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Cell Metabolism

Leptin, BMI, and a Metabolic Gene Expression Signature Associated with Clinical Outcome to VEGF Inhibition in Colorectal Cancer

Graphical Abstract



Authors

Aurélien J.C. Pommier, Matthew Farren, Bhavika Patel, ..., Shethah Morgan, Susan E. Critchlow, Simon T. Barry

Correspondence

simon.t.barry@astrazeneca.com

In Brief

Response to VEGF signaling inhibitors is poorly understood. Pommier et al. revealed circulating leptin, BMI, and a tumor glycolytic/angiogenic/hypoxia profile associated with clinical response to VEGFR inhibition. Tumor cell metabolic profile also influenced sensitivity in preclinical models. The findings suggest that patient physiology and tumor cell phenotype may influence response to VEGFRi.

Highlights

- High circulating leptin and high BMI correlate with VEGFRi benefit in mCRC
- Tumors with greater response have a glycolytic/hypoxic/ angiogenic phenotype
- Glycolytic/hypoxic/angiogenic phenotype influences preclinical VEGFRi sensitivity
- Leptin exposure induces a metabolic/angiogenic phenotype in cancer





CellPress

Leptin, BMI, and a Metabolic Gene Expression Signature Associated with Clinical Outcome to VEGF Inhibition in Colorectal Cancer

Aurélien J.C. Pommier,^{1,2} Matthew Farren,³ Bhavika Patel,¹ Mark Wappett,¹ Filippos Michopoulos,¹ Neil R. Smith,¹ Jane Kendrew,¹ Jeremy Frith,¹ Russell Huby,¹ Catherine Eberlein,¹ Hayley Campbell,¹ Christopher Womack,¹ Paul D. Smith,¹ Jane Robertson,¹ Shethah Morgan,¹ Susan E. Critchlow,¹ and Simon T. Barry^{1,*} ¹AstraZeneca, Oncology iMED, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

²Centre d'Immunologie Pierre Fabre, 5 Avenue Napoléon III, 74160 Saint-Julien-en-Genevois, France

³Cancer Research Technology, Angel Building, St. John Street, London EC1V 4AD, UK

*Correspondence: simon.t.barry@astrazeneca.com

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SUMMARY

VEGF (vascular endothelial growth factor) signaling inhibitors are widely used in different cancer types; however, patient selection remains a challenge. Analyses of samples from a phase III clinical trial in metastatic colorectal cancer testing chemotherapy versus chemotherapy with the small molecule VEGF receptors inhibitor cediranib identified circulating leptin levels, BMI, and a tumor metabolic and angiogenic gene expression signature associated with improved clinical outcome in patients treated with cediranib. Patients with a glycolytic and hypoxic/angiogenic profile were associated with increased benefit from cediranib, whereas patients with a high lipogenic, oxidative phosphorylation and serine biosynthesis signature did not gain benefit. These findings translated to pre-clinical tumor xenograft models where the same metabolic gene expression profiles were associated with in vivo sensitivity to cediranib as monotherapy. These findings suggest a link between patient physiology, tumor biology, and response to antiangiogenics, which may guide patient selection for VEGF therapy in the future.

INTRODUCTION

Angiogenesis plays an essential role in tumor growth and progression. Vascular endothelial growth factor (VEGF) is one of the key factors driving tumor angiogenesis. Many VEGF signaling inhibitors (VEGFi) have been tested clinically giving therapeutic benefit in a number of settings. Drugs targeting VEGF signaling pathways include: bevacizumab, a ligand-trapping monoclonal anti-VEGF antibody (Hurwitz et al., 2004); ramicurimab, an antibody targeting VEGFR2 (Lu et al., 2004); rediranib and other oral small-molecule VEGFR tyrosine kinase inhibitors that target VEGFR-1, VEGFR-2, VEGFR-3, and c-Kit (Brave et al., 2011; Wedge et al., 2005).

While VEGF inhibitors give clinical benefit in a range of tumor settings, use in unselected patient populations has resulted in disappointing overall survival outcomes. To optimize the use of VEGF inhibitors, there is a need to identify biomarkers that predict benefit, and improvement in our understanding of factors affecting sensitivity. Several possible hypotheses (Bergers and Hanahan, 2008; Ellis and Hicklin, 2008) for intrinsic and acquired resistance to VEGF therapies have been investigated, mainly focused on the tumor micro-environment. These mechanisms include: upregulation of alternative pro-angiogenic signaling pathways such as PDGF-C (Crawford et al., 2009), FGF2 (Casanovas et al., 2005), SDF1a (Xu et al., 2009), and DLL4 (Li et al., 2011); recruitment of vascular progenitor cells and pro-angiogenic monocytes from bone marrow (Shojaei and Ferrara, 2008; Shojaei et al., 2010; Shojaei et al., 2007) or T helper lymphocytes (Chung et al., 2013); increased protective coverage of tumor blood vessels by pericytes (Helfrich et al., 2010) and tumor-stromal architecture (Smith et al., 2013). However, none of these mechanisms have been adopted as a patient selection biomarker in the clinic.

The efficacy of cediranib plus FOLFOX/CAPOX (chemotherapy) versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer (mCRC) was assessed in the phase III HORIZON II trial (ClinicalTrials.gov identifier NCT00399035). This study met the co-primary endpoint of improved progression-free survival (PFS) with cediranib plus FOLFOX/CAPOX treatment, compared to FOLFOX/ CAPOX alone. However, the primary endpoint of improved overall survival (OS) was not met, a common outcome for VEGF-targeting agents (Bergers and Hanahan, 2008; Casanovas et al., 2005; Jain et al., 2006).

Serum biomarkers can be used to identify patient subgroups that respond differently to VEGFi-based therapy (Tran et al., 2012). In the HORIZON II trial, several prognostic and pharmacodynamic serum biomarkers were identified (Pommier et al., 2014; Spencer et al., 2013). Biomarkers for the selection of treatment-sensitive patients, however, are yet to be discovered. To identify potential patient stratification biomarkers, we have determined the predictive value of multiple serum proteins and tumor genes using samples from patients enrolled in HORIZON II. We have explored the mechanistic relevance of selected markers in preclinical models.





RESULTS AND DISCUSSION

Baseline Serum Proteins Profiling Reveals Markers Associated with PFS and OS in mCRC Patients Treated with Chemo Plus Cediranib

The concentration of 207 serum proteins (Table S1) was determined for 582 mCRC patients enrolled in the phase III randomized double-blind HORIZON II trial of the VEGFi inhibitor cediranib (Hoff et al., 2012). Patients were treated with either chemotherapy plus cediranib 20 mg (chemo-ced) or chemotherapy plus placebo (chemo-plac). For each protein, patients were dichotomized into high and low categories based on the median baseline serum concentrations. Correlation with OS was determined using two separated Cox proportional hazard models, comparing sensitivity of patients (high versus low categories) in response to (1) chemoced (Figure 1A) and (2) chemo-plac treatment (Figure 1B). Hazard ratio (HR) and p value are represented as volcano plots for all of the serum proteins. Proteins demonstrating a significant HR (p < 0.05) are highlighted (gray box). To focus our analysis on the identification of biomarkers related with cediranib benefit (Figure 1C), we excluded the proteins that were already associated with OS in chemo-plac (Figure 1B) from the volcano plot in Figure 1A. This revealed a number of biomarkers significantly associated with OS in patients receiving chemo-ced but not chemo-plac (Figure 1D). The same approach identified several biomarkers correlated with PFS in response to chemo-ced (Figure 1E). Given a p value cutoff of 0.05, 5% of the biomarkers would be expected to be associated with PFS or OS by chance alone. To reduce this false-positive rate, we focused on proteins associated with both PFS and OS (Figure 1F). HR, confidence interval (CI), and p values are represented by the forest plots for OS (Figure 1H) and PFS (Figure 1I). Patients classified as having high serum concentrations of leptin (LEP) or creatine kinase muscle and brain (CK-MB) had longer PFS and OS than did those with low concentrations. Patients with low serum concentrations of interleukin 10 (IL-10), plasminogen activator urokinase (PLAUR), interleukin 6 receptor beta (IL6Rb), TNF receptor superfamily member 6 (TNFSF6), and TNF related apoptosis inducing ligand receptor 3 (TRAILR3) had longer PFS and OS than did those with high concentrations. Figure 1G summarizes the biological functions of these proteins.

High Serum Leptin Associated with Prolonged Overall Survival in Cediranib-Treated Patients with mCRC

The association between leptin concentrations and clinical outcome in cediranib-treated patients was of particular inter-

est for several reasons. First, leptin was the most significant protein associated with prolonged OS only in cediranibtreated patients (Figures 1D and 1H). Second, leptin has been shown to modify many aspects of tumor biology including angiogenesis (Park et al., 2001). Third, leptin is an adipokine strongly correlated with obesity; elevated levels increase the risk of developing many types of cancers including CRC (Garofalo and Surmacz, 2006; Vucenik and Stains, 2012). The impact of leptin status versus therapy on OS is represented by Kaplan-Meier curves, with HR, CI, and p values demonstrating significant differences between arms (Figure 2A). Interaction between treatments and leptin status was significant for OS (pinteraction < 0.001) and PFS (pinteraction = 0.001) (Figure S1A). Patients with high serum leptin concentration showed an improved OS in response to chemo-ced when compared to low leptin patients (HR = 0.55, CI = 0.40-0.75, p < 0.001), but also when compared to patients treated with chemo-plac (HR = 0.66, CI = 0.47–0.93, p = 0.016) (Figure 2A). Importantly, serum leptin concentration was not associated with OS in patients treated with chemo-plac (HR = 0.90, CI = 0.66 - 1.23, p = 0.52).

High circulating leptin is often associated with obesity (Widjaja et al., 1997). To determine whether obesity was linked with clinical response to cediranib, we correlated the BMI with leptin concentrations (Figure 2B) and BMI with overall survival (Figure 2C, n = 859 patients). BMI and serum leptin concentration were positively correlated in this cohort (Figure 2B). We found a significant interaction between obesity (as defined by a BMI \geq 30 kg/m² by the current World Health Organization standard classification) and cediranib treatment on OS ($p_{interaction} = 0.024$) (Figure 2C) and PFS ($p_{interaction} =$ 0.028) (Figure S1B). Obese patients were associated with prolonged OS in response to chemo-ced compared to nonobese patients (HR = 0.551, CI = 0.36-0.85, p = 0.008). However, in chemo-plac-treated patients, obesity was not associated with benefit on OS (HR = 0.831, CI = 0.56-1.234, p = 0.359).

Correlations between obesity measures and responsiveness to anti-angiogenic drugs have been reported elsewhere. The predictive value of visceral fat area (VFA) or surface body area measures are variable. Both are predictive of PFS and OS benefit from VEGFi TKI in metastatic clear cell renal cancer (Steffens et al., 2011), though neither is associated with response to bevacizumab in patients with CRC (Guiu et al., 2010; Simkens et al., 2011). While there isn't a clear consensus, the majority of studies

Figure 1. Identification of Serum Biomarkers Associated with Clinical Outcome in Metastatic Colorectal Cancer Patients Related to Chemotherapy Plus Cediranib

The concentrations of 207 serum proteins were measured by multiplex analyses in 582 patients with metastatic colorectal cancer. Each quantified protein is represented as a dot. For each protein, patients were dichotomized into high and low categories based on the median baseline serum concentrations.

⁽A and B) Cox regression models were used to compare overall survival (OS) of patients (high versus low categories) in response to chemo-ced (A) and chemoplac treatment (B). Hazard ratio (HR) and p values (Cox regression model) associated with these analyses are represented by the volcano plots for all the serum proteins. The proteins showing a significant (p < 0.05) HR are highlighted in gray.

⁽C and D) These volcano plots show the proteins only associated with OS in patients treated with cediranib (C). Proteins found already associated with response to chemo-plac were excluded in these plots. A magnification on the proteins found with a p < 0.05 is shown (D).

⁽E) Identical analyses led to the identification of serum proteins correlated with progression-free survival (PFS) only in patients treated with chemo-ced.

⁽F) Venn diagram highlighting the number of proteins associated with PFS and OS, PFS exclusively and OS exclusively in patients treated with chemo-ced. (G) Main biological functions of the proteins found associated with PFS and OS.

⁽H and I) Forest plots (HR and confident interval) show the impact of serum concentrations and treatments on OS (H) and PFS (I). Full names of the analyzed proteins are detailed in Table S1.





Plus Cediranib

cediranib.

(C) Kaplan-Meier curves showing the impact of obesity (defined as BMI > 30) on OS in response to chemotherapy \pm cediranib.

Figure 2. High Serum Leptin Concentra-

tions and Obesity Improve Overall Survival

of Patients Treated with Chemotherapy

(A) Kaplan-Meier analyses showing the impact of

high versus low serum concentration of leptin and

overall survival (OS) in response to chemotherapy ±

HR, hazard ratio; CI, confidence interval.

Baseline Tumor mRNA Profiling Reveals Genes Associated with Longer Survival in mCRC Patients Treated with Cediranib

Aerobic glycolysis and angiogenesis are important enablers of tumor progression (Hanahan and Weinberg, 2011). Given the association of leptin with metabolism and angiogenesis (Park et al., 2001. 2010: Yehuda-Shnaidman et al., 2013), we explored the relationship between the expression of genes involved in angiogenesis and tumor metabolism (Table S2) and clinical response in HORIZON II (Figure 3A). Viable tumor area from 354 available formalin-fixed diagnostic biopsies (Figure S2A) were marked and macro-dissected, excluding gross necrotic regions or non-tumor tissue, and RNA extracted (Figure S2B). 95 samples were excluded due to poor tissue quality, lack of tumor content, or low RNA yield/quality (Figure S2A). Gene expression was analyzed in 259 samples representing 26.5% of the patients treated with chemotherapy plus placebo (n = 95/358), 21.1% of the patients treated with chemotherapy plus cediranib 20 mg (n = 106/502), and 26.9% of the patients treated with chemotherapy plus cediranib 30 mg (n = 58/216) (Figure S2A).

We used two statistical analysis strategies to identify genes potentially predictive for response to cediranib. Patients

suggest high leptin concentrations and obesity are associated with a higher risk of colon cancer, and possibly poor outcome (Larsson and Wolk, 2007; Ma et al., 2013). Our data suggest that circulating leptin levels are a surrogate measure for BMI and may be associated with improved clinical outcomes in mCRC patients receiving VEGFi-based therapy. It will be important to consider which of these features associate with outcome in other tumor types.

600

800

Time (days)

1200

1000

1400

0.2

0.0 +

200

400

were stratified into two groups for each gene based on high and low gene expression (relative to median) and the OS and PFS compared in the patients treated with chemo-plac versus chemo-ced using a Cox regression model. The genes significantly associated with OS (Figure 3) and PFS (Figure S2C) are listed on the forest plots showing the HR, CI, and p values. Overall, high expression of genes involved in glucose metabolism, angiogenesis, hypoxia, glutamine metabolism, and



Figure 3. Expression of Genes Involved in Key Tumor Metabolic Pathways Is Associated with the Clinical Outcome Benefit of Cediranib in Metastatic Colorectal Cancer Patients

Baseline gene expression was quantified from diagnostic fixed formalin colorectal cancer biopsies using NanoString technology.

(A) The forest plot represents the impact of treatment (chemotherapy plus placebo versus chemotherapy plus cediranib) in patient groups defined as high and low expression (relative to the median for each gene) on overall survival (OS) for the significant genes (p < 0.05). The biological functions of the genes are shown by a color code. Pink stars indicate the genes also found associated with chemotherapy plus cediranib benefit on progression-free survival (PFS) (Figure S2C). (B) Diagram representing the genes associated with cediranib sensitivity (CDS)/cediranib insensitivity (CDInS) and associated with OS benefit on chemotherapy plus cediranib compared to chemotherapy plus placebo treatment.

(C) Model summarizing the association between the expression of CDS/CDInS genes and OS benefit in response to chemotherapy plus cediranib. HR, hazard ratio; CI, confidence interval. leptin signaling (cediranib-sensitive signature [CDS]) correlated with an improved OS in patients treated with chemo-ced compared to chemo-plac (Figure 3A). However, low expression of genes involved in lipid metabolism, oxidative activity, proliferation, and serine synthesis (cediranib-insensitive signature [CDInS]) associated with improved survival in patients treated with chemo-ced compared with chemo-plac. Many of these genes (pink stars) were also found to be associated with PFS as illustrated by Venn diagrams (Figures S2D and S2E). Figures 3B and 3C summarize the biological pathways/genes associated with improved OS in response to chemo-ced.

Hierarchical clustering identified groups of genes associated with differential response to chemotherapy ± cediranib. This stratified the mCRC patient population based on sub-clusters of co-expressed genes involved in common biological functions (Figures S3A-S3C). Two clusters of genes associated with cediranib sensitivity (Figure 4A) and cediranib insensitivity (Figure 4D) were identified that impacted OS (Figures 4B, 4C, 4E, and 4F) and PFS (Figure S5) in response to chemotherapy \pm cediranib. Importantly, independent of the treatments received, these signatures were not prognostic on OS (Figures 4B and 4E). However, we found a significant interaction between treatment effects and cediranib-sensitive (pinteraction = 0.028) and cediranib-insensitive (p_{interaction} = 0.002) signatures on OS (Figures 4C and 4F). These data indicate that patients with high expression of the cediranib-sensitive gene signature showed improved OS in response to cediranib addition to chemotherapy when compared to chemotherapy plus placebo (HR = 0.50; CI = 0.30-0.83, p = 0.007). No benefit on OS was observed in response to cediranib treatment in patients with low expression of this signature (HR = 1.03; CI = 0.62–1.71, p = 0.900). The cediranib-sensitive signature (CDS) was not associated with PFS benefit (p_{interaction} = 0.204; Figure S3D). A significant interaction between treatment effects and the cediranib-insensitive signature (CDInS) (p = 0.002) was observed (Figure 4F). Patients with low gene expression of this signature showed improved OS in response to chemo-ced (Figure 4F), particularly when compared to patients treated with chemotherapy plus placebo (HR = 0.42; CI = 0.26-0.68, p < 0.001). The cediranib-sensitive signature (CDS) was also predictive on PFS (pinteraction = 0.026; Figure S3E).

To explore the link between leptin and the metabolic gene profile of tumors, the correlation of baseline circulating leptin concentrations with tumor metabolic gene expression data from the HORIZON II clinical trial was determined. The patient population was stratified into two groups, high versus low, based on the median leptin serum level observed in the cohort (4.9 ng/ml). Patients with high circulating leptin concentrations express higher levels of hypoxic/glycolytic genes (CA-9, SLC16A3, HIF1a) and lower levels of PDP1 and SLC16A1 than those with low leptin concentration (Figure 4G). A similar correlation between leptin, LEPR, and HIF1a staining in CRC has been observed previously (Koda et al., 2007a). Leptin receptor (LEPR) is expressed on both tumor and endothelial cells (Bouloumié et al., 1998; Koda et al., 2007b; Wang et al., 2012); however, the major impact of leptin was associated with the tumor cells. In our study there was no correlation between serum leptin concentrations and the expression of mRNA biomarkers of vasculature in clinical samples.

In addition to the metabolism genes, the cediranib-sensitive signature associated with OS also included VEGFR1, VEGFR2, NRP2, and VEGF-A (Figures 3 and S2). VEGFR1 gene expression (Wilson et al., 2013) and a VEGF-dependent vasculature gene signature (including VEGFR1, VEGFR2, VEGFR3, NRP1, and NRP2) associated with better outcomes in mCRC treated with bevacizumab-containing therapies (Brauer et al., 2013). The association between the angiogenic genes and the metabolic genes is interesting and warrants further investigation. The cancer glycolytic phenotype is also influenced by other factors such as upregulation of HIF1 α or mutation/deletion of VHL. These additional biomarkers should also be considered as we seek to understand drivers of VEGFi sensitivity. Overall, our data show that baseline expression of genes involved in angiogenesis and tumor metabolism can segregate mCRC patients into subgroups that may predict response to cediranib-based therapy.

