AGT CAA ATT AAG CCG CAG GC - 3'

**Table S2:** Transcript validation in randomly selected patients. Three patients are from the propofol anesthesia group (H02\_P, H04\_P, and H12\_P) and three are from the sevoflurane anesthesia group (H11\_S, H15\_S, and H20\_S).

<b>CCAAT/enhancer binding protein (C/EBP), delta (NM_005195)</b>				
<b>patient</b>	<b>drug</b>	<b>fold change chip</b>	<b>fold change PCR</b>	<b>validation status</b>
H02_P	propofol	3.91	12.5	+
H04_P	propofol	5.47	5.67	+
H11_S	sevoflurane	7.91	13.3	+
H12_P	propofol	5.20	3.49	+
H15_S	sevoflurane	6.67	22.2	+
H20_S	sevoflurane	5.44	6.62	+
<b>G protein-coupled receptor 4 (NM_005282)</b>				
H02_P	propofol	1.76	2.64	+
H04_P	propofol	1.79	1.90	+
H11_S	sevoflurane	4.70	6.82	+
H12_P	propofol	3.18	3.12	+
H15_S	sevoflurane	3.10	2.92	+
H20_S	sevoflurane	2.93	5.49	+
<b>Sodium- and chloride-activated ATP-sensitive potassium channel SLICK (AU145191)</b>				
H02_P	propofol	0.14	0.05	+
H04_P	propofol	0.38	1.40	-
H11_S	sevoflurane	0.17	0.42	+
H12_P	propofol	0.12	0.07	+
H15_S	sevoflurane	0.15	0.15	+
H20_S	sevoflurane	0.23	0.16	+
<b>methyl-CpG binding domain protein 2 (AF072242)</b>				
H02_P	propofol	0.60	0.80	+

H04_P	propofol	0.73	0.78	+
H11_S	sevoflurane	0.78	0.72	+
H12_P	propofol	0.61	0.26	+
H15_S	sevoflurane	0.65	0.55	+
H20_S	sevoflurane	0.76	0.61	+
<b>serine protease 23 (NM_007173)</b>				
H02_P	propofol	0.43	0.24	+
H04_P	propofol	1.25	1.16	+
H11_S	sevoflurane	0.58	0.35	+
H12_P	propofol	0.57	0.19	+
H15_S	sevoflurane	0.24	0.22	+
H20_S	sevoflurane	0.76	0.50	+
<b>Fas apoptotic inhibitory molecule 2 (NM_012306)</b>				
H02_P	propofol	0.87	0.99	+
H04_P	propofol	2.53	2.14	+
H11_S	sevoflurane	0.42	0.40	+
H12_P	propofol	0.61	0.12	+
H15_S	sevoflurane	1.20	0.83	-
H20_S	sevoflurane	0.56	0.31	+
<b>eukaryotic translation initiation factor 3, subunit 12 (AF119846)</b>				
H02_P	propofol	1.02	1.14	+
H04_P	propofol	0.71	0.77	+
H11_S	sevoflurane	1.04	0.90	-
H12_P	propofol	0.90	0.40	+
H15_S	sevoflurane	1.12	1.16	+
H20_S	sevoflurane	0.97	0.90	+
<b>SH3 domain containing ring finger 2 (AW082633)</b>				

H02_P	propofol	0.81	0.68	+
H04_P	propofol	0.47	0.88	+
H11_S	sevoflurane	0.53	1.10	-
H12_P	propofol	0.70	0.18	+
H15_S	sevoflurane	0.94	1.34	-
H20_S	sevoflurane	0.83	0.97	+

**Table S3:** List of transcripts in the PGC-1 $\alpha$  pathway and in the three pathways differentially regulated by the anesthetics sevoflurane and propofol (fatty acid oxidation pathway, G-CSF survival pathway, and DNA-damage signaling pathway).