Glucose, Serine, and Lipid Metabolism Gene Expression Correlates with Sensitivity to Cediranib in Xenograft Models

The association between baseline expression of genes associated with metabolism and clinical responsiveness to cediranib suggests that the metabolic phenotype of the tumor may determine sensitivity/resistance to VEGFi. This was investigated using pre-clinical models. The mRNA expression of genes involved in metabolism and proliferation using TagMan assays (Table S3) was determined across 13 xenograft models (Figure S4G). To focus specifically on the tumor cells, only human transcripts were assessed. Individual genes associated with sensitivity to monotherapy cediranib across 13 models were determined by linear regression analysis (Figure 5A). Tumor growth inhibition (TGI) after approximately 20 days of 3 mg/kg/day cediranib treatment was greatest in the A498 clear cell renal carcinoma (ccRCC) model, which exhibited tumor regression (TGI = 112%). NCI-H526, a small cell lung cancer model, was the least sensitive with an average of 35% TGI. Examples of cediranib efficacy are shown for the NCI-H526, Lovo, SW620, and A498 models (Figure 5B). The expression of genes known to be associated with a glycolytic phenotype, namely SLC16A3, CA-9, MYC, PKM2, PGAM1, SLC2A1, EPAS1, and LDHA were positively and significantly (p < 0.05) correlated with sensitivity to cediranib (Figure 5A). However, high expression of genes involved in serine metabolism (PHGDH) and lipid metabolism (ME2, SREBF2, ME3, and FASN) was associated with a lack of response to cediranib. No correlation between mutation status and sensitivity to cediranib was found for VHL, PTEN, PIK3CA, KRAS, and MYC (Figure 5A).

The activation of the glycolytic pathway in xenograft models highly sensitive to cediranib treatment was confirmed by mass spectrometric metabolomic analyses of in vivo tumor samples (Figure 5C). We found higher fructose-6-phosphate levels and lower NADPH levels in highly sensitive models (786-O, SW620, A498) compared with less sensitive models (NCI-H526, HCT-15, Calu-6, Lovo), consistent with the metabolic gene expression profile of the cediranib-sensitive versus cediranib-insensitive clinical samples.

Similar reductions in micro-vessel density (MVD) occurred in NCI-H526 and Lovo versus SW620 xenografts (Figure 5D), suggesting this does not contribute to the efficacy of cediranib.



Figure 4. Expression Signatures of Genes Involved in Key Tumor Metabolic Pathways Predict Overall Survival Benefit in Metastatic Colorectal Cancer Patients Treated with Chemotherapy Plus Cediranib

(A) Stratification of the patients based on hierarchical clustering of co-expressed genes associated with cediranib sensitivity (CDS).

(B) Comparison of the overall survival (OS) in patients with high and low expression CDS genes showing the absence of prognostic value of this signature independently of treatments.

(C) Kaplan-Meier curves and Cox regression analyses comparing the effect of chemotherapy plus placebo and chemotherapy plus cediranib in patients with high and low CDS gene expression on OS.

(D) Stratification of the patients based on hierarchical clustering of co-expressed genes associated with cediranib insensitivity (CDInS) genes.

(E) Comparison of the OS in patients with high and low expression of CDInS genes showing the absence of prognostic value of this signature independently of treatments.

(F) Kaplan-Meier curves and Cox regression analyses comparing the effect of chemo-plac and chemo-ced in patients with high and low CDInS expression on OS. (G) Genes correlated with serum leptin concentration were quantified in patients from HORIZON II clinical trial. Patient groups with high versus low leptin concentrations were determined based on the median concentration (4.9 ng/ml).

p values were determined by a Mann-Whitney test, and p < 0.05 was considered significant.

(figure continued on next page)



Tumour with high CDInS gene expression

Tumour with low CDInS gene expression



Figure 4. Continued

Consistently, tumor progression in the absence of re-vascularization has been described as a mechanism of escape after cediranib therapy in GBM (di Tomaso et al., 2011).

Raised expression of glycolytic enzymes and a corresponding increased sensitivity to VEGFi has been observed in xenografts (Nardo et al., 2011) and in the clinic (Koukourakis et al., 2011; Wilson et al., 2013). Tumors display a range of metabolic phenotypes, some more dependent on the glycolytic pathway, others on mitochondrial oxidative activity (Zheng, 2012). The latter is likely to favor tumor growth following changes in vasculature



Figure 5. Glycolytic Phenotype Correlates with Sensitivity to Cediranib in Xenograft Models

(A) Human (tumor-derived) genes significantly correlated with sensitivity to cediranib in xenograft models are represented. The heatmap shows the relative expression level for each gene across the 13 xenografts. Each square represents a biological sample. Sensitivity to cediranib was determined by the tumor growth inhibition after 20 (\pm 3) days of cediranib treatment at 3 mg/kg/day. The average gene expression for each individual model (n = 3–5 animals) was correlated with sensitivity to cediranib by linear regression. p < 0.05 was considered significant. Mutation status for *VHL*, *PTEN*, *PIK3CA*, *TP53*, *KRAS*, and *MYC* is shown. (B) Examples of cediranib efficacy is shown for NCI-H526, Lovo, SW620, and A498. Error bars represent SD of 6–10 biological replicates.

(C) The level of fructose-6-phosphate and NADPH were quantified in vivo in less- and highly sensitive models to cediranib. For each metabolite, levels were averaged (n = 5–6 animal per model). p values were determined by a t test comparison between less- and highly sensitive models. Error bars represent SD of 5 biological replicates.

(D) Effect of cediranib treatment on micro vessels density (MVD) in NCH-H526, Lovo, and SW620. Error bars represent SD of 5 biological replicates. p values were determined by a t test comparison, and p < 0.05 was considered significant. CDS, cediranib sensitive; CDInS, cediranib insensitive.

that decrease blood flow and vascular permeability (Bokacheva et al., 2013), limit the supply of nutrients and oxygen (Ebos et al., 2009), and restrict levels of glucose and ATP (Nardo et al., 2011). Dependency on the glycolytic pathway may render a cell more sensitive to these changes, as supply of glycolytic intermediates is critical for biomass production and proliferation (Vander Heiden et al., 2011). However, efficient utilization of nutrients or elevation of de novo biosynthetic pathways could enable adaption to VEGFi treatment. High expression of *FASN* (Swinnen et al., 2002), *PHGDH* (Locasale et al., 2011; Possemato et al., 2011), and *SHMT2* (Jain et al., 2012) supporting lipid, serine, and glycine synthesis in tumor cells with low glycolytic activity may favor tumor survival.

Taken together, the data are consistent with the hypothesis that the intrinsic tumor metabolic phenotype affects responsiveness to cediranib, with a glycolytic phenotype associated with high sensitivity to cediranib. Conversely, low activity of the glycolytic pathway and high expression of genes involved in serine synthesis and lipid biosynthesis is associated with lack of responsiveness to cediranib.

Changes in Hypoxic and Metabolic Gene Expression following Cediranib Treatment

Given that sensitivity to cediranib is in part endowed by a glycolytic gene expression profile, using gene expression profiling we investigated whether xenografts adapt to cediranib treatment and whether such adaptation depends on the sensitivity of the xenografts to cediranib (Figure S4). Although a large number of genes changed on cediranib treatment, the amplitudes of the changes were relatively small. The most consistent change was increased expression of several glycolytic/hypoxic genes (including CA-9), upregulated in the less-sensitive xenografts NCI-H526 and Calu-6 (Figures S4D and S4E). This suggests that cediranib causes hypoxia in these tumors, inducing the



Figure 6. Leptin Modulates Tumor Metabolic Phenotype

(A) In vitro relative glucose consumption rate is compared between less- and highly sensitive models to cediranib. Error bars represent SD of 3 biological replicates.

(B) Kinetics of glucose consumption in cancer cells treated with increasing doses of leptin. Error bars represent SD of 3 biological replicates.

(C) Correlation between LEPR expression and lactate release in a panel of in vitro cell lines.

observed changes in gene expression. This did not occur in the highly sensitive A498, SW620, and 786-O models, despite a significant reduction in tumor vessel density following treatment. Consistently, bevacizumab treatment can also increase CA-9 expression, and forced downregulation of CA-9 increases responsiveness to bevacizumab (McIntyre et al., 2012). Importantly, the modest change in metabolic gene expression following cediranib treatment was less marked than the difference in expression seen between tumors at baseline. This is illustrated on the PCA plot (Figure S4F).

A recent study demonstrated that switching to a lipogenic phenotype enables tumors to rebound from anti-angiogenic therapy; blocking lipid synthesis via downregulation of FASN prevented re-growth (Sounni et al., 2014). To determine whether FASN limits cediranib efficacy, mice bearing either NCI-H526 or Calu-6 tumor xenografts were treated with a FASN inhibitor (Schug et al., 2015) in combination with cediranib. The anti-tumor effect of cediranib was not significantly improved, suggesting that FASN alone is not responsible for the lack of activity in these models (Figure S5A). Together, the published studies and the data outlined here support the concept that both the intrinsic and "on-therapy" metabolic profile of the tumor cell may be important considerations when treating with anti-angiogenics. The data suggest that a "low" glycolytic tumor such as NCI-H526 may undergo a metabolic switch on treatment, whereas the glycolytic VHL null ccRCC A498 model cannot become more glycolytic. Although this concept of metabolic adaption needs further investigation, it provides a plausible link between metabolic phenotype and sensitivity to VEGFi (Sounni et al., 2014).

Leptin Can Modulate the Tumor Metabolic Phenotype

The functional relevance of the metabolic gene expression profiles observed in vivo was explored in vitro. Cell lines from the cediranib-sensitive (CDS) models had a higher glucose consumption rate than insensitive models in vitro, consistent with the glycolytic gene expression signature (Figure 6A). To determine whether leptin influences tumor metabolism, the impact of leptin on glucose utilization in less-sensitive (NCI-H526 and Lovo) and sensitive (SW620) cell lines was analyzed. To mimic the stresses of oxygen and nutrient deficiency caused by cediranib-mediated vessel reduction, cell lines were grown in serum-free media. Leptin caused an increase in glucose consumption by Lovo and NCI-H526 cells, but not by SW620 cells (Figure 6B). Across the panel of cell lines, leptin receptor (LEPR) mRNA expression correlated with lactate release (Figure 6C). In the Lovo cell line, glycolytic flux and capacity in response to glucose was increased by leptin, shown by increased extracellular acidification rate (ECAR) without modification of oxygen consumption rate (Figures 6D and S5B). Moreover, leptin-treated Lovo cells were preferentially lost from culture when deprived of glucose, suggesting that leptin increases demand for glucose (Figure S5C).

Leptin-mediated changes in metabolic pathway biomarkers were explored. An increase in PDH phosphorylation occurred in Lovo, but not in NCI-H526, cells (Figure S5D). However, leptin treatment of Lovo cells reduced expression of genes involved in lipid and cholesterol synthesis, including SREBF2, FASN, ACACA, and NR1H2 in NCI-H526 (Figure 6E). Leptin combined with cediranib treatment also downregulated FASN (Figures S5E and S5F). The leptin-induced changes in metabolic gene expression could be attributed to an inhibition of mTOR expression (Figures 6E and 6F). mTOR is involved in the regulation of cell growth, cell proliferation, and metabolism protein synthesis (Morita et al., 2015). The level of pS6, a downstream biomarker of mTOR, was also reduced in NCI-H526 and Lovo, but not in SW620, cells (Figure 6F). Combined leptin and cediranib treatment reduced pS6 staining in Lovo xenografts (Figures 6G and 6H). To model the potential of micro-environmental stress on the tumor cell compartment, cell proliferation of leptin-treated cells in hypoxic and serum-starved conditions was compared. Inhibition of proliferation in NCI-H526 and Lovo cells treated with leptin was seen under hypoxia conditions (Figure S5G). In SW620, leptin had no significant effect on proliferation under any of the conditions explored. It therefore appears that short-term leptin treatment can influence tumor cell metabolic status, stimulating glucose metabolism. In addition, leptin can reduce cell proliferation under conditions of stress such as low oxygen, glucose or serum. The association with changes in the mTOR pathway, in vivo and in vitro, requires further exploration.

Leptin Treatment Does Not Influence the Impact of **Cediranib on Endothelial Cells**

Leptin receptor (LEPR) can be expressed on endothelial cells as well as tumor cells (Bouloumié et al., 1998; Koda et al., 2007b; Wang et al., 2012). Leptin may therefore affect the sensitivity of vessels to cediranib, thereby modulating its efficacy. This was investigated in vitro and in vivo. Leptin did not increase vessel sensitivity to cediranib, as judged by MVD measurements in a tube formation assay in vitro (Figure 7A) or in the Lovo xenograft model (Figures 7B and 7C). This suggests that leptin affects cediranib efficacy primarily via effects on the tumor cell compartment.

Obese Phenotype Increases Cediranib Sensitivity in Mouse Model

To explore whether high leptin associated with obesity affects the efficacy of cediranib, we used the well-characterized Db/ Db (obese, high leptin) mouse model. Db/Db and WT (wildtype) control model mice were implanted with B16F10 syngeneic tumors and treated with 3 mg/kg cediranib (Figures 7D and S6). Tumors in both strains responded to cediranib, but cediranib gave greater benefit to tumors in the Db/Db mice (Figure S6A). Although initial tumor growth rate was slower in the Db/Db

⁽D) Lovo cells were treated with vehicle or leptin 10 ng/ml for 48 hr in serum-free media, and extracellular acidification rate (ECAR) was quantified to assess the glycolytic activity. Error bars represent SD of 3 biological replicates.

⁽E) Relative gene expression changes observed post-leptin treatment (48 hr) in H526 and Lovo cells lines. Error bars represent SD of 3 biological replicates. (F) Western blots against mTOR, pS6, S6, and beta-actin on cells treated with leptin.

⁽G and H) pS6 staining by immunohistochemistry in Lovo xenograft from mice treated with leptin ± cediranib (G) and quantification of the staining (H). Student's t tests were used to determine significance; *p < 0.05.



Figure 7. Leptin Treatment Does Not Influence Impact of Cediranib on Endothelial Cells, and Obesity Improves Response to Cediranib in Syngeneic Model

(A) CD31 staining on HUVEC treated with increasing doses of leptin and cediranib in a tube formation assay.

(B and C) CD31 staining in Lovo xenograft from mice treated with leptin ± cediranib (B) and quantification of the staining (C). For (C), error bars represent SD of 3–6 biological replicates.

(D) Body weight of the non-obese wild-type (WT) and obese Db/Db mice prior to B16F10 implantation. Error bars represent SD of 3–6 biological replicates. (E) Kaplan-Meier and Cox regression analyses showing the impact of obesity on the response to cediranib. Time to event was defined as time on study. Mice were taken out of study when tumors reached 1 cm³ and/or showed signs of ulceration.

(F and G) Cediranib-sensitive (CDS), -insensitive (CDInS) (F), and vasculature (G) gene signature expression changes in tumors from the non-obese wild-type (WT) and obese Db/Db mice treated or not with cediranib. Error bars represent SD of 3–6 biological replicates.

Student's t tests were used to determine significance; *p < 0.05. CDS, cediranib sensitive; CDInS, cediranib insensitive.

mice, ulceration with inflammation was more severe and occurred when tumors were smaller. This was accompanied by increased expression of genes involved in matrix remodeling (*mmp2* and *mmp9*) and inflammation (*ccl12, ccl2, cxcl1, cxcl12,* and *il6*) in the tumors of Db/Db mice (Figure S6B). Using the endpoint of tumors either ulcerating or reaching 1 cm³ (Figure S6C), Kaplan-Meier analysis showed that tumors were more sensitive to cediranib in Db/Db compared to WT mice (Figure 7E).

Expression profiling showed that *pdk4*, *hk1*, *pfkfb3*, and *vegfa* were upregulated in tumors from the Db/Db mice (Figure 7F). These genes are also part of the gene signature associated with cediranib sensitivity (Figures 3A and 4A). The expression of genes associated with the cediranib-insensitive signature (CDInS) was not significantly changed in obese compared to non-obese control mice (Figure 7F). Due to high melanin expression in the B16F10 melanoma model, it is challenging to accurately assess MVD by standard immunohistochemical staining of CD31. We therefore analyzed changes in mRNA of the endothelial transcripts *cd31*, *dll4*, *vegfr1*, *vegfr2*, and *vegfr3* to gain insight into changes in vasculature (Farren et al., 2012). Consistent with the observation in Lovo tumors, the tumor vessels in the Db/Db (obese) mice were not more sensitive to cediranib (Figure 7G).

Conclusions

Identifying mechanisms influencing tumor sensitivity to VEGFi is key to effective use of these agents in the clinic. This retrospective analysis of a phase III clinical trial in mCRC comparing chemotherapy versus chemotherapy plus cediranib identified an association of circulating leptin and tumor metabolic status with response to the VEGFi cediranib. It is not clear whether acute signaling or long-term tumor selection pressure are the drivers of the metabolic phenotype. The tumor metabolic profile also associated with response to cediranib in pre-clinical models. These observations reveal a novel link between patient physiology, tumor biology, and clinical response to therapy in mCRC that may apply to other tumor types. To build on these observations, other mCRC clinical samples sets should be interrogated and these biomarkers tested prospectively in a clinic trial.

We suggest that the metabolic status can be listed alongside alternate angiogenic drives (Casanovas et al., 2005), high myeloid-derived cell infiltrate (Shojaei et al., 2007, 2010), and the organization of blood vessels (Bergers et al., 2003; Smith et al., 2013) as a factor that influences tumor response to VEGFi (highlighted in Figure S7). These mechanisms confer tumors with intrinsic resistance or potential to adapt to the reduction in vessels. These additional biomarkers should also be considered to develop an in depth understanding of factors that contribute to VEGFi sensitivity.

EXPERIMENTAL PROCEDURES

HORIZON II Patients

The cohort of patients enrolled in the phase III double-blind HORIZON II study has been detailed previously (Hoff et al., 2012). Because recruitment to the cediranib 30 mg arm was discontinued (Hoff et al., 2012), this study was restricted to patients treated with cediranib 20 mg or placebo in combination with FOLFOX/CAPOX. The HORIZON II clinical trial was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Serum Protein Analysis

Serum sample collection and quantification of soluble biomarkers was performed as summarized in the Supplemental Experimental Procedures and described previously (Pommier et al., 2014; Spencer et al., 2013). Samples from 582 eligible patients were included as described in the CONSORT diagram (Figure S1).

Gene Expression Analysis from Biopsy Samples

Tumor sample collection was an optional procedure for consenting patients in the HORIZON II study. Investigator sites submitted paraffin-embedded samples from the primary tumor as well as any liver metastases. The samples were handled, formalin fixed, and processed according to local routine practice in clinical pathology. Tissue quality was confirmed by review of an H&E slide by a pathologist. 354 formalin-fixed paraffin-embedded (FFPE) biopsy samples were available in AstraZeneca from this trial. Two sections were cut (Figure S2B), one stained with H&E, and the other retained for RNA extraction. Viable tumor areas were marked on the H&E slide and traced onto the unstained section (Figure S2B). Tumor areas were then macro-dissected for RNA extraction, taking care to exclude normal tissue and areas of necrosis. 95 samples failed QC checks and were excluded (71 for insufficient tumor, 24 for poor RNA quality).

The remaining samples were randomized and total RNA extracted from batches of 24 using the RNeasy FFPE kit from QIAGEN (#73504) following manufacturer's instructions summarized in the Supplemental Experimental Procedures. 100 ng of RNA was used to quantify gene expression using Nano-String. Genes associated with leptin, cell metabolism, and angiogenesis were chosen for analysis. Expression was normalized against a pool of house-keeping genes (Table S2).

In Vivo Studies

Tumor xenograft tissue was derived from experiments conducted in accordance with licenses issued under the UK Animals (Scientific Procedures) Act 1986. Cell lines were maintained in the recommended growth medium and implanted subcutaneously into the left flank of 5- to 8-week-old immune-compromised mice (Figure S4G). Mice with established tumors were dosed daily with 3 mg/kg cediranib, 100 mg/kg FASNi (AZ62) (Schug et al., 2015), or vehicle per os (P.O.) as required. For syngeneic experiments, 1×10^5 B16F10 cells were implanted subcutaneously into the left flank of 7-week-old WT or Db/Db mice. Mice were treated daily with 3 mg/kg cediranib or vehicle P.O. Tumors were harvested between 0.8 and 1 cm³ and snap frozen in liquid nitrogen. The mutational status of xenografts was obtained from the Catalogue of Somatic Mutations in Cancer (COSMIC) database based at the Wellcome Trust Sanger Institute.

All animal studies were conducted in accordance with U.K. Home Office legislation, the Animal Scientific Procedures Act 1986, as well as the AstraZeneca Global Bioethics policy. All experimental work is outlined in project license 40/3483, which has gone through the AstraZeneca Ethical Review Process.

Immunohistochemistry

Immunohistochemistry was carried out using routine procedures. The following antibodies were used: CD31 (in-house polyclonal) with Elite ABC (Vector Labs); fatty acid synthase (C20G5) and pS6 (2215S, both Cell Signaling Technology) with anti-rabbit HRP complex (Dako). Counterstained mounted slides were scanned with a ScanScope AT (Aperio), images were quantitated with HALO (Indica Labs) software, and data were processed in Excel (Microsoft) and Spotfire (Tibco).

Cell Culture and Treatment

For the baseline LEPR gene expression analysis, cell lines were grown in phenol-free RPMI 1640 (Sigma), 2 mM glutamine (Gibco), and 10% FCS (SigmaF#7524) in a 5% CO2 atmosphere at 37°C. When 80% confluent, cells were scraped into 1 ml cold PBS, centrifuged at 1,000 rpm for 2 min, pellets snap frozen, and stored at -80° C. Recombined human leptin (R&D Systems) at

10 or 100 ng/ml concentration (from 1 mg/ml stock reconstitute in sterile 20 mM Tris-HCL [pH 8.0]) was used. Cells were transferred into FCS-free media 24 hr prior to leptin treatment. NCI-H526, LoVo, and SW620 cells were seeded into 96-well plates at a density of $2.5-3 \times 10^3$ cells per well and incubated at 37° C, 5% CO₂ at either normoxic (21% oxygen) or hypoxic (0.5% oxygen) conditions. Cells were treated the following day with PBS (vehicle control) or leptin diluted in PBS at 100 ng/ml and 10 ng/ml. Cell numbers were read at 24, 48, and 72 hr for the normoxic plates and at 24 and 48 hr for the hypoxic plates. For each read, cells were incubated in 2 4 and 48 hr green (LifeTech) in TBS + 5 mM EDTA and left for 1 hr at room temperature and read on Acumen at 380V to give the "dead count." Following this, cells were then incubated in 0.25% Saponin (LifeTech) in TBS + 5 mM EDTA and left for 15 hr at room temperature and read gain on the Acumen at 380V to give the "total count." Live cell number was calculated by taking the total count away from the dead count.

Extracellular Acidification Rate Assay

Cells were plated in a total volume of 80 μ l phenol-free RPMI 1640 (Sigma), 2 mM glutamine (Gibco), and 10% FCS (SigmaF#7524) at 8,000 cell/well density in XF96 PET Cell Culture Microplates (Seahorse Bioscience, #101104-004) and left to adhere overnight at 37°C, 5% CO₂. The next day, cells were transferred in a FCS-free media. After 24 hr, cells were treated with 10 ng/ml leptin in FCS-free RPMI 1640 for 48 hr. The medium was then replaced with 180 μ l unbuffered, glucose-free DMEM XF assay medium (Seahorse Bioscience, #100965-000) containing 2 mM glutamine (Gibco), 1% penicillin/streptavinin (Invitrogen), and the appropriate concentration of leptin. The pH was adjusted to 7.41 using 1N sodium hydroxide, and the medium was filter-sterilized through a 0.2 μ M pore size filter (Fischer Scientific, #TKV260030S). ECAR measurement was performed as recommended by the manufacturer and described in the Supplemental Experimental Procedures.

Measuring Glucose Levels in the Media

Glucose levels were measured at room temperature using the Accu-Chek Mobile System (Roche) according to manufacturer's protocol. Cells were seeded in duplicate in triplicate experiments (4×10^3 cells per well, 100μ I) into Costar clear flat bottom 96-well plates. Cell medium was changed 24 hr after seeding to DMEM (#D5921) (Sigma) supplemented with 10 mM D-glucose (Sigma), 2 mM L-glutamine (Sigma), and 10% dialysed fetal bovine serum (FBS) (Thermo Scientific). Following a second medium change, cells were treated with leptin diluted in phosphate-buffered saline (PBS) or PBS alone as a control. Medium samples were taken at 0, 1, 6, 24, and 48 hr post-treatment, and glucose levels were normalized to the initial cell number made on a parallel 96-well plate, read at 0 hr.

Tube Formation Assay

Normal human dermal fibroblasts (NHDFs) (Promocell) were seeded at 2,000 cells per well in 96-well collagen-coated plates in fibroblast growth media (Promocell) (100 µl per well) and incubated at 37°C, 5% CO₂ for 72 hr. The media was aspirated and HUVECs (Promocell) seeded onto the NHDF monolayer at 5,400 cells per well in 100 µl of MCDB131, 10% FCS, 2 mM L-glutamine and incubated overnight at 37°C, 5% CO₂. The following day, day 1 of the assay, the co-cultures were treated with VEGF, leptin, and cediranib titrations as indicated in growth media supplemented with 2% FBS. Media was aspirated and the tube plates redosed on days 4 and 8 and the assay finished and the cells fixed with 100% ethanol on day 11. The cells were washed once with PBS and blocked for 1 hr at 37°C in PBS, 1% BSA. The block was removed and the cells stained with mouse anti-human CD31-Alexa 488 (BD Biosciences) (1:500 dilution) and Hoescht 33342 (1 in 5.000 dilution) in PBS. 1% BSA. The cells were washed 2× with PBS and 100 μl of PBS added to the well. The fluorescence was imaged on the Cellomics Arrayscan and tube formation quantitated.

Gene Expression Profiling from Xenografts and Cell Lines

 1×10^6 cells or 50 mg of tissue were cut from the frozen tumors, and RNA was isolated by using the RNeasy MiniKit (QIAGEN), following the manufacturer's protocol. On-column DNase digestion was performed using the RNase-free DNase Kit (QIAGEN). RNA concentration was measured using the NanoDrop ND1000 (NanoDrop); RNA integrity (RIN) was assessed using

the RNA 6000 Nano Assay (Agilent Technologies); RIN values for all samples were between 7 and 10. Human-specific assays were designed and supplied by Applied Biosystems. Eukaryotic 18S rRNA was used as the endogenous control. Reverse transcription and preamplification were performed as recommended by Applied Biosystems and further described in the Supplemental Experimental Procedures. Samples were diluted 1 in 5 with TE and stored at -20°C. Sample and assay preparation for 48.48 Fluidigm Dynamic arrays was done according to the manufacturer's instructions. Briefly, samples were mixed with 20× sample loading reagent (Fluidigm) and TaqMan Gene Expression Master Mix (Applied Biosystems). Assays were mixed with 2× assay loading reagent (Fluidigm). The 48.48 Fluidigm Dynamic Arrays (Fluidigm) were primed and loaded on an IFC Controller (Fluidigm), and qPCR experiments were run on a Biomark System (Fluidigm) using the following thermal profile: 50°C for 2 min, 95°C for 10 min, and 40 cycles of 95°C for 15 s and 60°C for 1 min. Data were collected and analyzed using the Fluidigm Real-Time PCR Analysis 2.1.1 software. Gene expression values were calculated using the comparative CT ($-\Delta$ CT) method as previously described in User Bulletin #2 ABI PRISM 7700 Sequence Detection System 10/2001, using the corrected 18S rRNA CT value to determine changes in the context of the entire mRNA pool.

Metabolomic Analyses

Metabolites were extracted from frozen tissue. Chromatographic analysis was performed on an Ultimate 3000 RS pump combined with an Ultimate 3000 autosampler operating at 4°C through Chromeleon software package (Thermo). Mass spectrometry was performed on a 4000 QTRAP hybrid triple quadrupole linear ion trap mass spectrometer operating through Analyst 1.5.1 (Applied Biosystems/MDS Sciex). Further information is provided in the Supplemental Experimental Procedures.

Western Blot

Proteins were extracted using 100 μl cell lysis buffer composed of: 25 mM Tris/ HCI (Sigma #T-1535), 3 mM EDTA (Sigma #E-7889), 3 mM EGTA (Sigma #E-0396), 50 mM NaF (Sigma #S-1504), 2 mM orthovanadate (Sigma #S-6508), 0.27 M sucrose (Fisher #S/8600/60), 10 mM β-glycerophosphate (Sigma #G-6251), 5 mM Na-pyrophosphate (Sigma #S-6422), 0.5% Triton X-100 (Sigma #T-9284) supplemented with fresh complete protease inhibitor (Roche #11-836-153-001) and phosphatase inhibitor cocktail 3 (Sigma #-P0044). Proteins of interest were detected with the following antibodies: Anti-PDH-E1a (pSer²⁹³) (Millipore #AP1062), Anti-PDH (CST #2784), AntimTOR (CST #2972), Anti-β-Actin (Sigma #A2228), Anti-Phospho-S6 Ribosomal Protein (Ser235/236) (2F9) (CST #4856), and Anti-S6 Ribosomal Protein (CST #4856).

Statistical Methods

Clinical Analyses

The association with clinical end points was estimated using a Cox regression model performed in R 2.13 for the large-scale analyses (Figures 1, 3, and S3). To verify the predictive values for BMI, leptin, and gene signatures on PFs and OS, we used a Kaplan-Meier method and Cox model in SigmaPlot 11. Hierarchical clusters, heatmaps, volcano plots, and forest plots were created using TIBCO Spotfire. The primary covariates used in the trial were World Health Organization (WHO) performance status, chemotherapy received, baseline liver function, and study phase; these were balanced between treatment arms. Due to the reduced sample size, we chose to omit the primary covariates from the analyses. A comparison of the full HORIZON II analysis with and without the covariates showed very comparable HRs and Cls (Spencer et al., 2013).

Regarding the statistical analyses aiming to assess the impact of the 207 serum protein concentrations on clinical outcome in patients treated with chemotherapy \pm cediranib, we used a methodology different from that described by Spencer et al. (2013). In Spencer et al. (2013), the predictive analysis on OS and PFS was performed by comparison of chemotherapy plus placebo versus chemotherapy plus cediranib using two Cox regression models: (1) in patients defined as a low group and (2) in patients defined as high group (relative to median). Here, we have compared the impact of biomarker concentrations (high versus low groups, still relative to median) using two Cox regression models: (1) in patients (1) in patients (1) in patients treated with chemotherapy plus

placebo and (2) in patients treated with chemotherapy plus cediranib. p < 0.05 was considered significant.

To examine the association between tumor gene expression and clinical outcomes, we used statistical approaches. First we dichotomized patients into high and low groups (relative to median expression) and compared the PFS and OS in patients treated with chemotherapy plus placebo versus chemotherapy plus cediranib using a Cox model (R 2.13). Genes found significantly correlated with outcomes (p < 0.05) were then classified into two categories according to whether they were associated with improved outcome in response to cediranib in high or low group. Within each category, genes were classified according the p value of the HR obtained by the Cox regression model. To obtain co-expressed gene clusters and patient stratification, hierarchical clustering analysis was used with the following parameters: Ward's clustering method, half-square Euclidean for the distance measure, average value for the ordering weight, and *Z* score calculation for the normalization.

The correlation between BMI and leptin concentrations was assessed using linear regression analysis with TIBCO Spotfire.

Mann-Whitney test was used to examine the significance of the correlations observed between gene expression and serum leptin concentrations.

Pre-clinical Analyses

Gene expression values were calculated using the comparative Ct (–DCt) method as previously described in UserBulletin #2 ABI PRISM 7700 Sequence Detection System 10/2001, using the human 18S rRNA Ct values for normalization. Validation experiments of this platform indicated the confidence limit of detection of this technology was a Ct of 35. Therefore, missing data and Ct values of 35 were imputed with a Ct value of 35. This ensured that correlation analysis incorporated the low expression data rather than excluding it. Linear regression was performed using TIBCO Spotfire, with p values < 0.05 considered as significant. Relative expression changes were calculated using DDCt method. In Figure 5A, highly sensitive or less-sensitive groups were defined based on the average of the sensitivity (76.7% tumor growth inhibition) across the 13 models.

For the mass spectrometry analyses, coefficients of variation (CVs, SD/ mean \times 100) were calculated for each QC analyte. Modulated metabolites met all of the following criteria: (a) QC CV < 30, (b) p value < 0.05 and absolute log2 fold change > 0.05. Unless indicated otherwise, t tests were used to determined significance.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, seven figures, and three tables and can be found with this article online at http://dx.doi.org/10.1016/j.cmet.2015.10.015.

CONFLICT OF INTEREST

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Supplemental Information

Leptin, BMI, and a Metabolic Gene Expression Signature Associated with Clinical Outcome to

VEGF Inhibition in Colorectal Cancer

Aurélien J.C. Pommier, Matthew Farren, Bhavika Patel, Mark Wappett, Filippos Michopoulos, Neil R. Smith, Jane Kendrew, Jeremy Frith, Russell Huby, Catherine Eberlein, Hayley Campbell, Christopher Womack, Paul D. Smith, Jane Robertson, Shethah Morgan, Susan E. Critchlow, and Simon T. Barry

Supplemental experimental procedures

Serum protein analysis

Collection of blood samples from consenting patients was prescribed (but not monitored) as follow: sampling into serum separated tubes and centrifuged within 1 hour for 15 minutes at 3000g, aliquoted into vials and stored immediately at -80°C. Frozen serum samples were shipped and analyzed centrally at Rules-Based Medicine (Myriad RBM, Austin, TX). Analyzed proteins were selected based on their relevance to angiogenesis and linked to tumor progression. Additional analytes were included if they were multiplexed with the requested markers. Each aliquot was thawed to measure 207 proteins that were quantified by using a Luminex bead-based multiplex immunodetection methodology. Myriad RBM's multi-analyte profiles (MAPs) have been validated to Clinical Laboratory Standards Institute (formerly NCCLS) guidelines based upon the principles of immunoassay. Each assay is developed as a single test to establish the sensitivity and dynamic range necessary for that analyte. Key performance parameters such as lower limit of quantification, precision, cross-reactivity, linearity, spike-recovery, dynamic range, matrix interference, freeze-thaw stability, and short-term sample stability are established for every assay (http://www.myriadrbm.com/).

RNA extraction from biopsy samples, quantification and quality control

Total RNA was extracted from FFPE samples using RNeasy FFPE kit from Qiagen (cat. number #73504) following manufacturer's instructions. Briefly, using a scalpel, one 5uM tumor section was scraped from a slide into a microcentrifuge tube containing deparaffinization solution from Qiagen (#19093). Samples were vortexed for 10s, centrifuged and incubated at 56°C with proteinase K overnight. The next day, samples were incubated with DNAse I for 15 min and RNA was purified using Qiagen columns as described in the kit's instructions in 28uL elution volume.

RNA was quantified by NanoDrop and samples with a yield $< 5 \text{ ng/}\mu\text{L}$ and/or a 260/280 ratio < 1.6 were not included in any further analysis.

Glucose dependency assay

All cell lines were cultured RPMI 1640 (Sigma), 2 mM glutamine (GIBCO) and 10% FCS (SigmaF#7524). Assay media was composed of phenol red-free, glucose-free DMEM (Sigma), 1% Pen-strep (GIBCO) and 10% sterile filtered dialyzed fetal calf serum (GIBCO). Cells were incubated at 37°C/5% CO₂ during the whole assay. Cells were seeded in 384 well plates accordingly to allow 90% confluence after 7 days growth in assay media supplemented with 25 mM glucose (Sigma) and 2 mM L-glutamine (GIBCO). Cultures were seeded in assay media and incubated overnight to allow adherence. Cells were dosed the following day with appropriate doses of glucose. The assay plates were stained after 7 days for 1 hour at room temperature and pressure (rtp) with 2 mM Sytox Green in TBS + 5mM EDTA and a "dead" cell count was measured using the Acumen reader at 390V. Immediately following the "dead" read the cells were incubated with 0.25% Saponin in TBS + 5 mM EDTA for 16 hours at rtp and read again on the Acumen reader to give a "total" cell count. The "total" cell count was then subtracted from the dead cell count to give a "live" cell number. The live cell count was normalized against growth in 25 mM glucose and 2 mM glutamine to give a relative % growth.

Extracellular acidification rate assay

The plate was transferred into a 37 °C, CO₂ free incubator for 2 hours prior to XF96 assay start. Before XF96 assay strats, the disposable sensor cartridges were hydrated in 200 μ l Seahorse Calibrant fluid (Seahorse Bioscience, #100840-000), as advised by the manufacturer overnight and various compounds (20 μ l Glucose for 11 mM final concentration), 22 μ l of Oligomycin A, (Sigma, # 75351 for 1 μ M final concentration) and 24 μ l of 2-Deoxy-Glucose (20mM final concentration) injection were added to either port A, B or C of the cartridge. ECAR measured at baseline and monitored over time using XF96 Seahorse Analyzer Data Analysis Program. This

calculated averages, standard deviation, % increases / decreases over baseline measurements and accounted for background readings in media-only control wells.

Reverse transcription and pre-amplification of RNA from xenografts and cell lines

5 ng of RNA was used in the reverse transcription using the High Capacity cDNA Reverse transcription kit (Applied Biosystems) in final volume of 20 μ l. The following thermal profile was used: 25°C for 10 minutes, 37°C for 120 minutes, 85°C for 5 second and 4°C for 2 minutes in a total volume of 20 μ l. 1.25 μ l were pre-amplified using a pool of TaqMan primers at a final dilution of 1 in 100 and pre-amplification master Mix (Applied Biosystems) in a final volume of 5 μ l. The following thermal profile was used; 95°C for 10 minutes, 14 cycles of 95°C for 15 seconds and 60°C for 4 minutes.

Metabolomic analyses

Frozen tissue was homogenized and extracted using a 2 ml CK14 Precellys kit. 1ml ACN/MeOH/H2O 40/40/20 (-20C) per 100mg of tissue was added to the lysing tube and samples followed to cycle of 20sec shake each at 6500rpm with the interim pause of 20 seconds. Precellys chamber temperature was kept at 8-9°C throughout the extraction. Clear supernatant was obtained after centrifugation at 20900g at 4°C for 5min and aliquoted to cryogenic vials to store at -20C. Prior to sample analysis 25 µl of each sample was placed on a polypropylene HPLC vial and reduce to dryness using under vaccum conditions in a Savant SPD2010 SpeedVac (Thermo Fisher) for approximately 1 hour. Dry residual was resuspended at 50ml of ultrapure water and centrifuged at 3270 g for 10 min at 4°C (Allegra X12R equipped with SX4750A swinging backet rotor Beckam Coulter). To monitor analytical variability a pooled sample (QC) was generated by mixing equal aliquotes of each individual tissue extracts and treated another sample through the sample preparation procedure.

Chromatographic analysis was performed on an Ultimate 3000 RS pump combined with an Ultimate 3000 autosampler operating at 4°C through Chromeleon software package (Thermo).

Separations were performed on an Acquity HSS T3 UPLC column (2.1×100 mm, 1.8μ m particle size, Waters). Column temperature was maintained at $60\pm0.5^{\circ}$ C during the analysis. 5 µl of samples were injected and elution was performed using a binary solvent system consisting of solvent A (H2O, 15mM TBA, 10mM Acetic Acid) and solvent B (80% MeOH and 20% isopropanol). The optimum chromatographic separation was achieved with a flow rate of 400 µl/min and the following gradient elution profile: 0 min, 0% B; 0.5 min, 0% B; 4 min, 5% B; 6 min, 5% B; 6.5 min, 20% B; 8.5 min, 20% B; 14 min, 55% B; 15 min, 100% B; 17 min, 100% B; 18 min, 0% B; 21 min 0% B. Samples were analysed in random order with QC sample been analysed in regular intervals to access system performance and variability.

All of the MS data was acquired on a 4000 QTRAP hybrid triple quadrupole linear ion trap mass spectrometer operating through Analyst 1.5.1 (Applied Biosystems/MDS Sciex, Warrington, U.K.). The TurboIonSpray voltage was set at -3500 V, curtain gas at 10, temperature to 550°C, Gas1 and 2 were set at 60 and 50 respectively and entrance potential at -10V. Data was acquired in negative mode using the scheduled MRM transitions shown in Table S1. To obtain the optimum MS parameters each individual standard was dissolved in MeOH/H2O 50/50 at concentration of 10 μ M and infused at 10 μ L/min flow. Peak integration was performed using the MultiQuant software. All sample peaks were compared to the standards and standards+QC mix to ensure that the correct peak was selected. Normalisation to median sample metabolic profile was applied.

Supplemental legends

Figure S1 (Related to Figure 2)

A. Kaplan-Meier analyses showing the impact of high versus low leptin serum concentrations and PFS in response to chemotherapy \pm cediranib. **B**. Kaplan-Meier curves showing the impact of high versus low BMI on PFS in response to chemotherapy \pm cediranib.

PFS: Progression Free Survival; HR: Hazard Ratio; CI: Confident Interval; BMI: Body Mass Index.

Figure S2 (Related to Figure 3)

A. CONSORT diagram of the tumor biopsies used for gene expression profiling in HORIZON II trial. **B**. Schematic view of the methodology used to identify genes associated with clinical outcomes in HORIZON II trial. **C.** The forest plot represents the impact of treatment (chemo-plac vs chemo-ced) in patient groups defined as high and low expression (relative to the median for each gene) on PFS for the significant genes (P<0.05). The biological functions of the genes are shown by a color code. Pink stars indicate the genes also found associated with OS benefit (Figure 3). **D** and **E**. Venn diagrams showing the number and the name of genes associated with OS and/or PFS.