## PGC-1alpha

<b>Affy probe</b>	<b>Pgc1a_description</b>	<b>gene symbol</b>	<b>enriched</b>
1487_at	estrogen-related receptor alpha	ERR alpha	Yes
202455_at	histone deacetylase 5	HDAC5	Yes
203004_s_at	MADS box transcription enhancer factor 2, polypeptide D (myocyte enhancer factor 2D)	MEF 2D	Yes
207000_s_at	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	PPP3CC	Yes
209926_at	MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B)	MEF 2B	Yes
210404_x_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II beta	CaMK II beta	Yes
210771_at	peroxisome proliferative activated receptor, alpha	PPARalpha	Yes
211483_x_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II beta	CaMK II beta	Yes
212535_at	MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	MEF 2A	Yes
212669_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma	CaMK II gamma	Yes
213276_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II beta	CaMK II beta	Yes
214684_at	MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	MEF 2A	Yes
219195_at	peroxisome proliferative activated receptor, gamma, coactivator 1, alpha	PGC-1alpha	Yes
223437_at	peroxisome proliferative activated receptor, alpha	PPARalpha	Yes
223438_s_at	peroxisome proliferative activated receptor, alpha	PPARalpha	Yes
226978_at	peroxisome proliferative activated receptor, alpha	PPARalpha	Yes
244689_at	peroxisome proliferative activated receptor, alpha	PPARalpha	Yes
32540_at	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	PPP3CC	Yes
32541_at	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	PPP3CC	Yes
204652_s_at	nuclear respiratory factor 1	NRF1	Yes
211279_at	nuclear respiratory factor 1	NRF1	Yes
200622_x_at	calmodulin 3 (phosphorylase kinase, delta)	CALM3	No
200623_s_at	calmodulin 3 (phosphorylase kinase, delta)	CALM3	No
200653_s_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
200655_s_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
201020_at	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	YWHAH	No
202425_x_at	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)	PPP3CA	No
202429_s_at	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)	PPP3CA	No
202432_at	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform (calcineurin A beta)	PPP3CB	No
202457_s_at	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)	PPP3CA	No
203003_at	MADS box transcription enhancer factor 2, polypeptide D (myocyte enhancer factor 2D)	MEF 2D	No
203193_at	estrogen-related receptor alpha	ERR alpha	No
204392_at	calcium/calmodulin-dependent protein kinase I	CAMK1	No
205124_at	MADS box transcription enhancer factor 2, polypeptide B (myocyte enhancer factor 2B)	MEF 2B	No
206603_at	solute carrier family 2 (facilitated glucose transporter), member 4	GLUT4	No
207243_s_at	calmodulin 2 (phosphorylase kinase, delta)	CALM2	No
207613_s_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II alpha	CaMK II alpha	No
207968_s_at	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	MEF 2C	No
208095_s_at	signal recognition particle 72kDa	SRP72	No
208328_s_at	MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	MEF 2A	No
209199_s_at	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	MEF 2C	No
209200_at	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	MEF 2C	No
209563_x_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
209697_at	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	PPP3CC	No
209817_at	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform (calcineurin A beta)	PPP3CB	No
209956_s_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II beta	CaMK II beta	No
210349_at	calcium/calmodulin-dependent protein kinase IV	CAMK4	No
211984_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
211985_s_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
212757_s_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma	CaMK II gamma	No
213108_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II alpha	CaMK II alpha	No
213688_at	calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
213710_s_at	Calmodulin 1 (phosphorylase kinase, delta)	CALM1	No
213950_s_at	Protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	PPP3CC	No
214322_at	calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma	CaMK II gamma	No

## PGC-1alpha

215161_at	calcium/calmodulin-dependent protein kinase IG	CaMKI gamma	No
217128_s_at	calcium/calmodulin-dependent protein kinase IG	CaMKI gamma	No
34846_at	Calcium/calmodulin-dependent protein kinase (CaM kinase) II beta	CaMK II beta	No

## G-CSF\_survival

<b>Affy probe</b>	<b>G-CSF_description</b>	<b>gene symbol</b>	<b>enriched</b>
215037_s_at	BCL2-like 1	BCL2L1	Yes
207082_at	colony stimulating factor 1 (macrophage)	CSF1	Yes
210229_s_at	colony stimulating factor 2 (granulocyte-macrophage)	CSF2	Yes
207442_at	colony stimulating factor 3 (granulocyte)	CSF3	Yes
205841_at	Janus kinase 2 (a protein tyrosine kinase)	JAK2	Yes
205842_s_at	Janus kinase 2 (a protein tyrosine kinase)	JAK2	Yes
211108_s_at	Janus kinase 3 (a protein tyrosine kinase, leukocyte)	JAK3	Yes
202743_at	phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	PIK3R3	Yes
211580_s_at	phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	PIK3R3	Yes
208991_at	signal transducer and activator of transcription 3 (acute-phase response factor)	STAT3	Yes
208992_s_at	signal transducer and activator of transcription 3 (acute-phase response factor)	STAT3	Yes
203808_at	v-akt murine thymoma viral oncogene homolog 2	AKT2	Yes
212171_x_at	vascular endothelial growth factor	VEGF	Yes