FFPE: Fixed Formalin Paraffin Embedded; H&E: Hematoxylin and Eosin; OS: Overall Survival; PFS: Progression Free Survival; HR: Hazard Ratio; CI: Confident Interval; CDS: CeDiranib Sensitive; CDInS: CeDiranib Insensitive.

Figure S3 (Related to Figure 4)

A. Global hierarchical clustering analysis identified co-expressed CDS and CDInS genes. **B**. Patients stratification based on CDS genes only. **C**. Patients stratification based on CDInS genes only. **D**. Kaplan-Meier curves and Cox regression analyses comparing the effect of chemo-plac and chemo-ced in patients with high and low expression of CDS genes on PFS.

E. Kaplan-Meier curves and Cox regression analyses comparing the effect of chemo-plac and chemo-ced in patients with high and low expression of CDInS genes on PFS.

HR: Hazard Ratio; CI: Confident Interval; CDS: CeDiranib Sensitive; CDInS: CeDiranib Insensitive.

Figure S4 (Related to Figure 5)

A-E. Heat maps showing gene expression changes in response to cediranib *in vivo*. **F.** PCA (Principal Component Analyse) of the xenograft models treated or not with cediranib based on metabolic gene expression level. **G.** Xenograft models information.

FC: Fold change

Figure S5 (Related to Figure 5 and 6)

A. Effect of Cediranib and/or FASNi treatment in Calu-6 and NCI-H526 xenograft models. **B** . Oxygen Consumption Rate in response to the Glycolytic test shown on Figure 6.D. **C**. Effect of glucose titration on proliferation of leptin treated Lovo cells. Lovo cells were treated with vehicle, leptin 10 ng/ml for 48 hours in serum free media. **D**. Western blot showing the protein accumulation for total and phospho-PDHE1a, total and phospho-S6 and beta-actin in response to leptin treatment. **E.** FASN staining in Lovo xenograft from mice treated with leptin +/- cediranib and quantification of the staining (**F**). **G.** Effect of leptin on cell proliferation in normoxia and hypoxic conditions. Cells were treated with vehicle, leptin 10 ng/ml for 48 hours in serum free media in normoxia and hypoxic conditions. t-test were used to determine significance and * indicates P<0.05.

Figure S6 (Related to Figure 7)

A. B16F10 tumour growth curves in non-obese WT (Wild Type) and obese Db/Db mice treated with cediranib. **B.** Expression of genes involved in invasion, metastasis and inflammation in tumors from the non-obese WT (Wild Type) and obese Db/Db mice. t-tests

were used to determine significance and * indicates P<0.05. **C.** Timing and number of mice taken out of study when tumors reached 1 cm³ or showed signs of ulceration.

Figure S7 (Related to Figure 2, 3 and 4)

Summary diagram showing the factors associated with sensitivity and resistance to VEGFi treatment.

Table S1 (Related to Figure 1)

List of serum proteins and abbreviations.

Table S2 (Related to Figure 3 and 4)

List, abbreviations and accession numbers of the genes analyzed by NanoString technology in mCRC patients (HORIZON II).

Table S3 (Related to Figure 5)

List, abbreviations, accession numbers and Applied Biosience references of the genes analyzed by Taqman assays in xenograft models.





Pommier et al. Figure S1 (Related to Figure 2)







Pommier et al. Figure S2 (Related to Figure 3)



0.0

. 1200 Days Time

0.0

Pommier et al. Figure S3 (Related to Figure 4)







G



Model	Tumour/ Tissue Type	Mouse model
786-0	Renal	SCID
A431	Epidermoid carcinoma	Nude
A498	Renal	Nude
Calu-6	Lung Carcinoma	Nude
Colo205	Colorectal Adenocarcinoma	Nude
H526	Lung Carcinoma	Nude
HCI-15	Colorectal Adenocarcinoma	Nude
HT29	Colorectal Adenocarcinoma	Nude
LoVo	Colorectal Adenocarcinoma	Nude
MDAMR231	Breast adenocarcinoma	Nuue
		Nude
FC-3	Prostate Adenocarcinoma	Nude
PC-9	Lung Adenocarcinoma	SCID
Sw620	Colorectal Adenocarcinoma	Nude
		11000



Pommier et al. Figure S5 (Related to Figure 5 and 6)

В



С

		Days on Study								
		13	14	15	16	17	18	21	24	25
	Tumor >1cm3		9		6					
WI + Venicle	Ulcerated tumor						3 1			
WT L Codironih	Tumor >1cm3				5		3			
WI + Ceullallin	Ulcerated tumor					1				
	Tumor >1cm3					1				
Db/Db + Vehicle	Ulcerated tumor	1		1		5				
	PD analysis						6			
	Tumor >1cm3								1	2
Db/Db + Cediranib	Ulcerated tumor							1	1	1
	PD analysis						6			

Pommier et al. Figure S6 (Related to Figure 7)



Pommier et al. Figure S7 (Related to Figure 2, 3 and 4)

Biomarkers A2M ACE ACTH ADIPOQ A-FABP AFP	Biomarker full name		Piomarkor full name
AZM ACE ACTH ADIPOQ A-FABP AFP		Biomarkers	
ACE ACTH ADIPOQ A-FABP AFP	Alpha-2-Macroglobulin	 IL-13	Interleukin 13
ACTH ADIPOQ A-FABP AFP	Angiotensin I Converting Enzyme (PeptidyI-Dipeptidase A) 1	 IL-15	Interleukin 15
ADIPOQ A-FABP AFP	Adrenocorticotrophic Hormone	 IL-16	Interleukin 16
A-FABP AFP	Adiponectin	 IL-18	Interleukin 18
AFP	Fatty Acid-Binding Protein, Adipocyte	 IL-1b	Interleukin 1b
	Alpha-Fetoprotein	 IL-1RA	Interleukin 1 Receptor Antagonist
AGER	Advanced Glycosylation End Product-Specific Receptor	 IL-1α	Interleukin 1 Alpha
AgRP	Agouti-Related Protein	IL-2	Interleukin 2
AGT	Angiotensinogen	 IL-25	Interleukin 25
Ang	Angiogenin, Ribonuclease, RNase A Family, 5	IL-2RA	Interleukin-2 Receptor, Alpha
Ang-2	Angiopoietin 2	IL-3	Interleukin 3
AREG	Amphiregulin	IL-4	Interleukin 4
\ST	Aspartate Aminotransferase	IL-5	Interleukin 5
XL-RTK	AXL Receptor Tyrosine Kinase	IL-6	Interleukin 6
32M	Beta-2-Microglobulin	IL-6R	Interleukin 6 Receptor
AFF	B Cell-Activating Factor	 III-6Rb	Interleukin-6 Recentor Subunit Beta
	Brain Derived Neurotrophic Factor		Interleukin 7
	Bono Morphogonatic Protain 6	 11.0	Interleukin 7
	Detered with phogenetic Protein 6		Interleukino
51C	Setacenum		Interferon Gamma
A 125	Carbonydrate Antigen 125	 INS	Insuin Kelliusia Deleted Destidens 5
A 15-3	Carbonydrate Antigen 15-3	 KLK5	Kallikrein-Related Peptidase 5
A 19-9	Carbonydrate Antigen 19-9	 KLK7	Kallikrein-Related Peptidase 7
A 72-4	Cancer Antigen 72-4	 LEP	Leptin
ALB1	Calbindin 1, 28kDa	 L-FABP	Fatty Acid-Binding Protein, Liver
CCL1	Chemokine (C-C Motif) Ligand 1	 LGALS3BP	Lectin, Galactoside-Binding, Soluble, 3
CL11	Chemokine (C-C Motif) Ligand 11	LH	Luteinizing Hormone
CL13	Chemokine (C-C Motif) Ligand 13	 Lp(a)	Lipoprotein (a)
CL16	Chemokine (C-C Motif) Ligand 16	 MB	Myoglobin
CL19	Chemokine (C-C Motif) Ligand 19	M-CSF	Macrophage-Colony-Stimulating Factor
CCL2	Chemokine (C-C Motif) Ligand 2	MDA-LDL	Malondialdehyde-Modified Low Density Lipoprotein
CL20	Chemokine (C-C Motif) Ligand 20	MICA	MHC Class I Polypeptide-Related Sequence A
CL21	Chemokine (C-C Motif) Ligand 21	MIF	Macrophage Migration Inhibitory Factor
CL22	Chemokine (C-C Motif) Ligand 22	MMP1	Matrix Metallopeptidase 1
CL23	Chemokine (C-C Motif) Ligand 23	MMP10	Matrix Metallopeptidase 10
CL24	Chemokine (C-C Motif) Ligand 24	MMP2	Matrix Metallopeptidase 2
CL26	Chemokine (C-C Motif) Ligand 26	MMP3	Matrix Metallopentidase 3
CI3	Chemokine (C-C Motif) Ligand 3		Matrix Metallopentidase 7
2013	Chemokine (C.C.Motif) Ligand 4		Matrix Metallopoptidase 9
CL4	Chemokine (C-C Motif) Ligand 4	 NINP 9	Matrix Metallopeptidase 9
CL7		 IVIIVIP91	inatitx metallopeptidase 9, Free
.CL8	Chemokine (C-C Motif) Ligand 8	 MPO	Myeloperoxidase
CD40L	CD40 Ligand	 MRC2	Mannose Receptor, C Type 2
CD62E	E-Selectin	 MSLN	Mesothelin
EA	Carcinoembryonic Antigen	MST1	Macrophage Stimulating 1 (Hepatocyte Growth Factor-Like
`gA	Chromogranine A	NCAM	Neuronal Cell Adhesion Molecule
CHI3L1	Chitinase 3-Like 1 (Cartilage Glycoprotein-39)	NGF	Nerve Growth Factor (Beta Polypeptide)
-Kit	Mast/Stem Cell Growth Factor Receptor	NRP1	Neuropilin 1
CK-MB	Creatine Kinase, MB	NT-proBNP	N- Terminal Pro-Brain Natriuretic Peptide
CLEC3B	C-Type Lectin Domain Family 3, Member B	OLR1	Oxidized Low Density Lipoprotein (Lectin-Like) Receptor
:LU	Clusterin	OPN	Osteopontin
NF	Ciliary Neurotrophic Factor	 PAI-1	Plasminogen-Activator-Inhibitor-1
OL15A1	Collagen, Type XVIII, Alpha 1	PAP	Prostatic Acid Phosphatase
014		 ΡΑΡΡΑ	Pregnancy-Associated Plasma Protein A Pappalysin 1
2014	C Reactive Protein		Distalet Derived Crowth Factor PD
.RP	C-Reduive Protein		
.5F2	Colony-Stimulating Factor 2	 PGA	pepsinogen i
.1	Calcitonin	 PGF	Placental Growth Factor
TGF	Connective Tissue Growth Factor	 PLAU	Plasminogen Activator, Urokinase
TSD	Cathepsin D	 PP	Pancreatic Polypeptide
XCL1	Chemokine (C-X-C Motif) Ligand 1	 PRL	Prolactin
XCL10	Chemokine (C-X-C Motif) Ligand 10	 PRS	Prostasin
XCL11	Chemokine (C-X-C Motif) Ligand 11	 PSA	Prostate Specific Antigen, Free
XCL12	Chemokine (C-X-C Motif) Ligand 12	РҮҮ	Peptide YY
XCL13	Chemokine (C-X-C Motif) Ligand 13	RANTES	T-Cell-Specific Protein RANTES
XCL5	Chemokine (C-X-C Motif) Ligand 5	RETN	Resistin
XCL9	Chemokine (C-X-C Motif) Ligand 9	S100-A12	S100 Calcium Binding Protein A12
	Epidermal Growth Factor	S100B	5100D
GF	Epidermal Growth Factor Receptor		S100B
GF		SAP	S100B Amyloid P Component, Serum
GF GFR NG	Endoglin, Quant	SAP SCF	S1008 Amyloid P Component, Serum Stem Cell Factor
GF GFR NG PCAM	Endoglin, Quant Epithelial Cell Adhesion Molecule	 SAP SCF SCT	S1008 Amyloid P Component, Serum Stem Cell Factor Secretin
GF GFR NG PCAM	Endoglin, Quant Epithelial Cell Adhesion Molecule Ervthropoietin	 SAP SCF SCT SERPINB5	S1008 Amyloid P Component, Serum Stem Cell Factor Secretin Masoin
GF GFR NG PCAM PO	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Foiregulin	 SAP SCF SCT SERPINB5 SHBG	SubuB Amyloid P Component, Serum Stern Cell Factor Secretin Maspin Sex Hormone Binding Globulin
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GF GFR NG PCAM PO PR RBB3 T-1	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1	SAP SCF SCT SERPINB5 SHBG SOD1 SORT1	SLOUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sontilin 1
GF GFR PCAM PO PR RBB3 T-1 ASIG	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Erythroplastic Leukemia Viral Onco H3 Endothelin 1 Esa Lizand (TNE Superfamily, Mamher 6)	SAP SCF SCT SERPINB5 SHBG SOD1 SORT1 TBG	SUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Turoroine Binding Globuline
2GF 2GFR 2DCAM 2PO 2PR 2PR 2PR 2PR 2PR 2PR 2PR 2PR 2PR 2PR	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Eibulin-1 C	SAP SCF SCT SERPINB5 SHBG SOD1 SORT1 TBG Tø	SUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroxine Binding Globuline
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GF GGF CGFR PDG PPC RBB3 CT-1 CASLG B1-1C GF2 GF4 CGF4	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration	SAP SCF SCF SERPINB5 SHBG SOD1 SORT1 TBG TGF-α TGF-β1 TGF-β3 TUPEC	SLOUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3
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GF GFR inG ipCAM PPO PPO RBB3 CT-1 ASLG B1-1C GF2 GF2 GF4 III III N N SH	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropiotetin Epiregulin Erythropolastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follice Stimulating Hormon	SAP SCF SCT SERPINB5 SHBG SOD1 SORT1 TBG TGF-α TGF-β1 TGF-β1 TGF-β3 THBS1 THPO TFC2	Anyloid P Component, Serum Stern Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortillin 1 Thyrosine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospondin 1
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GF GGR GGR MG GCAM PO PO FPR RBB3 CT-1 ASLG BF-1 CGF2 GF2 GF4 GF2 GF4 GF4 SH T VII SH T VII CCSF SH H GLP-1	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythropolastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follicle Stimulating Hormon Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total	SAP SCF SCT SERPINBS SHBG SOD1 SORT1 TBG TGF-β1 TGF-β1 TGF-β1 TGF-β3 THBS1 THPO TGF-β3 THBS1 THPO THF-Ω TNC TNF-Ω	Anyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospondin 1 Thrombospoitin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombomodulin Tenascin C Tumor Necrosis Factor, Alfa
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GF GGFR GGFR (PO GPA (PO PPR RRBB3 CT-1 ASLG GF2 GF2 GF2 GF2 GF2 GF4 GF2 GF2 GF4 SH SH T VII SSH SH SH SH SH SH SH SH SH SH SH SH SH	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropiotein Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follicle Stimulating Hormon Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glutathione S-Transferase Alpha Hepatitis AV Urus Cellular Receptor 1 Hepatin-Binding EGF-Like Growth Factor Human Epididymis Protein 4 Human Epididymis Protein 4	SAP SCF SCT SCR SCT SREND SOD1 SORT1 TBG TGF-A TGF-G TGF-FA1 TGF-FA1 TGF-FA1 TMFA1 THPO TIE-2 TIMP1 TMF-α TNF-R1 TNFR12 TNFR5FG TMFR5FG TMFR5FG TMFR5FG	SLUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospoletin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombospoletin Tumor Necrosis Factor, Receptor-Like 2 Tumor Necrosis Factor Receptor Type 1 Fas (TNF Receptor Superfamily, Member 6) Tumor Necrosis Factor Receptor Superfamily. Member 11
GF GFR GFR GFR GFR GFA GFA GFA GFA GFA GF2 GF2 GF2 GF2 GF2 GF4 III II I SH T VII SSH T VII SSH GF2 GF4 HE4 HER2 FABP	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follicle Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glutathione S-Transferase Alpha Hepatitis A Virus Cellular Receptor 1 Heparin-Binding EGF-Like Growth Factor Human Epideirmal Growth Factor Receptor 2 Heart-Type Erity Acid-Binding Protein 4	SAP SCF SCT SCT SERPINB5 SHBG SOD1 SORT1 TBG TGF-Q TGF-Q1 TGF-Q1 TGF-Q1 TGF-Q1 TGF-Q1 TGF-Q1 TGF-Q1 TGF-Q1 THFS1 THPO TIE-2 TMF1 TMF1 TMF1 TMF2 TMF3 TMF4 TMF4 TMF4 TMF4 TMF4 TMF4 TMF4 TMF4	Anyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombopoletin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombopoletin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombomodulin Tenascin C Tumor Necrosis Factor, Alfa Tumor Necrosis Factor, Reta Tumor Necrosis Factor Receptor-Like 2 Tumor Necrosis Factor Receptor Type I Fas (TNF Receptor Superfamily, Member 6) Tumor Necrosis Factor Receptor Superfamily, Member 11 Tissue Plasmingeen Artivatra ranisen
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GF GGFR SGFR SPGGFR SpCAM SPC SPC SPR RBB3 T-1 ASLG B1-1C GF2 GF4 III N SGF SH T VII SCSF SH ST AVCR1 BE-GF IFAPP IGF IGF IGF GGF INL IPN GF-1 GFBP1 GFBP1 GFBP1 GFBP1 GFBP1 ST	Endoglin, Quant Epithelial Cell Adhesion Molecule Erythropoietin Epiregulin Erythroblastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follicle Stimulating Hormon Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glutathione S-Transferase Alpha Hepatitis A Virus Cellular Receptor 1 Human Epidermal Growth Factor Receptor 2 Heart-Type Faty Acid-Binding Protein Hepatoyte Growth Factor Human Epidermal Growth Factor Receptor 2 Heart-Type Faty Acid-Binding Protein Hepatocyte Growth Factor 1 Human Epidermal Growth Factor Receptor 2 Heart Type Faty Acid-Binding Protein Hepatophil Epocaline Hepsin Intercellular Adhesion Molecule-1 Insulin-Like Growth Factor 1 Insulin-Like Growth Factor Sind. Prot 1 Insulin-Like Growth Factor Sind. Prot 2 Interleukin 10	SAP SCF SCT SCT SCR SCT SRENDES SHBG SOD1 SORT1 TBG TGF-A TGF-FA3 TGF-FA3 TGF-FA3 THFA THPO TIE-2 TIMP1 TNF-G TNF-FA TNFRSF11 TPA TSH VCGAM1 VEGFA VEGFD VEGFC VEGFR1 VEGFR3	SLUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombopoletin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombopoletin Tenascin C Tumor Necrosis Factor, Alfa Tumor Necrosis Factor, Beta Tumor Necrosis Factor, Beta Tumor Necrosis Factor Receptor-Like 2 Tumor Necrosis Factor Receptor Superfamily, Member 10 Tissue Plasminogen Activator antigen TNF-Related Apoptosis-Inducing Ligand Receptor 3 Thyroid Stimulating Hormone Vascular Endothelial Growth Factor Vascular Endothelial Growth Factor Vascular Endothelial Growth Factor C Vascular Endothelial Growth Factor D FMS-Related Tyrosine Kinase 1 Kinase Insert Domain Receptor
GF GGR GGR GGR GGRA SpCAM PO SpCAM PO PR RBB3 TT1 ASLG B1-1C GF2 GF4 III N SGF JH T VII GCSF SH T SSN SST JAVCR1 BE-GF EE4 IER2 IFABP IGF IGFR MNL PPN CAM1 gE GFP1 GFBP1 L-10 L-11	Endoglin, Quant Epithelial Cell Adhesion Molecule Epithegulin Epitegulin Erythropolastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follicle Stimulating Hormon Ferritin Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glutathione S-Transferase Alpha Heppatits A Virus Cellular Receptor 1 Heppatits A Virus Cellular Receptor 1 Human Epidermal Growth Factor Receptor 2 Heat-Type Fatty Acid-Binding Protein Heppatine Liberowth Factor Receptor 1 Human Neutrophil Lipocaline Hepsin Intercellular Adhesion Molecule-1 Immunoglobulin E Insulin-Like Growth Factor Bind. Prot 1 Insulin-Like Growth Factor Bind. Prot 2 Interleukin 11	SAP SCF SCT SCT SCRPINDS SRNINDS SOD1 SORTI TBG TGF-G1 TGF-β1 TGF-β2 THPO TH2-2 TIMP1 TM TNF-Q TNF-R TNFRS TNFRSF5 TNFRSF511 t-PA TRAILR3 TSH VEGFB VEGFR VEGFR VEGFR1 VEGFR2 VEGFR3 VWF	SLUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyroxine Binding Globuline Thyroglobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospoidin 1 Thrombopoidin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombomodulin Tenascin C Tumor Necrosis Factor, Alfa Tumor Necrosis Factor, Beta Tumor Necrosis Factor, Receptor Type I Fas (TNF Receptor Superfamily, Member 6) Tumor Necrosis Factor Receptor Superfam5 Tumor Necrosis Factor Receptor Superfam6 Vascular Cell Adpesion Molecule 1 Vascular Cell Adpesion Molecule 1 Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D FMS-Related Tyrosine Kinase 1 Kinase Insert Domain Receptor Fms-Related Tyrosine Kinase 4 von Willebrand Factor
GF GGR GGR GGR GGRA ipCAM ipCAM iPO iPR iRBB3 :T1 :ASLG BB-1CC :GF2 :GF4 :GF2 :GF4 :III :N :SH :T VII :SCF :H :GF1 :ST :HAVCR1 :B-EGF :E4 :E62 :GFA :GF :GF <td< td=""><td>Endoglin, Quant Epithelial Cell Adhesion Molecule Epithegulin Erythropolastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follice Stimulating Hormon Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glucathione S-Transferase Alpha Hepatris A Virus Cellular Receptor 1 Hepatrins A Virus Cellular Receptor 1 Hepatrins Virus Cellular Receptor 1 Hepatrins Virus Cellular Receptor 2 Heart-Type Fatty Acid-Binding Protein Hepatrocyte Growth Factor Muman Epidemial Growth Factor Receptor 2 Heart-Type Fatty Acid-Binding Protein Hepatocyte Growth Factor 1 Intercellular Adhesion Molecule-1 Immunoglobulin E Insulin-Like Growth Factor Rind. Prot 1 Insulin-Like Growth Factor Bind. Prot 2 Interleukin 10 Interleukin 12 (p40)</td><td>SAP SCF SCT SCT SCR SCR SCR SCR SCT SCR SORT1 TBG TGF-A3 TGF-β1 TGF-β3 THBS1 THPO TIE-2 TIMP1 TM TNF-G TNFRJ TNFRJ TMFRSF5 TNFRSF51 TSH VEGFR VEGFR VEGFR VEGFR3 VWF XCL1</td><td>SLUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyrogiobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospoietin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombospoietin Tumor Necrosis Factor, Reta Tumor Necrosis Factor Receptor-Like 2 Tumor Necrosis Factor Receptor Type 1 Fas (TNF Receptor Superfamily, Member 6) Tumor Necrosis Factor Receptor Superfamily, Member 11 Tissue Plasminogen Activator antigen TNF-Related Apoptosis-Inducing Ligand Receptor 3 Thyroid Stimulating Hormone Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Nase Itaket Tyrosine Kinase 1 Kinase Insert Domain Receptor</td></td<>	Endoglin, Quant Epithelial Cell Adhesion Molecule Epithegulin Erythropolastic Leukemia Viral Onco H3 Endothelin 1 Fas Ligand (TNF Superfamily, Member 6) Fibulin-1C Basic Fibroblast Growth Factor Fibroblast Growth Factor 4 Factor III Concentration Cellular Fibronectin Follice Stimulating Hormon Ferritin Factor VII Concentration Colony Stimulating Factor 3 (Granulocyte) Growth Hormone Glucagon-Like Peptide 1, Total Gelsolin Glucathione S-Transferase Alpha Hepatris A Virus Cellular Receptor 1 Hepatrins A Virus Cellular Receptor 1 Hepatrins Virus Cellular Receptor 1 Hepatrins Virus Cellular Receptor 2 Heart-Type Fatty Acid-Binding Protein Hepatrocyte Growth Factor Muman Epidemial Growth Factor Receptor 2 Heart-Type Fatty Acid-Binding Protein Hepatocyte Growth Factor 1 Intercellular Adhesion Molecule-1 Immunoglobulin E Insulin-Like Growth Factor Rind. Prot 1 Insulin-Like Growth Factor Bind. Prot 2 Interleukin 10 Interleukin 12 (p40)	SAP SCF SCT SCT SCR SCR SCR SCR SCT SCR SORT1 TBG TGF-A3 TGF-β1 TGF-β3 THBS1 THPO TIE-2 TIMP1 TM TNF-G TNFRJ TNFRJ TMFRSF5 TNFRSF51 TSH VEGFR VEGFR VEGFR VEGFR3 VWF XCL1	SLUUB Amyloid P Component, Serum Stem Cell Factor Secretin Maspin Sex Hormone Binding Globulin Superoxide Dismutase 1, Soluble Sortilin 1 Thyrogiobulin Transforming Growth Factor, Alpha Transforming Growth Factor, Alpha Transforming Growth Factor, Beta 1 Transforming Growth Factor, Beta 3 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospondin 1 Thrombospoietin Receptor Tyrosine Kinase, Endothelial, TIE-2 TIMP Metallopeptidase Inhibitor 1 Thrombospoietin Tumor Necrosis Factor, Reta Tumor Necrosis Factor Receptor-Like 2 Tumor Necrosis Factor Receptor Type 1 Fas (TNF Receptor Superfamily, Member 6) Tumor Necrosis Factor Receptor Superfamily, Member 11 Tissue Plasminogen Activator antigen TNF-Related Apoptosis-Inducing Ligand Receptor 3 Thyroid Stimulating Hormone Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Vascular Endothelial Growth Factor D Nase Itaket Tyrosine Kinase 1 Kinase Insert Domain Receptor