## FA\_oxidation

<b>Affy probe</b>	<b>FAO_description</b>	<b>gene symbol</b>	<b>enriched</b>
218322_s_at	acyl-CoA synthetase long-chain family member 5	ACSL5	Yes
211207_s_at	acyl-CoA synthetase long-chain family member 6	ACSL6	Yes
219986_s_at	acyl-Coenzyme A dehydrogenase family, member 10	ACAD10	Yes
206068_s_at	acyl-Coenzyme A dehydrogenase, long chain	ACADL	Yes
206069_s_at	acyl-Coenzyme A dehydrogenase, long chain	ACADL	Yes
226030_at	acyl-Coenzyme A dehydrogenase, short/branched chain	ACADSB	Yes
200710_at	acyl-Coenzyme A dehydrogenase, very long chain	ACADVL	Yes
209601_at	acyl-Coenzyme A oxidase 1, palmitoyl	ACOX1	Yes
205364_at	acyl-Coenzyme A oxidase 2, branched chain	ACOX2	Yes
207820_at	alcohol dehydrogenase 1A (class I), alpha polypeptide	ADH1A	Yes
209614_at	alcohol dehydrogenase 1A (class I), alpha polypeptide /// alcohol dehydrogenase 1bH1C; ADH1A; ADH	ADH1C	Yes
206262_at	alcohol dehydrogenase 1C (class I), gamma polypeptide	ADH1C	Yes
208847_s_at	alcohol dehydrogenase 5 (class III), chi polypeptide	ADH5	Yes
209613_s_at	alcohol dehydrogenase IB (class I), beta polypeptide	ADH1B	Yes
209612_s_at	alcohol dehydrogenase IB (class I), beta polypeptide	ADH1B	Yes
212224_at	aldehyde dehydrogenase 1 family, member A1	ALDH1A1	Yes
202054_s_at	aldehyde dehydrogenase 3 family, member A2	ALDH3A2	Yes
202053_s_at	aldehyde dehydrogenase 3 family, member A2	ALDH3A2	Yes
210544_s_at	aldehyde dehydrogenase 3 family, member A2	ALDH3A2	Yes
207583_at	ATP-binding cassette, sub-family D (ALD), member 2	ABCD2	Yes
204573_at	carnitine O-octanoyltransferase	CROT	Yes
227468_at	carnitine palmitoyltransferase 1C	CPT1C	Yes
204264_at	carnitine palmitoyltransferase II	CPT2	Yes
204263_s_at	carnitine palmitoyltransferase II	CPT2	Yes
241929_at	CD36 antigen (collagen type I receptor, thrombospondin receptor)	CD36	Yes
236923_x_at	CD36 antigen (collagen type I receptor, thrombospondin receptor)	CD36	Yes
242197_x_at	CD36 antigen (collagen type I receptor, thrombospondin receptor)	CD36	Yes
203475_at	cytochrome P450, family 19, subfamily A, polypeptide 1	CYP19A1	Yes
219903_s_at	cytochrome P450, family 2, subfamily C, polypeptide 8	CYP2C8	Yes
214235_at	cytochrome P450, family 3, subfamily A, polypeptide 5	CYP3A5	Yes
210096_at	cytochrome P450, family 4, subfamily B, polypeptide 1	CYP4B1	Yes
238032_at	dehydrogenase/reductase (SDR family) member 3	DHRS3	Yes
201135_at	enoyl Coenzyme A hydratase, short chain, 1, mitochondrial	ECHS1	Yes
205222_at	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase	EHHADH	Yes
243574_at	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	HADHSC	Yes
201036_s_at	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	HADHSC	Yes
211569_s_at	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	HADHSC	Yes
239516_at	Lysophospholipase-like 1	LYPLAL1	Yes
218869_at	malonyl-CoA decarboxylase	MLYCD	Yes
226728_at	solute carrier family 27 (fatty acid transporter), member 1	SLC27A1	Yes
222217_s_at	solute carrier family 27 (fatty acid transporter), member 3	SLC27A3	Yes
225779_at	solute carrier family 27 (fatty acid transporter), member 4	SLC27A4	Yes
214763_at	thioesterase, adipose associated	THEA	Yes
202366_at	acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain	ACADS	No
202502_at	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain	ACADM	No
1556923_at	acyl-Coenzyme A oxidase 1, palmitoyl	ACOX1	No
213501_at	acyl-Coenzyme A oxidase 1, palmitoyl	ACOX1	No
227962_at	acyl-Coenzyme A oxidase 1, palmitoyl	ACOX1	No
207656_s_at	acyl-Coenzyme A oxidase 1, palmitoyl	ACOX1	No
243817_at	acyl-Coenzyme A oxidase 3, pristanoyl	ACOX3	No
204242_s_at	acyl-Coenzyme A oxidase 3, pristanoyl	ACOX3	No
204241_at	acyl-Coenzyme A oxidase 3, pristanoyl	ACOX3	No
210687_at	carnitine palmitoyltransferase 1A (liver)	CPT1A	No
210688_s_at	carnitine palmitoyltransferase 1A (liver)	CPT1A	No
203634_s_at	carnitine palmitoyltransferase 1A (liver)	CPT1A	No

## FA\_oxidation

203633_at	carnitine palmitoyltransferase 1A (liver)	CPT1A	No
210070_s_at	choline kinase beta /// carnitine palmitoyltransferase 1B (muscle)	CHKB; CPT1B	No
210069_at	choline kinase beta /// carnitine palmitoyltransferase 1B (muscle)	CHKB; CPT1B	No
200789_at	enoyl Coenzyme A hydratase 1, peroxisomal	ECH1	No
208629_s_at	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-	HADHA	No
208630_at	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-	HADHA	No
208631_s_at	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-	HADHA	No
201007_at	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-	HADHB	No
201035_s_at	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	HADHSC	No
210636_at	peroxisome proliferative activated receptor, delta	PPARD	No
208044_s_at	peroxisome proliferative activated receptor, delta	PPARD	No
37152_at	peroxisome proliferative activated receptor, delta	PPARD	No
242218_at	peroxisome proliferative activated receptor, delta	PPARD	No

## DNA\_damage\_signaling

Affy probe	DNA_DAMAGE_SIGNALING_description	gene symbol	enriched
210027_s_at	APEX nuclease (multifunctional DNA repair enzyme) 1	APEX1	Yes
212672_at	ataxia telangiectasia mutated (includes complementation groups A, C and D)	ATM	Yes
209902_at	ataxia telangiectasia and Rad3 related	ATR	Yes
209903_s_at	ataxia telangiectasia and Rad3 related	ATR	Yes
208860_s_at	alpha thalassemia/mental retardation syndrome X-linked (RAD54 homozygous)	ATRX	Yes
211022_s_at	alpha thalassemia/mental retardation syndrome X-linked (RAD54 homozygous)	ATRX	Yes
211833_s_at	BCL2-associated X protein	BAX	Yes
201848_s_at	BCL2/adenovirus E1B 19kDa interacting protein 3	BNIP3	Yes
202870_s_at	CDC20 cell division cycle 20 homolog (S. cerevisiae)	CDC20	Yes
204696_s_at	cell division cycle 25A	CDC25A	Yes
201853_s_at	cell division cycle 25B	CDC25B	Yes
202246_s_at	cyclin-dependent kinase 4	CDK4	Yes
205709_s_at	CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 1	CDS1	Yes
210416_s_at	CHK2 checkpoint homolog (S. pombe)	CHEK2	Yes
205162_at	excision repair cross-complementing rodent repair deficiency, complementation group C	CKN1	Yes
203409_at	damage-specific DNA binding protein 2, 48kDa /// LIM homeobox 3	DDB2	Yes
218194_at	small fragment nuclease	DKFZP566E144	Yes
213468_at	excision repair cross-complementing rodent repair deficiency, complementation group C	ERCC2	Yes
202176_at	excision repair cross-complementing rodent repair deficiency, complementation group C	ERCC3	Yes
202414_at	excision repair cross-complementing rodent repair deficiency, complementation group C	ERCC5	Yes
215942_s_at	G-2 and S-phase expressed 1	GTSE1	Yes
219019_at	leucine-rich repeats and death domain containing	LRDD	Yes
203686_at	N-methylpurine-DNA glycosylase	MPG	Yes
209421_at	mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)	MSH2	Yes
213806_at	purine-rich element binding protein A	PURA	Yes
204020_at	purine-rich element binding protein A	PURA	Yes
211228_s_at	RAD17 homolog (S. pombe)	RAD17	Yes
207405_s_at	RAD17 homolog (S. pombe)	RAD17	Yes
210826_x_at	RAD17 homolog (S. pombe)	RAD17	Yes
201046_s_at	RAD23 homolog A (S. cerevisiae)	RAD23A	Yes
208393_s_at	RAD50 homolog (S. cerevisiae)	RAD50	Yes
204828_at	RAD9 homolog A (S. pombe)	RAD9A	Yes
219370_at	reprimo, p53 dependent G2 arrest mediator candidate	RPRM	Yes
207113_s_at	tumor necrosis factor (TNF superfamily, member 2)	TNF	Yes
204781_s_at	Fas (TNF receptor superfamily, member 6)	TNFRSF6	Yes
215719_x_at	Fas (TNF receptor superfamily, member 6)	TNFRSF6	Yes
204780_s_at	Fas (TNF receptor superfamily, member 6)	TNFRSF6	Yes
216252_x_at	Fas (TNF receptor superfamily, member 6)	TNFRSF6	Yes
201746_at	tumor protein p53 (Li-Fraumeni syndrome)	TP53	Yes
202330_s_at	uracil-DNA glycosylase	UNG	Yes
209375_at	xeroderma pigmentosum, complementation group C	XPC	Yes
203655_at	X-ray repair complementing defective repair in Chinese hamster cells 1	XRCC1	Yes
207598_x_at	X-ray repair complementing defective repair in Chinese hamster cells 2	XRCC2	Yes
208442_s_at	ataxia telangiectasia mutated (includes complementation groups A, C and D)	ATM	No
210858_x_at	ataxia telangiectasia mutated (includes complementation groups A, C and D)	ATM	No
208861_s_at	alpha thalassemia/mental retardation syndrome X-linked (RAD54 homozygous)	ATRX	No
208859_s_at	alpha thalassemia/mental retardation syndrome X-linked (RAD54 homozygous)	ATRX	No
204531_s_at	breast cancer 1, early onset	BRCA1	No
211851_x_at	breast cancer 1, early onset	BRCA1	No
204695_at	cell division cycle 25A	CDC25A	No
205167_s_at	cell division cycle 25C	CDC25C	No
217010_s_at	cell division cycle 25C	CDC25C	No
203968_s_at	CDC6 cell division cycle 6 homolog (S. cerevisiae)	CDC6	No
203967_at	CDC6 cell division cycle 6 homolog (S. cerevisiae)	CDC6	No
202284_s_at	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	CDKN1A	No