Seneral nathway	Gene name	Gene full name	Accession number
eneral patriway	SLC1A4	solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	NM_003038.4:3030
	SLC1A5/ASCT2	solute carrier family 1 (neutral amino acid transporter), member 5	NM_001145144.1:180
	SLC38A1	solute carrier family 38, member 1	NM_001077484.1:582
	SLC38A2	solute carrier family 38, member 2	NM_018976.4:1170
Amino acids metabolism	SLC38A7	solute carrier family 38, member 7	NM_018231.1:1810
	SLC7A10	solute carrier family 7 (neutral amino acid transporter light chain, asc system), member 10	NM_019849.2:1470
	SLC22A6 SLC22A8	Solute carrier family 22 (organic anion transporter igni Chain, Esystem), member 5 solute carrier family 22 (organic anion transporter), member 6 solute carrier family 22 (organic anion transporter). member 8	NM_004790.3:900 NM_004254.3:1170
Proliferation	CCND2	cyclin D2	NM_001759.2:5825
	MKI67	antigen identified by monoclonal antibody Ki-67	NM_002417.2:4020
	PCNA	proliferating cell nuclear antigen	NM_002592.2:280
	PCK1	phosphoenolpyruvate carboxykinase 1 (soluble)	NM_002591.2:1870
	SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	NM_006516.2:2500
	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	NM_001042.2:2120
	ENO1	enolase 1, (alpha)	NM_001428.2:1689
	ENO2	enolase 2	NM_001975.2:1855
	G6PD	glucose-6-phosphate dehydrogenase	NM_000402.2:1155
	HK1	hexokinase 1	NM_000188.2:3355
	PDHK2 PDHK3	nexokinase z pyruvate dehydrogenase kinase, isozyme 2 nynuszte dehydrogenase kinase isozyme 3	NM_000189.4:6880 NM_002611.3:435 NM_005391.1:585
	PDK1 PDK4	pyruvate dehydrogenase kinase, isozyme 1 pyruvate dehydrogenase kinase, isozyme 1 pyruvate dehydrogenase kinase inzyme 4	NM_002610.3:1170 NM_002612.3:1675
Glucose metabolism	PFKFB1	6-phosphofructo-2-kinase/fructose-2.6-biphosphatase 1	NM_002625.2:564
	PFKFB2	6-phosphofructo-2-kinase/fructose-2.6-biphosphatase 2	NM_001018053.1:445
	PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	NM_001145443.1:49
	PFKFB4	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4	NM_004567.2:400
	PGAM1	phosphoglycerate mutase 1 (brain)	NM_002629.2:1037
	PGAM4	phosphoglycerate mutase family member 4	NM_001029891.2:120
	PKM2	pyruvate kinase, muscle	NM_182471.1:2105
	TIGAR	Tp53-induced glycolysis and apoptosis regulator	NM_020375.2:5245
	LDHA	lactate dehydrogenase A	NM_005566.1:985
	LDHB	lactate dehydrogenase B	NM_001174097.1:11
	SLC16A1	solute carrier family 16, member 1 (monocarboxylic acid transporter 1)	NM_003051.3:635
	SLC16A3	solute carrier family 16, member 3 (monocarboxylic acid transporter 4)	NM_004207.2:370
	GEPT1 GLS	glutaminetructose-6-phosphate transaminase 1 glutaminase glutaminase 7 (juver, mitochondriji)	NM_001244710.1:60 NM_014905.3:985
Glutamine metabolism	GLS2 GLUD1 GLUD2	glutaminase 2 (liver, mitochondrial) glutamate dehydrogenase 1 elutamate dehydrogenase 2	NM_005271.2:2680
	IDH1	isocitrate dehydrogenase 2 isocitrate dehydrogenase 1 (NADP+), soluble	NM_005896.2:105
Нурохіа	CAV1	caveolin 1, caveolae protein, 22kDa	NM_001753.3:434
	EPAS1	endothelial PAS domain protein 1	NM_001430.3:4246
	HIF1A	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	NM_001530.2:1985
	SOCS3	suppressor of cytokine signaling 3	NM_003955.3:1870
Leptin signaling	LEP LEPR	leptin receptor	NM_000230.2:1875 NM_001003679.1:20
	DHCR7	7-dehydrocholesterol reductase	NM_001360.2:780
	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	NM_000859.2:3905
	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	NM_002130.4:420
	MVD	Mevalonate (Diphospho) Decarboxylase	NM_002461.1:128
	MVK	Mevalonate Kinase	NM_000431.2:201
	SQLE	squalene epoxidase	NM_003129.3:250
	ACACA	acetyl-CoA carboxylase alpha acetyl-CoA carboxylase beta	NM_198834.1:3681 NM_001093.3:3365
	ACLY ACSS2	ATP citrate lyase acyl-coA synthetase short-chain family member 2	NM_001096.2:3195 NM_001076552.2:65
	DGAT1	diacylglycerol O-acyltransferase 1	NM_012079.4:544
	ELOVL5	ELOVL fatty acid elongase 5	NM_001242831.1:46
Lipid metabolism	ELOVL6	ELOVL fatty acid elongase 6	NM_001130721.1:10
	FADS1	fatty acid desaturase 1	NM_013402.3:1560
	FASN	tatty acid synthase	NM_004104.4:5387
	MLYCD	malonyl-CoA decarboxylase	NM_012213.2:1530
	ACSL3	stearoy-LoA desaturase (deita->-desaturase) Acyl-CoA Synthetase Long-Chain Family Member 3 craiting any introductor and filing)	NM_005063.4:2025 NM_203372.1:220
	CPT1B	carritine palmitoyitransferase 18 (muscle)	NM_004377.3:2578
	MAGI	Monoplyceride Linase	NM_007283.5:1355
	APOB	apolipoprotein B (including Ag(x) antigen)	NM_000384.2:2833
	APOC1	apolipoprotein C-I	NM_001645.3:270
	APOE	apolipoprotein E	NM_000041.2:96
	SREBF1	sterol regulatory element binding transcription factor 1	NM_001005291.1:13
	SREBF2	sterol regulatory element binding transcription factor 2	NM_004599.2:4080
	FABP3	fatty acid binding protein 3	NM_004102.3:915
	COX4I1	cytochrome c oxidase subunit IV isoform 1	NM_001861.2:160
	CS	citrate synthase	NM_004077.2:740
	FH	fumarate hydratase	NM_000143.2:203
	IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial	NM_002168.2:944
	MDH1	malate denydrogenase 1, NAD (soluble)	NM_005917.3:970
	MDH2	malate dehydrogenase 2, NAD (mitochondrial)	NM_005918.2:475
	ME2 ME3	mail: enzyme 1, WADY(+)-dependent, Kytoson: malic enzyme 2, NADY(+)-dependent, mitochondrial malic enzyme 3, NADP(+)-dependent, mitochondrial	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:10
	NDUFA4	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa	NM_002489.2:35 NM_002490.3:430
	NDUFB2	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	NM_004546.2:230
	NDUFB4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex. 4, 15kDa	NM_004547.4:254
xidative Metabolism /TCA	NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	NM_002492.3:115
	NDUFB6	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa	NM_001199987.1:9
	NDUFB9	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa	NM_005005.2:80
	NDUFC2	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa	NM_001204054.1:12
	OGDH	oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)	NM_002541.2:65
	PC	pyruvate carboxylase	NM_000920.3:2055
	PDHB	pyruvate dehydrogenase (lipoamide) beta	NM_000925.3:555
	PDP1	pyruvate dehyrogenase phosphatase catalytic subunit 1	NM_001161778.1:95
	PDP2	pyruvate dehyrogenase phosphatase catalytic subunit 2	NM_020786.2:6505
	SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	NM_004168.1:230
	SLC25A1	solute carrier family 25 (mitochondrial carrier; citrate transporter), member 1	NM_005984.2:964
	SLC25A10	solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10	NM_012140.3:390
	SLC25A11	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11	NM_003562.4:860
	HNF4A	hepatocyte nuclear factor 4, alpha	NM_178850.1:1116
Oxidative stress	NFE2L2/nrf2	Kelch-like ELH-associated protein 1 nuclear factor (erythroid-derived 2)-like 2	NM_006164.4:746
	SOD2	superoxide dismutase 2, mitochondrial	NM_000636.2:640
	SOD3	superoxide dismutase 2, extracellular	NM_003102.2:1135
	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta	NM_006549.3:1710
	CREB1	CAMP responsive element binding protein 1	NM_134442.2:200
	ENTPD5	Ectonucleoside Triphosphate Diphosphohydrolase 5	NM_001249.2:1585
	PEBP1	phosphatidylethanolamine binding protein 1	NM_002567.2:1335
	GSK3A	glycogen synthase kinase 3 alpha	NM_019884.2:480
	GSK3B	glycogen synthase kinase 3 beta	NM_002093.2:925
	INSIG1 INSIG2	insulin induced gene 1 insulin induced gene 2	NM_005542.3:1120 NM_016133.2:513
legulator of metabolism	MLXIPL	MLX interacting protein-like	NM_032951.2:2805
	MTOR	mechanistic target of rapamycin (serine/threonine kinase)	NM_004958.2:5095
	MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	NM_002467.3:1610
	NR1D1	nuclear receptor subfamily 1, group D, member 1	NM_021724.3:1080
	NR1H2	nuclear receptor subfamily 1, group H, member 2	NM_007121.4:30
	NR1H3	nuclear receptor subfamily 1, group H, member 3	NM_005693.2:1575
	PPARA	perconsome promerator-activated receptor alpha peroxisome proliferator-activated receptor delta consistence pacificated, activated receptor delta	NM_001001928.2:52 NM_006238.4:107
	PPARGC1A	pervisionite promierator-activated receptor gamma peroxisome proliferator-activated receptor gamma, coactivator 1 alpha hososhoelyverate dehvfropensso	NM_013261.3:1505
erine/glycine synthesie	PSAT1 PSPH	proceptos processor and an	NM_021154.3:1445
, o., one synthesis	SHMT1	serine hydroxymethyltransferase 1 (soluble)	NM_148918.1:1800
	SHMT2	serine hydroxymethyltransferase 2 (mitochondrial)	NM_001166356.1:1/
	FLT1	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor recentor)	NM_002019.4:530
	FLT3	fms-related tyrosine kinase 3	NM_004119.1:580
	FLT4	fms-related tyrosine kinase 4	NM_002020.1:955
	KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	NM_002253.2:1420
	NRP1	neuropilin 1	NM_003873.5:370
ngiogenesis/Vasculature	NRP2	neuropilin 2	NM_003872.2:805
	PECAM1	platelet/endothelial cell adhesion molecule 1	NM_000442.3:1365
	TIE1 VEGFA	tyrosine kinase with immunoglobulin-like and EGF-like domains 1 vascular endothelial growth factor A	NM_005424.2:2610 NM_001025366.1:13
	VEGFB	vascular endothelial growth factor B	NM_003377.3:687
	VEGFC	vascular endothelial growth factor C	NM_005429.2:565
	RPLPO	ribosomal protein, large, PO	NM_001002.3:250
Househood	PGK1	nuosuniai protein L19 phosphoglycerate kinase 1 alweenaldewide 3. oberahata dobudeen	NM_000291.2:1030
ноиsekeeping	CLTC P2M	Nyyeeraruenyde-3-prospnate denydrogenase Clathrin, heavy chain heta 2. microalabulia	NM_004859.2:290
	32191		ww004046.2.25

Pommier et al. Table S2 (Related to Figure 3 and 4): List, abbreviations and accession numbers of the genes analyzed by NanoString technology in mCRC patients (HORIZON II).