## DNA\_damage\_signaling

205393_s_at	CHK1 checkpoint homolog (S. pombe)	CHEK1	No
205394_at	CHK1 checkpoint homolog (S. pombe)	CHEK1	No
208619_at	damage-specific DNA binding protein 1, 127kDa	DDB1	No
203720_s_at	excision repair cross-complementing rodent repair deficiency, complem	ERCC1	No
203719_at	excision repair cross-complementing rodent repair deficiency, complem	ERCC1	No
210158_at	excision repair cross-complementing rodent repair deficiency, complem	ERCC4	No
204768_s_at	flap structure-specific endonuclease 1	FEN1	No
204767_s_at	flap structure-specific endonuclease 1	FEN1	No
204318_s_at	G-2 and S-phase expressed 1	GTSE1	No
204315_s_at	G-2 and S-phase expressed 1	GTSE1	No
211040_x_at	G-2 and S-phase expressed 1 /// G-2 and S-phase expressed 1	GTSE1	No
204883_s_at	HUS1 checkpoint homolog (S. pombe)	HUS1	No
217618_x_at	HUS1 checkpoint homolog (S. pombe)	HUS1	No
204884_s_at	HUS1 checkpoint homolog (S. pombe)	HUS1	No
211832_s_at	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mous	MDM2	No
217373_x_at	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mous	MDM2	No
205386_s_at	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mous	MDM2	No
210947_s_at	mutS homolog 3 (E. coli)	MSH3	No
205887_x_at	mutS homolog 3 (E. coli)	MSH3	No
211450_s_at	mutS homolog 6 (E. coli)	MSH6	No
211449_at	mutS homolog 6 (E. coli)	MSH6	No
202911_at	mutS homolog 6 (E. coli)	MSH6	No
222063_s_at	CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 1	null	No
216914_at	cell division cycle 25C	null	No
1555186_at	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	null	No
239310_at	Damage-specific DNA binding protein 2, 48kDa	null	No
205385_at	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mous	null	No
204021_s_at	purine-rich element binding protein A	PURA	No
210216_x_at	RAD1 homolog (S. pombe)	RAD1	No
204460_s_at	RAD1 homolog (S. pombe)	RAD1	No
204461_x_at	RAD1 homolog (S. pombe)	RAD1	No
211300_s_at	tumor protein p53 (Li-Fraumeni syndrome)	TP53	No
221642_at	three prime repair exonuclease 1	TREX1	No
34689_at	three prime repair exonuclease 1	TREX1	No
205875_s_at	three prime repair exonuclease 1	TREX1	No

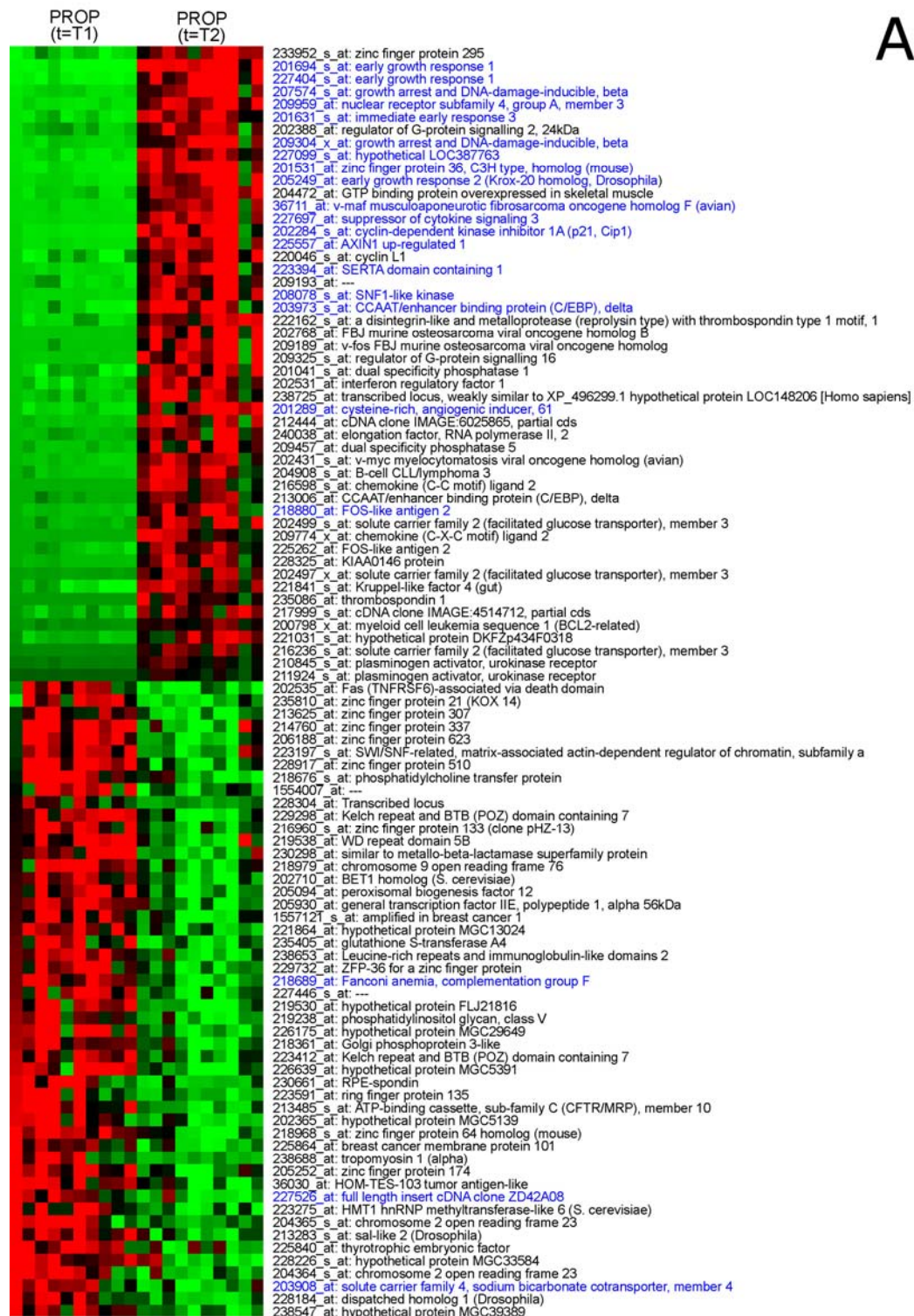
## Supplementary Figure Legends

- Figure S1** Heat maps of the fifty top-ranked up- and downregulated genes in propofol (PROP) patients at T1 and T2 (Suppl. Figure 1A) and sevoflurane (SEVO) patients at T1 and T2 (Suppl. Figure 1B). Blue color indicates jointly regulated transcripts between sevoflurane and propofol.
- Figure S2** Heat maps of the constitutive (preoperative) gene expression of the OXPHOS pathway (Suppl. Figure 2A) and the fatty acid metabolism pathway (Suppl. Figure 2B) in the enrolled patients, marked on top by their randomization code H01 to H20 and the label S for sevoflurane or P for propofol.
- Figure S3** Gene Set Enrichment Analysis (GSEA) of chip data (Affymetrix U34A) obtained from isolated perfused rat hearts exposed to isoflurane, another ether-based anesthetic gas, showing similar downregulation of genes involved in fatty acid metabolism. The rat hearts were exposed to 15 min of 2.1 vol.% isoflurane followed by 180 min of reperfusion, as previously described in detail.<sup>1</sup> Control = time-matched perfusion. Squares indicate individual experiments (n=5 for each group).

## Supplementary reference

1. da Silva R, Lucchinetti E, Pasch T, Schaub MC, Zaugg M. Ischemic but not pharmacological preconditioning elicits a gene expression profile similar to unprotected myocardium. *Physiol Genomics*. 2004;20:117-30.