	Gene Symbol Fluidigm	Full gene name	Accession number	Human specific assay ID
	SLC1A4	solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	NM_003038.4:3030	Hs01046029_m1
	SLC1A5/ASCT2	solute carrier family 1 (neutral amino acid transporter), member 5	NM_001145144.1:180	Hs00153715_m1
	SLC38A1	solute carrier family 38, member 1	NM_001077484.1:5825	Hs01071209_m1
	SLC38A2	solute carrier family 38, member 2	NM_018976.4:1170	Hs03037377_m1
Amino acids transport	SLC38A7	solute carrier family 38, member 7	NM_018231.1:1810	Hs00171168_m1
	SLC7A10	solute carrier family 7 (neutral amino acid transporter light chain, asc system), member 10	NM_019849.2:1470	Hs00982744_m1
	SLC7A5/LAT1	solute carrier family 7 (amino acid transporter light chain, L system), member 5	NM_003486.5:785	Hs01120918_m1
	SIC22A0	solute carrier family 22 (organic anion transporter), member 6	NM 004254 2:1170	Hs00758892 c1
	CCND2	ordin D2	NM_004234.3.1170	Hs00608644 m1
Cell cycle	MK167	antigen identified by monoclonal antibody Ki-67	NM_002417.2:4020	Hs00154208 m1
	PCNA	proliferating cell nuclear antigen	NM 002592.2:280	Hs00902177 m1
	PCK1	phosphoenolpyruvate carboxykinase 1 (soluble)	NM 002591.2:1870	Hs00264683 m1
	ENO1	enolase 1, (alpha)	NM_001428.2:1689	Hs00936368_m1
	G6PD	glucose-6-phosphate dehydrogenase	NM_000402.2:1155	Hs00855332_g1
	HK1	hexokinase 1	NM_000188.2:3355	Hs01032072_m1
	HK2	hexokinase 2	NM_000189.4:6880	Hs01034055_g1
	PDK1	pyruvate dehydrogenase kinase, isozyme 1	NM_002610.3:1170	Hs00168352_m1
	PDK4	pyruvate dehydrogenase kinase, isozyme 4	NM_002612.3:1675	Hs00940429_m1
	PFKFB1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1	NM_002625.2:564	Hs04260079_mH
	PFKFB2	6-phosphotructo-2-kinase/tructose-2,6-biphosphatase 2	NM_001018053.1:445	HS00940084_g1
Glucose metabolism	PEKERA	6-phosphoriucto-2-kinase/fructose-2,6-biphosphatase 3	NM_001143443.1.493	Hs00954278 m1
Glacose metabolism	PGAM1	phosphorucco-2-kmase/mecose-2,0-biphosphatase 4	NM_002629.2:1037	Hs01650979 m1
	PGAM4	phosphoglycerate mutase family member 4	NM 001029891.2:1207	Hs01013986 m1
	PKM2	pyruvate kinase, muscle	NM_182471.1:2105	Hs01003432_m1
	TIGAR	Tp53-induced glycolysis and apoptosis regulator	NM_020375.2:5245	Hs00947539_m1
	LDHA	lactate dehydrogenase A	NM_005566.1:985	Hs00900244_m1
	LDHB	lactate dehydrogenase B	NM_001174097.1:1190	Hs00159110_m1
	SLC16A1	solute carrier family 16, member 1 (monocarboxylic acid transporter 1)	NM_003051.3:635	Hs00938918_m1
	SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	NM_006516.2:2500	Hs00959073_g1
	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	NM_001042.2:2120	Hs00896610_m1
	SLC16A3	solute carrier family 16, member 3 (monocarboxylic acid transporter 4)	NM_004207.2:370	Hs00938109_m1
	GFPT1	glutaminetructose-6-phosphate transaminase 1	NM_001244710.1:606	Hs01014019_m1
	515 6152	giutaminase alutaminase 2 (liver, mitechondrial)	NIVI_U14905.3:985	ns00998/28_g1
Glutamine metabolism	GL32	giutanimase 2 (liver, mitochononal)	NM 005271 2:3690	ns0103204/_g1
	GLUD2	giutamate dehydrogenase 2	NM 012084 3:12	Hs00997938 m1
	IDH1	isocitrate dehydrogenase 1 (NADP+). soluble	NM 005896.2:105	Hs01047720 m1
	CA-9	Carbonic anhydrase 9	NM 001216.2:960	Hs00174877 m1
	CAV1	caveolin 1, caveolae protein, 22kDa	NM_001753.3:434	Hs04260076 g1
Hypoxia	EPAS1	endothelial PAS domain protein 1	NM_001430.3:4246	Hs00174497_m1
	HIF1A	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	NM_001530.2:1985	Hs00906383_m1
	SOCS3	suppressor of cytokine signaling 3	NM_003955.3:1870	Hs00751507_s1
Leptin signaling	LEP	leptin	NM_000230.2:1875	Hs00244618_m1
<u> </u>	LEPR	leptin receptor	NM_001003679.1:2000	Hs01059263_g1
	ACACA	acetyl-CoA carboxylase alpha	NM_198834.1:3681	Hs02574374_s1
	ACACB	acetyl-CoA carboxylase beta	NM_001093.3:3365	Hs00355045_m1
	ACLY	ATP citrate lyase	NM_001096.2:3195	Hs00201385_m1
	ACSS2	acyl-CoA synthetase short-chain family member 2	NM_001076552.2:655	Hs01023087_m1
	DGAT1	diacyigiycerol U-acyitransferase 1	NM_0120/9.4:544	HS00361415_m1
	ELOVIS	ELOVE fatty acid elongase 5	NM_001242831.1:40	HS01010957_m1
	ELOVED	fatty acid cynthace	NM_001150/21.1.1055	Hs01094707_111
	MIYCD	malonyl.CoA decarboxylase	NM_012213_2:1530	Hs01026042 m1
	SCD	stearovi-CoA desaturase (delta-9-desaturase)	NM_005063.4:2025	Hs00174860 m1
Lipid metabiolism	CPT1A	carnitine palmitovitransferase 1A (liver)	NM 001876.3:1355	Hs01067158 gH
	CPT1B	carnitine palmitoyltransferase 1B (muscle)	NM_004377.3:2578	Hs01005622_m1
	DHCR7	7-dehydrocholesterol reductase	NM_001360.2:780	Hs00971639_m1
	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	NM_000859.2:3905	Hs00971715_m1
	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	NM_002130.4:420	Hs00153380_m1
	SREBF1	sterol regulatory element binding transcription factor 1	NM_001005291.1:1392	Hs00892681_m1
	SREBF2	sterol regulatory element binding transcription factor 2	NM_004599.2:4080	Hs00168966_m1
	SQLE	squalene epoxidase	NM_003129.3:250	Hs00912671_m1
	APOB	apolipoprotein B (including Ag(x) antigen)	NM_000384.2:2833	Hs00929812_g1
	APOC1	apolipoprotein C-I	NM_001645.3:270	Hs00931443_m1
	APOE	apolipoprotein E	NM_000041.2:96	Hs01032443_m1
	C0X411	cytochrome cloxidase subunit tv isoform 1	NM_001801.2:100	HS00201955_m1
	C3	fumarate hudratase	NM_0001/2 2:202	Hs01042412_III1
	IDH2	isoritrate dehydrogenase 2 (NADP+) mitochondrial	NM_002168 2:944	Hs01037712 m1
	MDH1	malate dehydrogenase 1. NAD (soluble)	NM_005917.3:970	Hs00800172_s1
	MDH2	malate dehydrogenase 2, NAD (mitochondrial)	NM 005918.2:475	Hs00899690 m1
	ME1	malic enzyme 1. NADP(+)-dependent. cytosolic		
	MED		NM 002395.3:1405	Hs00190006 m1
	IVIEZ	malic enzyme 2, NAD(+)-dependent, mitochondrial	NM_002395.3:1405 NM_002396.3:610	Hs00190006_m1 Hs00853558_g1
	ME3	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(+)-dependent, mitochondrial	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1
	ME2 ME3 NDUFA4	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159583_m1
	ME2 ME3 NDUFA4 NDUFA6	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14KDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35 NM_002490.3:430	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159583_m1 Hs00601381_mH
	ME2 ME3 NDUFA4 NDUFA6 NDUFB2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35 NM_002490.3:430 NM_004546.2:230	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159583_m1 Hs00601381_mH Hs01072843_m1
Oxidative activity	MEZ ME3 NDUFA4 NDUFA6 NDUFB2 NDUFB4 NDUFB4	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35 NM_002499.3:430 NM_004546.2:230 NM_004547.4:254 NM_00252.2:255	Hs00190006_m1 Hs0083558_g1 Hs00159582_m1 Hs00159583_m1 Hs00601381_mH Hs01072843_m1 Hs00075961_g1 Ur04290007_c1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUFB2 NDUFB4 NDUFB5 NDUFB5	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (buiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (buiquinone) 1 alpha subcomplex, 6, 14KDa NADH dehydrogenase (buiquinone) 1 beta subcomplex, 2, 8KDa NADH dehydrogenase (buiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (buiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (buiquinone) 1 beta subcomplex, 5, 15KDa	NM_002395.3:405 NM_002396.3:610 NM_001014811.1:1080 NM_002499.2:35 NM_002490.3:430 NM_004546.2:230 NM_004547.4:254 NM_002492.3:115 NM_002492.3:115	Hs0019006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159583_m1 Hs000501381_mH Hs0072843_m1 Hs00775961_g1 Hs04260033_g1 Hs04260033_g1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUFB2 NDUFB4 NDUFB5 NDUFB6 NDUFB9	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 5KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35 NM_002490.3:430 NM_004546.2:230 NM_00454.2:254 NM_002492.3:115 NM_00119987.1:9 NM_00055.2:80	Hs00190006_m1 Hs00159522_m1 Hs00159582_m1 Hs00159583_m1 Hs000759561_g1 Hs0027561_g1 Hs0027561_g1 Hs0027511_g1 Hs0101275_f1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUF82 NDUF82 NDUF85 NDUF86 NDUF86 NDUF89 NDUF22	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 subcomplex, 9, 22KDa	NM_002395.3:1405 NM_002396.3:610 NM_001014811.1:1080 NM_002489.2:35 NM_004546.2:230 NM_004546.2:230 NM_004547.4:254 NM_001547.4:254 NM_001547.1:35 NM_005005.2:80 NM_005005.1:36	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159582_m1 Hs00159583_m1 Hs00072843_m1 Hs00072843_m1 Hs00072861_g1 Hs00127561_g1 Hs01027561_g1 Hs01027561_g1 Hs01027561_g1 Hs01027561_g1 Hs01027561_g1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUF82 NDUF84 NDUF85 NDUF86 NDUF86 NDUF89 NDUF22 OGDH	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 21KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa	NM_002395.3:1405 NM_002396.3:610 NM_00104811.1:1080 NM_002489.2:35 NM_002489.2:3420 NM_004547.4:254 NM_004547.4:254 NM_0019987.1:9 NM_005005.2:80 NM_001204054.1:1235 NM_002041.2:65	Hs00190006_m1 Hs00835558_g11 Hs00159582_m1 Hs00515958_m1 Hs00601381_mH Hs00601381_mH Hs00602841_m1 Hs00975661_g1 Hs00975661_g1 Hs0097561_g1 Hs01027211_g1 Hs01027211_g1 Hs010860_m1 Hs0108666_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB6 NDUFB6 NDUFB9 NDUFC2 OGDH PC	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 2KDa NADH dehydrogenase (ubiquinone) 1 subcomplex, 9, 2KDa NADH dehydrogenase (ubiquinone) 1 subcomplex, 9, 2KDa	NM_002395.3:1405 NM_002395.3:100 NM_002489.2:35 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:3115 NM_00129987.1:9 NM_00262.2:115 NM_002542.3:15 NM_002542.2:65	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159582_m1 Hs00013581_mH Hs00073243_m1 Hs00073561_g1 Hs00272711_g1 Hs0102258_g1 Hs01081860_m1 Hs01088886_m1 Hs00159588_m1_
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB6 NDUFB6 NDUFC2 OGDH PC PC PDHB	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 24KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 24KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate carboxylase pyruvate carboxylase	NM_002395.31405 NM_002395.3160 NM_00104811.1:1080 NM_002492.35 NM_002492.3430 NM_00546.2:330 NM_00546.2:330 NM_00546.2:331 NM_002492.3115 NM_002987.19 NM_002987.19 NM_002987.19 NM_00254.2:65 NM_00292.3:255	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159582_m1 Hs00195983_m1 Hs00195981_mH Hs00195961_g1 Hs01225_g1 Hs010225_g1 Hs010235_g1 Hs01085886_m1 Hs01085886_m1 Hs00195882_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUFB2 NDUFB5 NDUFB5 NDUFB5 NDUFB5 NDUFC2 OGOH PC PDHB PDHB	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 25KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-kteg)utarate) dehydrogenase (lipoamide) pyruvate carboxylase pyruvate dehydrogenase (lipoamide) beta	NM_002395.3:1405 NM_002395.3:100 NM_00104811.1:1080 NM_002490.2:35 NM_002490.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:31 NM_0019987.1:9 NM_001204954.1:1235 NM_002920.3:2055 NM_002923.3:055 NM_001161781.1950	Hs00190006_m1 Hs00159588_g1 Hs00159588_m1 Hs00159583_m1 Hs0001381_mH Hs00012843_m1 Hs0002781_g1 Hs0027511_g1 Hs0027511_g1 Hs00102158_g1 Hs001081860_m1 Hs0008686_m1 Hs00069666_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUF82 NDUF82 NDUF85 NDUF85 NDUF85 NDUF66 NDUF66 NDUF66 PC PC PC PDP1 PDP1 PDP2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 9kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17kDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5kDa oxoglutareta (alpha-ketoglutarete) 1 subcomplex unknown, 2, 14.5kDa pyruvate dehydrogenase (lipoamide) beta pyruvate dehydrogenase (lipoamide) beta pyruvate dehydrogenase phosphatase catalytic subunit 1 pyruvate dehydrogenase phosphatase catalytic subunit 2	NM_002395.3:1405 NM_002395.3:1405 NM_002489.2:35 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:3115 NM_002492.3:115 NM_00129987.1:9 NM_005005.2:80 NM_005241.2:65 NM_00253.3:55 NM_00253.3:55 NM_00253.3:55 NM_002162.1:505	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159582_m1 Hs00159583_m1 Hs001072813_m1 Hs00075961_g1 Hs00127211_g1 Hs00107211_g1 Hs00108586_m1 Hs00108586_m1 Hs001081860_m1 Hs00109586_m1 Hs00196862_m1 Hs00196862_m1 Hs00196862_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB6 NDUFB6 NDUFB6 NDUFC2 OGDH PC PC PDHB PDP1 PDP2 SDHA	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate carboxylase pyruvate dehydrogenase (lipoamide) beta pyruvate dehydrogenase cubiquingtic subunit 1 pyruvate dehydrogenase cubiquingtic subunit 1 pyruvate dehydrogenase cubiquingtic subunit 2 succinate dehydrogenase (ubiquingtic subunit 1)	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002482.235 NM_002480.2430 NM_004542.230 NM_004542.230 NM_001542.231 NM_0019087.19 NM_001204624.1:1235 NM_00252.805 NM_001204624.1:235 NM_002920.3:255 NM_00278.3:555 NM_00262.5555 NM_002662.6505 NM_002662.6505	Hs00130006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs000139581_m1 Hs0007565[_g1 Hs0097565[_g1 Hs00129213_g1 Hs01027211_g1 Hs01027213_g1 Hs01082586_m1 Hs01082586_m1 Hs01082586_m1 Hs01095918_m1 Hs00095366_m1 Hs00095366_m1 Hs0012747_s1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB9 NDUFB9 NDUFB9 NDUFC2 OGDH PC PC PC PC PC PDF1 PDP1 PDP2 SDFA4 SLC2SA1	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NADP(+)-dependent, mitochondrial NADH dehydrogenase (buipuinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 4, 9KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (buipuinone) 1 beta subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-kteg)utarate) dehydrogenase (lipoamide) pyruvate carboxylase pyruvate dehydrogenase phosphatase catalytic subunit 1 pyruvate dehydrogenase phosphatase catalytic subunit 2 sucinate dehydrogenase phosphatase catalytic subunit 1 pyruvate dehydrogenase phosphatase catalytic subunit 2 sucinate dehydrogenase phosphatase catalytic subunit 1 pyruvate dehydrogenase phosphatase catalytic subunit 1 pyruvate dehydrogenase phosphatase catalytic subunit 2 sucinate dehydrogenase phosphatase catalytic subunit 2 sucinate dehydrogenase phosphatase catalytic subunit 2 subute cariner family 25 (mitochondrial carrier; citrate transporter), member 1	NM_002395.3:1405 NM_002395.3:1405 NM_002489.2:35 NM_002489.2:35 NM_00249.2:33 NM_00546.2:230 NM_00546.2:230 NM_00546.2:230 NM_0024023.115 NM_00119997.1:9 NM_00502.80 NM_00252.3:55 NM_000253.355 NM_00015781.1950 NM_0011671781.1950 NM_0011671781.1950 NM_0011671781.1950 NM_001581.2:30	Hs00130006_m1 Hs00139588_g1 Hs00159588_g1 Hs00159582_m1 Hs00159582_m1 Hs00129583_m1 Hs00129583_m1 Hs0012911_g1 Hs0012711_g1 Hs01101235_g1 Hs010125845_m1 Hs01012918_g1 Hs01012918_g1 Hs01015918_m1 Hs00053666_m1 Hs0095866_m1 Hs0095836_m1 Hs00953166_m1 Hs00953166_g1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF82 NDUF85 NDUF85 NDUF85 NDUF62 OGOH PC PC PDP1 PDP1 PDP2 SDHA SLC25A10 SLC25A10	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (bubiquinone) 1 bates subcomplex, 5, 14KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate carboxylase privvate dehydrogenase complex, satalytic subunit 1 privvate dehydrogenase complex, subunit 7, flavoproterin (Fp) soulte carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10	NM_002395.3:1405 NM_002395.3:1405 NM_002489.2:35 NM_002489.2:35 NM_002489.2:35 NM_002489.2:31 NM_001546.2:230 NM_001546.2:230 NM_0012987.1:9 NM_0012987.1:9 NM_0012987.1:9 NM_0012940.5:80 NM_0012941.2:65 NM_0012941.2:65 NM_001251.3:55 NM_001278.1:950 NM_001261.2:650 NM_00168.1:230 NM_00253.3:55 NM_00168.1:230 NM_00253.3:55 NM_00168.1:230 NM_00254.2:65 NM_00168.1:230 NM_00168.1:230 NM_005984.2:64 NM_005984.2:64	Hs00190006_m1 Hs00853558_g1 Hs00159582_m1 Hs00159582_m1 Hs00159583_m1 Hs00125983_m1 Hs0012581_m1 Hs0012581_m1 Hs0012581_m1 Hs0012581_m1 Hs0012581_m1 Hs010255_g1 Hs01081860_m1 Hs00195861_m1 Hs00196562_m1 Hs0026663_m1 Hs0026663_m1 Hs0026666_m1 Hs0026666_m1 Hs0026666_m1 Hs0026666_m1 Hs0026666_m1 Hs0026666_m1 Hs002767_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB5 NDUFB5 NDUFB9 NDUFB9 NDUFC2 OGOH PC PDF1 PDF1 PDF1 PDF1 PDF2 SDF4 SLC25A11 SLC25A11 SLC25A11 SLC25A11	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa NADH dehydrogenase (ubiquinone) 1, subcomplex, 6, 17kDa NADH dehydrogenase (ubiquinone) 1, subcomplex, 6, 17kDa NaDH dehydrogenase (ubiquinone) 1, subcomplex, 6, 17kDa pyruvate dehydrogenase (ubiquinone) 1, subcomplex, 6, 17kDa Sucinate dehydrogenase (ubiquinone) 1, subcomplex, 6, 17kDa Sucinate dehydrogenase (ubiquinone) 1 beta pyruvate dehydrogenase (ubiquatirate) dehydrogenase (ubiquinone) sucinate dehydrogenase (ubiquinone) beta pyruvate dehydrogenase (ubiquatic subunit 1 pyruvate dehydrogenase (ubiquatic catalytic subunit 1 pyruvate dehydrogenase (ubiquinone) admir (1 dicromotif 1 admir (1	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002490.3:430 NM_004546.2:230 NM_005462.2:30 NM_002492.3:115 NM_002492.3:115 NM_00290492.3:115 NM_002104054.1:1235 NM_00292.3:2055 NM_00292.3:2555 NM_002161278.1:950 NM_00292.3:555 NM_002162.5:555 NM_002162.3:555 NM_0	Hs00130006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00075861_m1 Hs00075861_g1 Hs00129283_m1 Hs00129283_m1 Hs00129281_g1 Hs00120211_g1 Hs00120213_g1 Hs0012025_g1 Hs001262_m1 Hs0026362_m1 Hs00263166_m1 Hs0029316_g1 Hs00194174_s1 Hs00159438_m1 Hs00159438_m1 Hs00159438_m1 Hs00159438_m1 Hs00159438_m1 Hs00159437_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA6 NDUFB2 NDUFB4 NDUFB5 NDUFB5 NDUFB9 NDUFB9 NDUFC2 OGDH PC PC PDH8 PDP1 PDP1 PDP2 SDHA SLC25A1 SLC25A1 SLC25A1 SLC25A1 HNF4A FEAP1	malic enzyme 2, NAD(-)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pruvate dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pruvate dehydrogenase complex, subunit 1, pruvate dehydrogenase complex, subunit 2, succinate dehydrogenase complex, subunit 7, flavoproterin (fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 10 hepatocyte nuclear factor 4, alpha	NM_002395.3:1405 NM_002395.3:1405 NM_002499.2:35 NM_002499.2:35 NM_002499.2:33 NM_00546.2:230 NM_00546.2:230 NM_00546.2:230 NM_002492.3:115 NM_001199987.1:9 NM_00202495.3:55 NM_00252.3:255 NM_00252.3:55 NM_000252.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000253.3:55 NM_000254.2:964 NM_00112140.3:390 NM_003562.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860NM_00254.4:860 NM_00254.4:860NM_00254.4:860NM_00254.4:860NM_00254.4:860NM_00254.4:860NM_00254	Hs00120006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs001292843_m1 Hs00129281_m1 Hs00129211_g1 Hs0012928_g1 Hs0012918_m1 Hs00129583_m1 Hs00953166_m1 Hs00953166_m1 Hs00953166_m1 Hs0015474_11 Hs0015474_11 Hs0015483_m1 Hs0015833_m1 Hs0015833_m1 Hs0015483_m1