**FIGURE S1 (Panel A)**

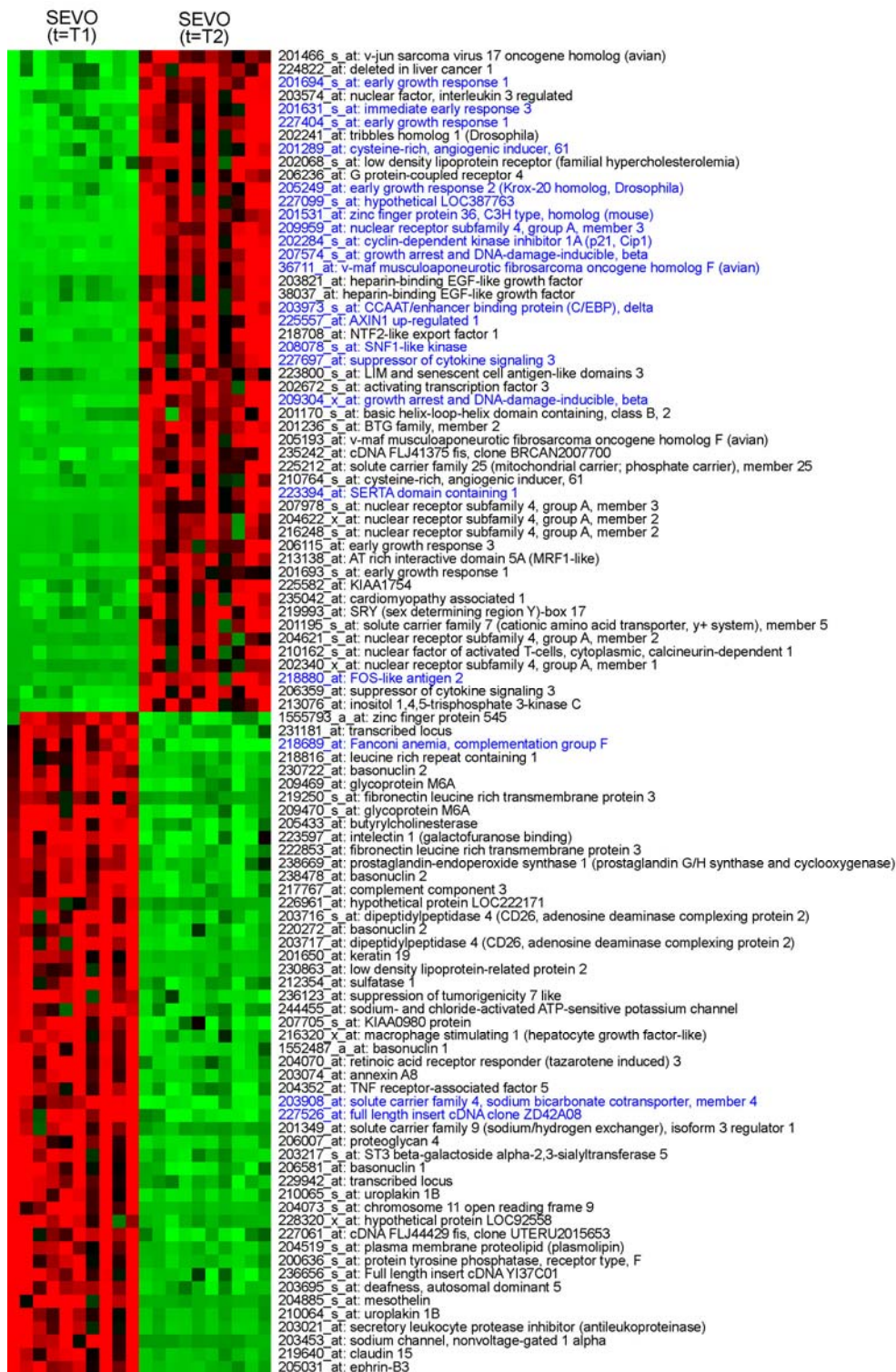
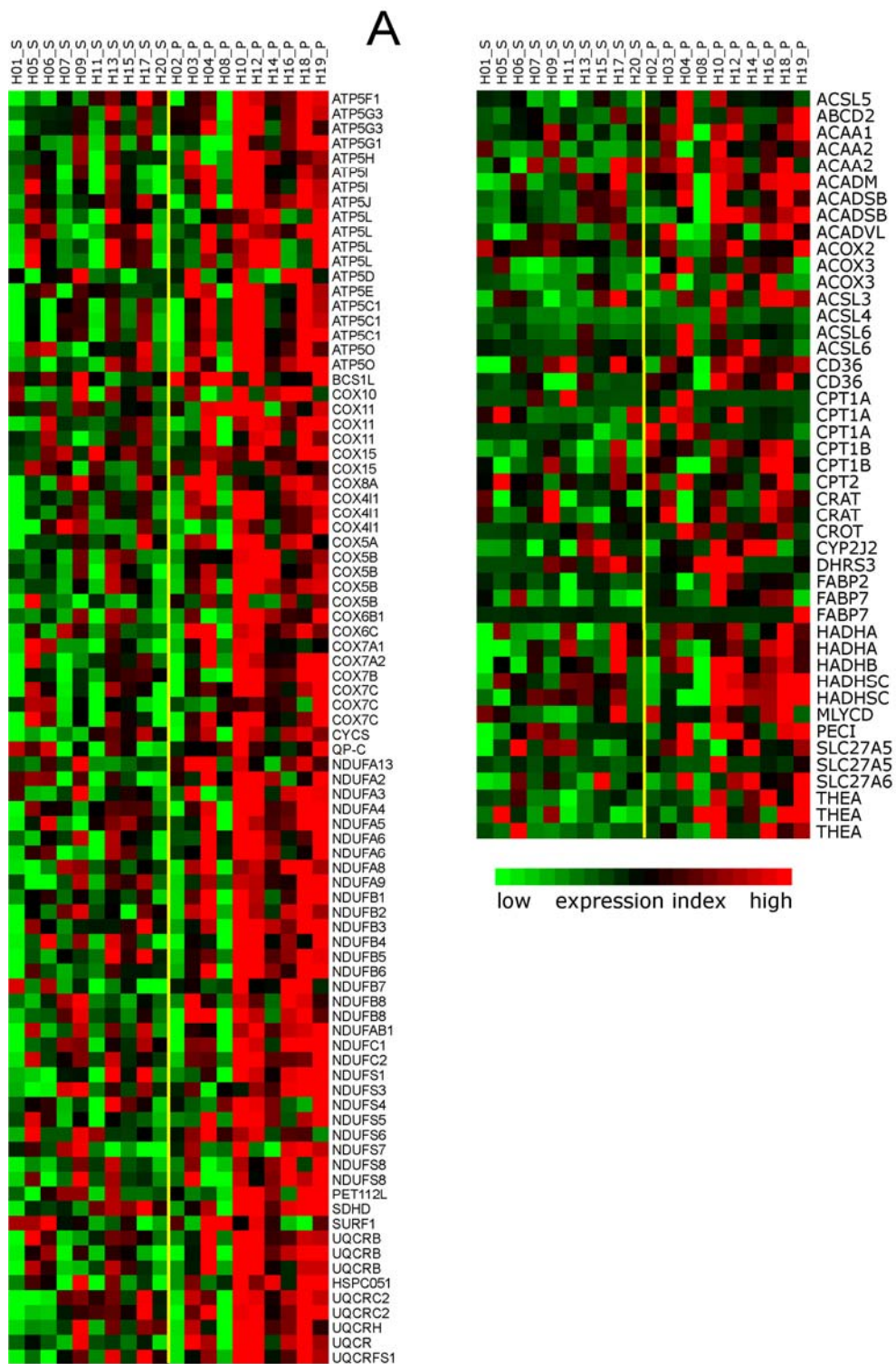
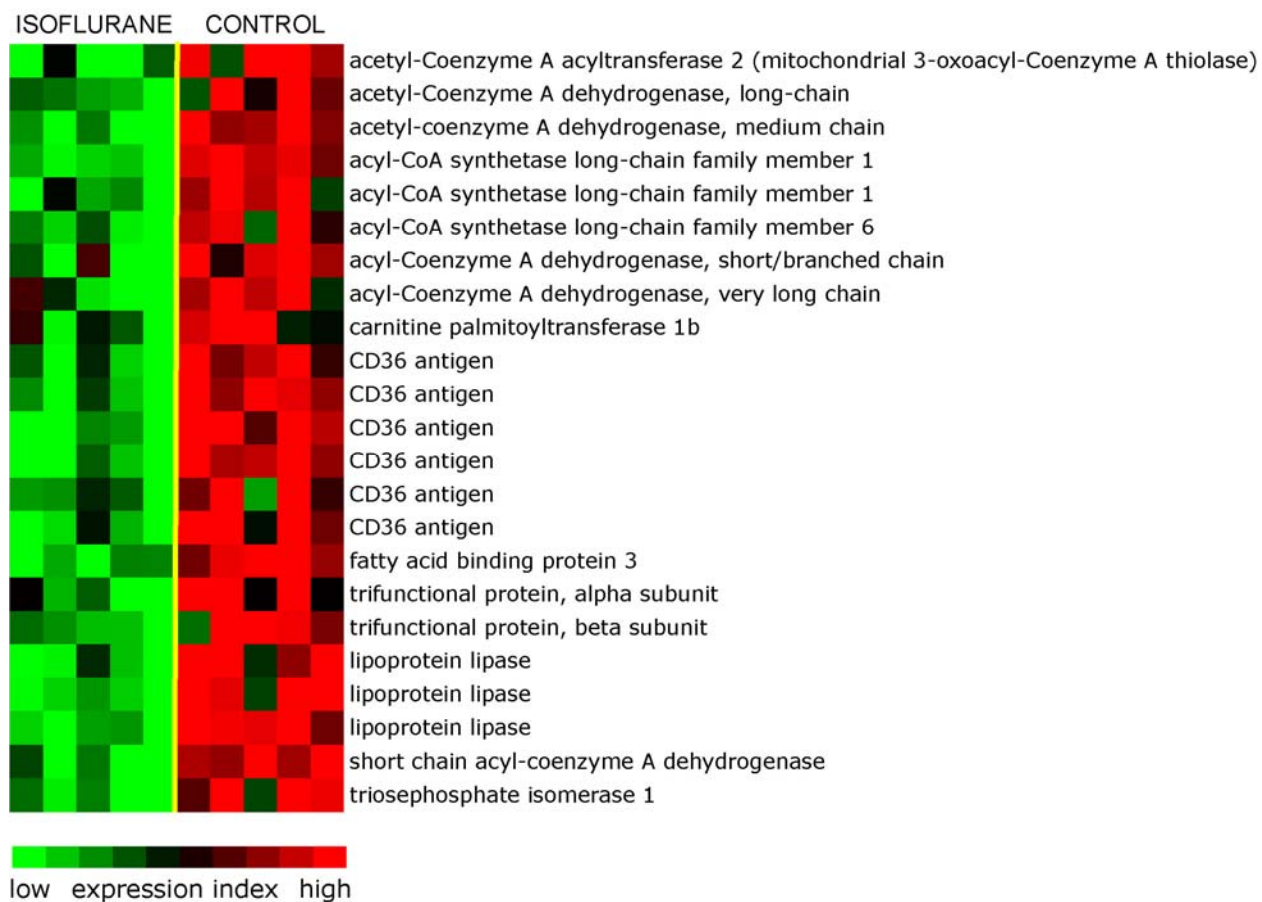


FIGURE S1 (Panel B)





**FIGURE S3**