Oxidative activity	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF82 NDUF83 NDUF83 NDUF85 NDUF89 NDUF20 OGOH PC PC PDP1 PDP2 PDP1 PDP2 SDHA SLC25A10 SLC25A11 SLC2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 6, 14KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (bubiquinone) 1 subcomplex, 9, 23KDa NADH dehydrogenase (bubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (bubiquinate) tataget (subunit 1 pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 1 solute arrier family 25 (mitochondrial carrier; dicarboxylate carrier), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate carrier), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate carrier), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate carrier), member 11 hepatoxyte nuclear factor 4, alpha	NM_002395.3:1405 NM_002395.3:1405 NM_00104811.1:1080 NM_002482.2:35 NM_002490.2:430 NM_004546.2:230 NM_004546.2:230 NM_0015472.2:31 NM_00129087.1:9 NM_00120492.3:115 NM_00120492.3:155 NM_0012178.1:255 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:255 NM_	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs000159582_m1 Hs000159582_m1 Hs000159582_m1 Hs0007565_g1 Hs00172582_g1 Hs0012258_g1 Hs0012258_g1 Hs0012582_g1 Hs0012583_m1 Hs00058366_m1 Hs00058366_m1 Hs00168353_m1 Hs00193166_g1 Hs00193166_g1 Hs0019333_m1 Hs0019333_m1 Hs0019333_m1 Hs0019333_m1 Hs0019333_m1 Hs0019322_g1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUF85 NDUF82 NDUF85 NDUF85 NDUF89 NDUF89 NDUF20 OG0H PC PDH8 POP1 PDP1 PDP2 SDHA SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 NF42A KEAP1 NF62L2/nf2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate carboxylase pyruvate dehydrogenase (ipoamide) beta pyruvate dehydrogenase complex, subunit 1 pyruvate dehydrogenase catalytic subunit 1 pyruvate dehydrogenase complex, subunit 2, 3 succinate dehydrogenase complex, subunit 7, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier, cirate transporter), member 1 solute carrier family 25 (mitochondrial carrier, cirate transporter), member 1 solute carrier family 25 (mitochondrial carrier, cirate transporter), member 1 hepatocyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (erythoid-derived 2)-like 2 superoxide dibymtase 1.50lble	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002489.235 NM_002489.233 NM_005462.230 NM_005462.230 NM_005462.230 NM_002492.3115 NM_001199987.19 NM_00502.80 NM_002492.3125 NM_002920.32055 NM_00220.32555 NM_002161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_001542.3555 NM_00154.4:345 NM_001544.4:35	Hs00130006_m1 Hs00159588_g11 Hs00159588_g11 Hs00159588_m1 Hs00159588_m1 Hs00159588_m1 Hs00159588_m1 Hs001292843_m1 Hs001292843_m1 Hs00127211_g1 Hs0012025_g1 Hs0012025_g1 Hs0012935_g1 Hs0012905_m1 Hs00268662_m1 Hs00383106_g1 Hs0012977_m1 Hs00129137_g1 Hs00129138_m1 Hs00129137_g1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB5 NDUFB9 NDUFB6 NDUFB9 PC C C PDH8 PC PC PDP1 PDP1 PDP2 SDHA SIC25A10 SIC25A10 SIC25A11 HINFAA KEAP1 NFE2L2/nrf2 SOD1 SOD2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (bubiquinone) 1 balta subcomplex, 5, 14KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 subcomplex unknown, 2, 14.5KDa NADH dehydrogenase (bubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) 6 beta pyruvate dehydrogenase (bubiquinone) 1 subcomplex unknown, 2, 14.5KDa Subte Carrier family 25 (mitochondrial carrier; dirate transporter), member 1 solute carrier family 25 (mitochondrial carrier; dirate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dirate transporter), member 11 hepatocyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (erythneid-derived 2)-like 2 superoxide dismutase 2, notoklon	NM_002395.3:1405 NM_002395.3:610 NM_002499.2:35 NM_002499.2:35 NM_002499.2:36 NM_002490.2:30 NM_00546.2:230 NM_00546.2:230 NM_002492.3:115 NM_0019987.1:9 NM_002002495.4:1235 NM_002920.3:205 NM_002920.3:205 NM_002925.3:55 NM_000925.	Hs00120006_m1 Hs00125825_g1 Hs00125825_g1 Hs00125823_m1 Hs00125823_m1 Hs00125823_m1 Hs00125823_m1 Hs0012581_m1 Hs0012711_g1 Hs00127211_g1 Hs00127211_g1 Hs0010225_g1 Hs0010255_g1 Hs0010256_m1 Hs0026662_m1 Hs0026662_m1 Hs0015997_m1 Hs00159933_m1 Hs00102566_m1 Hs0012566_m1 Hs0012562_s1 Hs0012566_m1 Hs00266868_1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUF85 NDUF82 NDUF86 NDUF89 NDUF89 NDUF89 NDUF89 NDUF22 OGOH PC PDF8 PDF1 PDF2 SDF4A SLC25A1 SLC	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (bubjuunne) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (bubjuunne) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubjuunne) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubjuunne) 1 subcomplex, 9, 23KDa NADH dehydrogenase (bubjuunne) 1 subcomplex, 9, 23KDa NADH dehydrogenase (bubjuunne) 1 subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruwate dehydrogenase (bubjuathase catalytic subunit 1 pyruwate dehydrogenase complex, subunit 7, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute arrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tarasporter), member 10 solute carrier family 25 (mitochondrial carrier), member 10 solute carrier famil	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002482.235 NM_002480.235 NM_002462.230 NM_005462.230 NM_002492.3115 NM_0029821.9 NM_001204054.1:1235 NM_002920.3205 NM_002920.3205 NM_002920.2205 NM_002920.2205 NM_002920.2205 NM_002920.220	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129283_m1 Hs0007565[_g1] Hs00129283_m1 Hs00129283_m1 Hs00129211_g1 Hs00129213_g1 Hs00129213_g1 Hs0018666_m1 Hs0018662_m1 Hs0018663_m1 Hs0018663_m1 Hs001983166_g1 Hs00198333_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0018603_m1 Hs0018603_m1 Hs0018603_m1 Hs0018603_m1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF84 NDUF85 NDUF89 NDUF89 NDUF89 NDUF89 OG0H PC P0H8 P0F1 P0F1 P0F2 SOFA4 SIC25A10 SIC25A10 SIC25A10 SIC25A11 HNF4A KEAP1 NFE2L2/nf2 SOD1 SOD2 SOD3 SOD3 SOD3 SOD3 SOD3	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial MADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 blata subcomplex, 4, 5KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 subcationer, 5, 12KDa NADH dehydrogenase (ubiquinone) 1 subcationer, 5, 12KDa NADH dehydrogenase (ubiquinone) 1 subcationer, 5, 12KDa NADH dehydrogenase (ubiquinone) 1 subcationer, 2, 14.5KDa oogdutartet (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquatinate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquatinate) and 1, subcomplex, 6, 12KDa Sucinate dehydrogenase (ubiquatinate) and 1, 12 pyruvate dehydrogenase (ubiquatinate) and 1, 12 pyruvate dehydrogenase (ubiquatic subunit 1 pyruvate dehydrogenase complex, subunit 7, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier, circate transporter), member 1 solute carrier family 25 (mitochondrial carrier, circatowlate tarrier, member 11 hepatocyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (erythroid-derived 2)-like 2 superoxide dismutase 1, soluble superoxide dismutase 2, mitochondrial superoxide dismutase 2, anticchondrial superoxide dismutase 2, anticchondrial	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002489.235 NM_002489.233 NM_00546.2:230 NM_00546.2:230 NM_00546.2:230 NM_002492.3115 NM_0019987.1:9 NM_00502.80 NM_00252.3:055 NM_00220.3:2055 NM_00220.3:255 NM_00220.3:255 NM_00252.3:655 NM_00252.3:655 NM_00252.3:655 NM_00252.3:655 NM_00252.3:655 NM_00352.4:860 NM_00352.4:860 NM_00352.4:861 NM_00352.4:861 NM_00352.4:861 NM_00352.4:35 NM_	Hs00130006_m1 Hs00139588_g1 Hs00159588_g1 Hs00159588_m1 Hs00159588_m1 Hs00129588_m1 Hs00129588_m1 Hs0012818_m1 Hs0012581_g1 Hs0012711_g1 Hs001258_g1 Hs001258_g1 Hs001258_g1 Hs001258_g1 Hs001258_g1 Hs00126862_m1 Hs0066366_m1 Hs0015665_m1 Hs0012831506_g1 Hs00128333_m1 Hs001258231_m1 Hs00126632_m1 Hs00125823_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs0012648_m1 Hs0012648_m1 Hs00126418_m1 Hs00126268_m1 Hs001261_1_m1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB5 NDUFB9 NDUFB6 NDUFB9 NDUFC2 OGDH PC PC PDP1 PDP1 PDP1 SDHA SLC25A1 SLC25A1 SLC25A1 SLC25A1 SLC25A1 NHFA4 KEAP1 NHFA2 KEAP1 NHFA2 KEAP1 SOD2 SOD3 GSK3A GSK3B	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 2 subcomplex, 9, 22KDa NaDH dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 2 subcinate catalytic subunit 1 pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; citrate transporter), member 10 solute carrier family 25 (mitochondrial carrier; citrate transporter), member 10 nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor 4, alpha buperoxide dismutase 2, soluble superoxide dismutase 2, soluble superoxide dismutase 3, alpha glycogen synthase kinase 3 alpha	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002490.3430 NM_00546.2:33 NM_00546.2:33 NM_00546.2:33 NM_00546.2:33 NM_002492.3115 NM_002987.1:9 NM_002987.1:9 NM_002987.1:9 NM_002987.1:9 NM_002987.1:25 NM_00205.2:80 NM_00205.2:80 NM_00205.3:55 NM_00151778.1:950 NM_00292.3:555 NM_001581.2:36 NM_00292.3:555 NM_001581.2:36 NM_00256.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:35 NM_00562.4:35 NM_00562.4:35 NM_00562.4:35 NM_00562.2:1135 NM_00362.2:1135 NM_00292.2:1135	Hs00120006_m1 Hs00283558_g1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129583_m1 Hs0012981_m1 Hs002711_g1 Hs0012711_g1 Hs00107281_g1 Hs00102711_g1 Hs00102751_g1 Hs0010256_g1 Hs0010256_g1 Hs00105836_m1 Hs0005862_m1 Hs0019983_m1 Hs0019863_m1 Hs0019863_m1 Hs0019863_m1 Hs0019883_m1 Hs0019833_m1 Hs0019833_m1 Hs0019833_m1 Hs0019838_m1 Hs0019838_m1 Hs0019838_m1 Hs0019838_m1 Hs0019838_m1 Hs00198463_m1 Hs0019852_51 Hs0019852_51 Hs00198510_51 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0108266_m1 Hs0
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB9 NDUFB9 NDUFB9 NDUFB9 POP1 PCC POP1 POP1 POP1 POP2 SOFA4 SLC25A10 SLC25A10 SLC25A11 SLC25A13 SLC25	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial MaDH dehydrogenase (bubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (bubiquinone) 1 alpha subcomplex, 6, 14KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (bubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (bubiquinone) 1 subcamplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (bubiquinone) 1, subcomplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (bubiquinates catalytic subunit 1 pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier, dirate transporter), member 1 solute carrier family 25 (mitochondrial carrier, dirate tarsporter), member 10 solute carrier family 25 (mitochondrial carrier, dirate carrier), member 10 solute carrier family 25 (mitochondrial carrier, dirate carrier), member 10 solute carrier family 25 (mitochondrial carrier, dirate tarsporter), member 10 solute carrier family 25 (mitochondrial carrier, dirate tarsporter), member 10 superoxide dismutase 1, soluble superoxide dismutase 1, soluble superoxide dismutase 2, antitochondrial superoxide dismutase 3, alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002490.3:430 NM_004546.2:230 NM_004546.2:230 NM_002492.3:115 NM_002492.3:115 NM_002902.9:205 NM_002104054.1:1235 NM_002920.3:2055 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_00295 NM_0	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129283_m1 Hs0027511_g1 Hs01027211_g1 Hs01027211_g1 Hs01027211_g1 Hs0102721_g1 Hs0102721_g1 Hs0102726_g1 Hs0102582_m1 Hs0102582_m1 Hs0102582_m1 Hs0076683_m1 Hs00797_m1 Hs00194174_51 Hs00194174_51 Hs0019433_m1 Hs00195418_m1 Hs0026582_m1 Hs0026582_m1 Hs00266m1 Hs00266m2_m1 Hs00266m2_m1 Hs00266m2_m1 Hs0038400_m1 Hs0038400_m1 Hs0038400_m1 Hs0038400_m1 Hs0038400_m1 Hs0038400_m1 Hs0038401_m1 Hs0038401_4_1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF83 NDUF83 NDUF89 NDUF89 NDUF89 NDUF20 OGOH PC PC PC PC PC PC PDF1 PDP2 SDFA SLC25A1 S	malic enzyme 2, NAD(-)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial MaDH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase complex, subunit 1, privvate dehydrogenase complex, subunit 7, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 miclear factor (erythroid-derived 2)-like 2 superoxide dismutase 2, mitochondrial superoxide dismutase 2, alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 beta phosphatdylethanolamie binding protein 1 insulin induced gene 1	NM_002395.3:1405 NM_002395.3:1405 NM_00104811.1:1080 NM_002480.2:35 NM_002480.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:31 NM_002492.3:115 NM_0019987.1:9 NM_002502.8:0 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002934.2:964 NM_002934.2:964 NM_002934.2:305 NM_00293.2:325 NM_00293.2	Hs00130006_m1 Hs0033358_g1 Hs0035358_g1 Hs00159582_m1 Hs00159582_m1 Hs00159583_m1 Hs00159583_m1 Hs00159583_m1 Hs00159583_m1 Hs00125843_m1 Hs00125843_m1 Hs00125843_m1 Hs00125813_g1 Hs00125813_g1 Hs0012582_g1 Hs00125865_m1 Hs00159918_m1 Hs00159918_m1 Hs0015865_m1 Hs0015865_m1 Hs0015863_m1 Hs0015863_m1 Hs0015863_m1 Hs0015863_m1 Hs0015266_g1 Hs0015266_m1 Hs0015266_m1 Hs0015266_g1 Hs0015265_1_1 Hs005261_g1 Hs003801_g1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB3 NDUFB5 NDUFB5 NDUFB5 NDUFC2 OGDH PC C POH8 PDP1 PDP2 SOHA SLC25A1 SLC25A1 SLC25A1 SLC25A1 SLC25A1 SLC25A1 NHF4A KEAP1 NF4A KEAP1 NF42 SOD1 SOD2 SOD3 GSK38 PEBP1 INSIG2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa Oxadutate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa Subta dehydrogenase (ubiquinate) 2 dehydrogenase (lipoamide) pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) subta carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 hepatoxyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (eryhneid-derived)-like 2 superoxide dismutase 1, soluble superoxide dismutase 3, apha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha superoxide dismutase 3, alpha superoxide dismutase 4, antracellular phosphatdylethanolamine binding protein 1 insulin induced gene 2	NM_002395.3:1405 NM_002395.3:1405 NM_00104811.1:1080 NM_002482.2:35 NM_002490.2:430 NM_004546.2:230 NM_005462.2:30 NM_0015472.51 NM_00159287.1:5 NM_001240254.1:235 NM_00120054.1:235 NM_00252.3:555 NM_00151778.1:950 NM_002920.3:255 NM_002562.4:555 NM_00151778.1:950 NM_002763.2:555 NM_0015178.1:950 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:800 NM_002562.4:1116 NM_0026362.5:400 NM_002562.2:1135 NM_002567.2:1335 NM_002567.2:1335 NM_002567.2:1325 NM_002567.2:135 NM_002567.2:1	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs0017565_g1 Hs0097565_g1 Hs00172813_m1 Hs0017211_g1 Hs0017211_g1 Hs0107211_g1 Hs0107211_g1 Hs0107211_g1 Hs0107211_g1 Hs0107565_m1 Hs0019836_m1 Hs001983166_m1 Hs001983166_m1 Hs001983166_m1 Hs0019833_m1 H
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB5 NDUFB9 NDUFC2 OGOH PC PDH8 PCP1 PDH8 PCP1 PDH8 PDP1 PDP2 SDHA SLC25A10 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A13 SLC25A13 SLC25A14 SLC25A14 SLC25A14 SLC25A15	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate darbydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14, 5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinone) 1, subcomplex (1, 12, 12, 12, 12, 12, 12, 12, 12, 12, 1	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:30 NM_002492.3:115 NM_00199891.19 NM_002697.1:25 NM_002920.3:2055 NM_0021024054.1:125 NM_002920.3:2055 NM_002162.5:55 NM_002162.5:55 NM_002162.3:555 NM_002162.3:555 NM_002162.3:555 NM_002162.3:555 NM_002162.3:551 NM_002562.4:860 NM_112880.1:1116 NM_002562.4:860 NM_002562.4:860 NM_002562.4:860 NM_002562.4:351 NM_002542.3:1126 NM_002542.3:1126 NM_002542.3:1126 NM_002542.3:1235 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:123 NM_002542.3:1285NM_002542.3:1285 NM_002542.3:1285NM_002542.3:1285 NM_002542.3:1285 NM_002542.3:1285NM_002542.3:1285 NM_002542.3:1285NM_002552.3:1285 NM_0025542.3:1285NM_002552.3:1285 NM_0025542.3:1285NM_002552.3:1285 NM_0025542.3:1285NM_00255 NM_0025542.3:1285 NM_0025542.3:1285NM_00255 NM_0025542.3:128	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00101258_g1 Hs00975661_g1 Hs00102155_g1 Hs00102155_g1 Hs00102155_g1 Hs00102156_m1 Hs00105866_m1 Hs0098166_m1 Hs0098166_m1 Hs0019817_g1 Hs0019817_g1 Hs0019818_m1 Hs0019817_g1 Hs00198136_m1 Hs0019817_g1 Hs0019817_g1 Hs0019817_g1 Hs0019818_m1 Hs0019818_m1 Hs0019817_g1 Hs0019812_g1 Hs0019812_g1 Hs001982_g1 Hs001982_g1 Hs00182761_m1 Hs002510_s1 Hs00182761_m1 Hs00182761_m1 Hs00182761_m1 Hs00182761_m1
Oxidative activity Oxidative stress	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB4 NDUFB5 NDUFB5 NDUFB9 NDUFC2 OGDH PC C PDH1 PDP1 PDP1 PDP2 SDHA SLC25A1 SLC	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial MaDH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) prruvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) prruvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) prruvate dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (lipoamide) prruvate dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) dehydrogenase (alpha/subite) prruvate dehydrogenase onsphatase catalytic subunit 1 prruvate dehydrogenase (ubiquinondrial carrier; citrate transporter), member 1 solute carrier family 25 (mitochondrial carrier; citrate transporter), member 10 solute arrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 hepatocyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (epythoid-derived) 2-like 2 superoxide dismutase 2, intochondrial superoxide dismutase 2, altochondrial glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha modhanisticitaretaretaretaretaretaretaretaretaretare	NM_002395.3:1405 NM_0021481.1:1080 NM_001481.1:1080 NM_002490.3:430 NM_00546.2:33 NM_00546.2:33 NM_00546.2:33 NM_002492.3:115 NM_002987.1:9 NM_002987.1:9 NM_002981.2:65 NM_00129045.1:1235 NM_00292.3:255 NM_00151778.1:590 NM_00292.3:255 NM_00151778.1:590 NM_00292.3:255 NM_00151778.1:590 NM_00292.3:255 NM_001547.2:561 NM_00295.4:2640 NM_00256.2:6505 NM_00154.4:35 NM_00256.4:860 NM_00256.4:860 NM_00256.4:860 NM_00256.4:860 NM_00256.4:860 NM_00256.4:2640 NM_00256.4:2640 NM_00256.2:31120 NM_002567.2:1335 NM_002567.2:135 NM_002567.2:13	Hs00190006_m1 Hs00159558_11 Hs00159558_m1 Hs00159582_m1 Hs00159583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs0012911_g1 Hs0129711_g1 Hs0101225_g1 Hs0101255_g1 Hs0102918_m1 Hs0005866_m1 Hs0005866_m1 Hs00958166_m1 Hs00958156_g1 Hs0015853_m1 Hs0015833_m1 Hs0015833_m1 Hs0015833_m1 Hs0015825_g1 Hs0015833_m1 Hs0015833_m1 Hs0015833_m1 Hs0015833_m1 Hs0015833_m1 Hs0015834_g1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1 Hs0015827_f1_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB9 NDUFB9 NDUFB9 NDUFB9 NDUFB9 NDUFB9 PDP1 PCC PDP1 PDP1 PDP2 SDP4 SLC25A10 SLC25A10 SLC25A11 SLC2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa NADH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 1, subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 2, subcomplex, 9, 22KDa NaDH dehydrogenase (ubiquinate) 1, subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase complex, subunit 1, pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 1 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate tansporter), member 11 hepatoxyte nuclear factor 4, alpha keth-like ECH-associated protein 1 nuclear factor 4, alpha glycogen synthase kinase 3	NM_002395.31405 NM_002395.31405 NM_0010481.1:1080 NM_002482.235 NM_002482.430 NM_004545.230 NM_004545.230 NM_005452.3115 NM_001294054.1:1235 NM_002104054.1:1235 NM_00252.3055 NM_00216245.2555 NM_00161278.1:950 NM_002920.3:2555 NM_00161278.1:950 NM_002920.3:2555 NM_00161278.1:950 NM_002920.3:2555 NM_00161278.1:950 NM_00293.2:555 NM_001614.7:46 NM_001246.4:35 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1355 NM_002562.2:1135 NM_002662.2:1135 NM_	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs0027581_g1 Hs0027581_g1 Hs001252_g1 Hs001258_g1 Hs001258_g1 Hs001258_g1 Hs0016860_m1 Hs0016862_m1 Hs0016863_m1 Hs0016833_m1 Hs0016833_m1 Hs0017683_m1 Hs00159917_m1 Hs0015918_m1 Hs0015418_m1 Hs00162566_m1 Hs00162566_m1 Hs00162566_m1 Hs0162561_m1 Hs0162561_m1 Hs0162561_m1 Hs0162561_m1 Hs0162561_m1 Hs0162561_m1 Hs00177_07_11 Hs0017207_m1 Hs0017207_m1 Hs0017207_m1 Hs0017207_m1 Hs0017207_m1 Hs0017207_m1 Hs0017207_m1 Hs00
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUF85 NDUF85 NDUF85 NDUF89 NDUF85 NDUF89 NDUF22 OGOH PC POH8 PDP1 PDP1 PDP2 SDHA SIC25A10 SIC25A10 SIC25A10 SIC25A10 SIC25A10 SIC25A11 HNF4A KEAP1 NFE2L2/nrf2 SOD1 SOD2 SOD3 GSK3A GSK38 PE8P1 INSIG1 INSIG2 MIXIPL MIXIPL MIXIPL MIXIPL MIXIPL	malic enzyme 2, NAD(-)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial MaDH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 bats aubcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privuxte dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privuxte dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privuxte dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privuxte dehydrogenase complex, subunit 3, flavoprotein (fp) solute carrier family 25 (mitochondrial carrier; drate transporter), member 10 solute carrier family 25 (mitochondrial carrier; drate transporter), member 10 solute carrier family 25 (mitochondrial carrier; drate transporter), member 10 miclear factor (erythroid-derived 2)-like 2 superoxide dismutase 2, intochondrial carrier; drate transporter), member 10 superoxide dismutase 2, intochondrial carrier; drate transporter), member 11 miclari induced gene 1 insulin induced gene 2 MXL interacting protein 1/ insulin induced gene 2 MXL interacting protein 1/ michare receptor subfamily 1, group 0, member 10	NM_002395.31405 NM_002395.31405 NM_00104811.1:1080 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:30 NM_002492.3:115 NM_001199987.1:9 NM_00252.80 NM_00252.80 NM_00252.81 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_00293.2:355 NM_00161778.1:950 NM_00161778.1:950 NM_00161778.1:950 NM_001632.4:35 NM_001632.4:350 NM_001634.4:35 NM_001634.4:35 NM_000332.2:1135 NM_001634.4:35 NM_001634.2:305 NM_001634.2:3150 NM_001632.2:3135 NM_001632.2:3151 NM_001632.2:3151 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:305 NM_002582.2:3151 NM_002582.2:305 NM_002582.2:3151 NM_002582.2:3151 NM_002774.3:1080 NM_0027774.3:1080 NM_0027774.3:1080 NM_00277774.3:1080 NM_00277777777777777777777777777777777777	Hs00130006_m1 Hs00153558_11 Hs00153558_m1 Hs00153558_m1 Hs00159583_m1 Hs00159583_m1 Hs00159583_m1 Hs00159583_m1 Hs00159583_m1 Hs00125843_m1 Hs00125843_m1 Hs00125843_m1 Hs00125843_m1 Hs001258_g1 Hs001258_g1 Hs00105856_m1 Hs0015991B_m1 Hs0015866_m1 Hs0015683_m1 Hs0015683_m1 Hs0015665_m1 Hs0015831506_g11 Hs0015833_m1 Hs0015833_m1 Hs0015823_1 Hs0015823_1 Hs00158276_m1 Hs00158276_m1 <
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 ME3 NDUFA4 NDUFA5 NDUF84 NDUF85 NDUF86 NDUF89 NDUF89 NDUF89 NDUF22 OGOH PC PDP1 PDP2 SDP4 SUC25A1 SUC2	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 25KDa NADH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinondri 1 subcomplex, 9, 25KDa NaDH dehydrogenase (ubiquinone) 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase complex, subunit 1 privvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 10 solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 hepatoxyte nuclear factor 4, alpha ketch-like ECH-associated protein 1 nuclear ractor (eryhneid-derived)-like 2 superoxide dismutase 2, anticchondrial superoxide dismutase 3, alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha mechanistic target of rapamydin (serine/threonine kinase) v-myc myelocytomatosisi viral oncogene homolog (avina) nuclear receptor subfamily 1, group M, member 2 mothase tracesubfamily 1, group M, member 2	NM_002395.3:1405 NM_002395.3:1405 NM_00104811.1:1080 NM_002482.2:35 NM_002490.2:430 NM_004546.2:230 NM_005462.2:30 NM_0015472.51 NM_00159287.1:5 NM_0012492.3:115 NM_00252.80 NM_00120054.1:235 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_00252.4:860 NM_00252.4:860 NM_00252.4:350 NM_00252.4:350 NM_002562.4:310 NM_002920.3:2135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.2:1135 NM_002562.3:1120 NM_002951.2:2305 NM_002562.3:1120 NM_002951.2:2305 NM_002467.3:1610 NM_002721.4:300	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00179582_m1 Hs0007565[_g1] Hs00172581_g1 Hs00172581_g1 Hs0017211_g1 Hs0107211_g1 Hs01076833_g1 Hs0076672_m1 Hs0076672_g1 Hs007566_m1 Hs00761782_g1 Hs00761782_g1 Hs00761782_g1 Hs00765178_m1 Hs00765178_m1 Hs00765178_m1 Hs00765178_m1 Hs007653701_m1 Hs007653791_m1 Hs007653791_m1 Hs007653791_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB5 NDUFB9 NDUFB9 NDUFC2 OGOH PC PDH8 PCP1 PDH8 PCP1 PDH8 PDP1 PDP2 SDHA SLC25A10 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A13 SLC25A10 SLC25A10 SLC25A10 SLC25A10 SLC25A11 SLC25A10 SLC25A11 SLC25A11 SLC25A10 SLC25A10 SLC25A10 SLC25A10 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A10 SLC25A11 SLC25A10 S	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pyruvate dehyrogenase phosphatase catalytic subunit 1 pyruvate dehyrogenase gomplex, subunit 2, filotochodrial carrier, dirate transporter), member 1 solute carrier family 25 (mitochondrial carrier, dirate transporter), member 10 solute carrier family 25 (mitochondrial carrier, dirate transporter), member 10 solute carrier family 25 (mitochondrial carrier, diratowglex tarates, 11 hepatoxyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (erythroid-derived 2)-like 2 superoxide dismutase 2, alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha mechanistic target of rapamycin (serine/threonine kinase) - vymc myelorytormatosis viral oncogene homolog (avian) nuclear receptor subfamily 1, group M, member 2 nuclear receptor subfamily 1, group M, member 2 nuclear receptor subfamily 1, group M, me	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:30 NM_002492.3:115 NM_002902.3:2055 NM_002104054.1:1235 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002932.9:255 NM_002932.9:225 NM_002932.9:2135 NM_002542.3:1120 NM_002542.3:1300 NM_002542.3:1300 NM_002542.3:1300 NM_002542.3:130	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129243_m1 Hs00125243_m1 Hs00125243_m1 Hs00975661_g1 Hs001252_g1 Hs0015418_m1 Hs0015418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125412_s1 Hs00125412_m1 Hs00125412_m1 Hs00125448_g1 Hs00125279_m1 Hs0015621_m1 Hs00125270_m1 Hs00125277_m1 Hs00125647_m1 Hs00125647_m1 Hs00125647_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF82 NDUF83 NDUF83 NDUF89 NDUF85 NDUF89 NDUF22 OGDH PC PC PC PC PC PC PC PC PC PC PDF1 PP2 SDFA SLC25A1	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, IAKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, JSKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, JSKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, IAKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, JXDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, JXDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, JXDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, JASKDa oxoglutareta (alpha-ktedgutarete) dehydrogenase (lipoamide) pruvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, JASKDa oxoglutareta (alpha-ktedgutarete) dehydrogenase (lipoamide) pruvate dehydrogenase (bosphatase catalytic subunit 1 pyruvate dehydrogenase complex, subunit A, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 muclear factor 4, alpha ketch-like ECH-associed protein 1 nuclear factor (erythroid-derived 2)-like 2 superoxide dismutase 2, solutbal superoxide dismutase 2, solutochondrial glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha mechanistic target of rapamycin (serine/threonine kinase) v-myc myelocytomatosis viral oncogen homolog (avian) nuclear receptor subfamily 1, group H, member 3 peroxisome proliferator-activated receptor anpmo	NM_002395.3:1405 NM_002395.3:1405 NM_0014811.1:1080 NM_001481.1:1080 NM_002490.3:430 NM_001546.2:330 NM_001546.2:330 NM_001546.2:330 NM_001546.2:330 NM_0012987.1:9 NM_00250.2:80 NM_0012987.1:9 NM_002541.2:65 NM_0012987.1:255 NM_00120454.1:1235 NM_001297.3:555 NM_00151778.1:590 NM_00252.3:555 NM_00151778.1:590 NM_00252.3:555 NM_00151778.1:590 NM_00252.4:2650 NM_00158.1:230 NM_00256.2:450 NM_00154.4:35 NM_00154.4:360 NM_00356.2:460 NM_00356.2:460 NM_00356.2:460 NM_00356.2:460 NM_00356.2:460 NM_00356.2:450 NM_00356.2:431120 NM_00356.2:431120 NM_00356.2:431120 NM_00356.2:431120 NM_00356.2:431120 NM_00356.2:431120 NM_00357.2:1335 NM_00	Hs001300006_m1 Hs00139588_g1 Hs00159588_g1 Hs00159588_g1 Hs00159588_m1 Hs00159588_m1 Hs00129588_m1 Hs00129588_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129583_m1 Hs00129918_m1 Hs00159918_m1 Hs00058366_m1 Hs00958166_m1 Hs0095816_m1 Hs00958166_m1 Hs0015883_m1 Hs0015818_m1 Hs0015818_m1 Hs0015818_m1 Hs00158216_m1 Hs00158216_m1 Hs00158216_m1 Hs00158216_m1 Hs00158216_m1 Hs0015827_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB9 NDUFB9 NDUFB9 NDUFB9 NDUFB9 NDUFB9 NDUFC2 OGOH PC PDP1 PDP1 PDP1 PDP2 PDP2 SDP4 SLC25A10 SLC25A13 SLC25A10 SLC25A13 SLC25A11 NIF4A KEAP1 NFE12(nf12 SOD1 SOD2 SOD3 GSK38 PE8P1 NISIG1 NISIG2 MLXIPL MTOR NTOR NTOR NTOR NTOR NTOR NTOR NTOR N	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial MADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pruvate dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) pruvate dehydrogenase complex, subunit 1 pyruvate dehydrogenase complex, subunit 1, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate taransporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate taransporter), member 10 solute carrier family 25 (mitochondrial carrier) (Fp) superoxide dismutase 1, soluble superoxide dismutase 2, apha ketch-like ECH-associated protein 1 nuclear recettor (rephroti-dented) 2-like 2 superoxide dismutase 3, apha glycogen synthase kinase 3 alpha glycogen synthase ki	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002482.2:35 NM_002482.3:35 NM_002482.3:15 NM_002492.3:115 NM_002492.3:115 NM_002104054.1:223 NM_00220454.1:2235 NM_002920.3:2055 NM_002124054.1:2235 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_00294.2:964 NM_002964.2:964 NM_002964.2:964 NM_002964.2:351 NM_002654.2:31120 NM_002642.3:1120 NM_002642.3:1120 NM_002642.3:1120 NM_002921.3:251 NM_002921.3:251 NM_002921.3:251 NM_00293.2:1575 NM_00293.2:1575 NM_000593.2:1575 NM_0005984.3:2520 NM_002984.2:320	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs000159582_m1 Hs000159582_m1 Hs00075661_f1 Hs0075661_f1 Hs00125281_m1 Hs0012561_f1 Hs0012562_m1 Hs0012562_m1 Hs0016863_m1 Hs0016863_m1 Hs0016863_m1 Hs0016833_m1 Hs00159918_m1 Hs0016863_m1 Hs001593166_m1 Hs001593136_m1 Hs001593136_m1 Hs001593136_m1 Hs001593136_m1 Hs00155418_m1 Hs00155418_m1 Hs00155418_m1 Hs0015266_m1 Hs01052661_m1 Hs01052661_m1 Hs0105267_m1 Hs002561944_s1 Hs0012977_m1 Hs0026178_m1 Hs0026178_m1 Hs0026178_m1 Hs0026178_m1 Hs0026178_m1 Hs0026178_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF85 NDUF85 NDUF89 NDUF89 NDUF22 OGOH PC PDH8 PCP1 PDF1 PDF2 SDHA SLC25A10 SLC25A11 SLC25A10 SLC25A10 SLC25A10 SLC25A10 SLC25A11 HNF4A KEAP1 NFE2L2/nf2 SOD1 SOD2 SOD3 SOD3 SOD3 SOD3 SOD3 SOD3 SOD3 SOD3	malic enzyme 2, NAD(-)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial MaDH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) ehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) ehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutarete) ehydrogenase (lipoamide) privvate dehydrogenase complex, subunit 1 privvate dehydrogenase complex, subunit 2 succinate dehydrogenase complex, subunit 7, flavoprotein (fp) solute carrier family 25 (mitochondrial carrier; cartrate transporter), member 10 solute carrier family 25 (mitochondrial carrier; cartrate transporter), member 10 solute arrier family 25 (mitochondrial carrier; cartrate tarsionerte), member 10 superoxide dismutase 2, intochondrial carrier; cartrate tarsionerter), member 11 hepatocyte nuclear factor (arythroid-derived 2)-like 2 superoxide dismutase 2, intochondrial superoxide dismutase 2, antochondrial superoxide dismutase 2, antochondrial supero	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002489.2:33 NM_005462.2:30 NM_005462.2:30 NM_005462.2:30 NM_002492.3:115 NM_00199891.19 NM_002605.2:80 NM_002492.3:115 NM_00252.2:80 NM_00252.2:80 NM_00252.2:80 NM_00252.2:80 NM_00252.2:55 NM_001161778.1:950 NM_002562.4:555 NM_00161778.1:950 NM_002562.4:555 NM_00161778.1:950 NM_002562.4:505 NM_001614.7:355 NM_001614.7:355 NM_001614.7:355 NM_001614.4:35 NM_002562.2:355 NM_001614.4:35 NM_002562.2:3155 NM_001614.4:35 NM_003562.2:3135 NM_001634.2:3135 NM_005522.3:1120 NM_002582.2:3120 NM_002582.2:3120 NM_002582.2:3120 NM_002582.2:3120 NM_002582.2:3120 NM_002582.2:3157 NM_001928.2:520 NM_001598.3:1710 NM_00549.3:1710NM_00549.3:1710 NM_00549.3:1710NM_00549.3:1710 NM_005552.30	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129243_m1 Hs00125243_m1 Hs00125243_m1 Hs001252_g1 Hs001252_g1 Hs001252_g1 Hs001255_g1 Hs001255_g1 Hs001256_m1 Hs0026566_m1 Hs0026566_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125418_m1 Hs00125448_g1 Hs00125444_s1 Hs0012977_m1 Hs0155276_m1 Hs0155276_m1 Hs0129277_m1 Hs0129277_m1 Hs0125644_s1 Hs0125647_m1 Hs0125647_m1 Hs0125647_m1 Hs0125647_m1 Hs0125647_m1 Hs0125647_m1 Hs0125647_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUF82 NDUF82 NDUF83 NDUF85 NDUF85 NDUF89 NDUF22 OGDH PC PC PDH1 PDP1 PDP2 SUC25A1 SIC25	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutartet (alpha-ketoglutarte) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxoglutartet (alpha-ketoglutarte) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 2 subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxoglutartet (alpha-ketoglutarte) dehydrogenase (lipoamide) pyruvate dehydrogenase complex, subunit 1, pyruvate dehydrogenase complex, subunit 1, pyruvate dehydrogenase complex, subunit 1, flavoproteni (Fp) solute carrier family 25 (mitochondrial carrier; citrate transporter), member 10 solute carrier family 25 (mitochondrial carrier; citrate transporter), member 10 solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11 hepatocyte nuclear factor 4, alpha kelch-like ECH-associated protein 1 nuclear factor (erythroid-derived)-like 2 superoxide dismutase 2, antochondrial superoxide dismutase 2, antochondrial superoxide dismutase 3, apha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 alpha geroxisome protein-like mechanistic target of raparnycin (serine/threonine kinase) w-myc myelocytomatosis wiral oncogene homolog (avian) nuclear receptor subfamily 1, group H, m	NM_002395.3:1405 NM_002395.3:1405 NM_0014811.1:1080 NM_002490.3:430 NM_002490.3:430 NM_001546.2:230 NM_001546.2:230 NM_001546.2:230 NM_00152.820 NM_00120052.80 NM_00120052.80 NM_00120052.81 NM_00252.820 NM_00252.820 NM_00252.825 NM_001161778.1:950 NM_002920.3:255 NM_001161778.1:950 NM_002964.2:964 NM_002562.4:860 NM_001562.4:860 NM_001562.4:860 NM_001562.4:860 NM_001562.4:860 NM_001562.4:860 NM_001562.4:860 NM_001562.4:860 NM_002562.4:860 NM_001562.4:870 NM_00562.4:870 NM_00562.4:870 NM_00562.4:870 NM_000562.2:1135 NM_001541.4:325 NM_001547.2:135 NM_002572.2:135 NM_00	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs0017561_g1 Hs0017561_g1 Hs0017251_g1 Hs0017211_g1 Hs0017251_g1 Hs0017561_g1 Hs0017561_g1 Hs00175635_m1 Hs0016866_m1 Hs0016866_m1 Hs0016866_m1 Hs0016866_m1 Hs00168365_m1 Hs00168355_m1 Hs00193166_m1 Hs001933166_m1 Hs0019333_m1 Hs0019333_m1 Hs0019333_m1 Hs0015418_m1 Hs0015418_m1 Hs0015542_m1 Hs0015542_m1 Hs00155413_m1 Hs00155414_s1 Hs00155414_s1 Hs001555144_s1 Hs0026379_1_m1 Hs0026379_1_m1 Hs00155644_s1 Hs0015647_m1 Hs0015647_m1 Hs0015664_g1 Hs0015664_g1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB5 NDUFB5 NDUFB9 NDUFC2 OGOH PC PD1 PCP1 PCP1 PCP1 PCP1 PCP3 SU25A10 SU25A11 SU25A11 SU25A11 SU25A11 SU25A11 SU25A11 SU25A13 SU25A1	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone) 1 subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 subcomplex, 9, 22KDa NADH dehydrogenase (ubiquinone) 1 subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase (ubiquinate) 1 subcomplex unknown, 2, 14.5KDa oxogutarate (alpha-ketogutarate) dehydrogenase (lipoamide) pyruvate dehydrogenase complex, subunit 1. pyruvate dehydrogenase complex, subunit 2. succinate dehydrogenase complex, subunit 7, flavoprotein (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 1 solute arrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute arrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 11 hepatoxyte nuclear factor 4, alpha keth-like ECH-associated protein 1 nuclear factor (alpha glycogen synthase kinase 3 alpha glycogen synthase kinase 3 a	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002489.2:35 NM_002492.3:15 NM_002492.3:15 NM_002492.3:15 NM_00252.80 NM_00252.80 NM_00252.80 NM_00252.80 NM_00252.80 NM_00252.82 NM_00252.85 NM_00252.1135 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.31120 NM_002542.3135 NM_002552.3135 NM_002552.3150 NM_002552.3150	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129243_m1 Hs00125243_m1 Hs00125243_m1 Hs0027511_g1 Hs001252_g1 Hs001252_g1 Hs001252_g1 Hs001252_g1 Hs001252_g1 Hs001252_g1 Hs00263166_m1 Hs0019417_s1 Hs00195418_m1 Hs00195418_m1 Hs0015418_m1 Hs0015418_m1 Hs0015418_m1 Hs0015418_m1 Hs0015418_m1 Hs0015418_m1 Hs0015418_m1 Hs0012500_m1 Hs0012501_01 Hs01380112_m1 Hs01380112_m1 Hs01380112_m1 Hs001380112_m1 Hs001380112_m1 Hs001380112_m1 Hs00042200_m1 Hs00260144_s1 Hs0004200_g1 Hs0026017_m1
Oxidative activity Oxidative stress Regulator of metabolism	ME2 ME3 NDUFA4 NDUFA5 NDUF85 NDUF85 NDUF85 NDUF89 NDUF85 NDUF89 NDUF22 OGOH PC POH8 PD1 PD1 PD2 SD4A SIC25A10 S	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, SKDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 15KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ktoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ktoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (phosphatase catalytic subunit 1 privvate dehydrogenase complex, subunit A, flavoproterin (Fp) solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10 hepatocyte nuclear factor 4, alpha ketdr-like ECH associated protein 1 nuclear factor (erythroid-derived 2)-like 2 superoxide dismutase 2, mitochondrial superoxide dismutase 2, alphaa glycogen synthase kinase 3 beta phosphatdylethanolamine binding protein 1 insulin induced gene 1 Mixt interacting protein 1. sinulear eceptor subfamily 1, group 0, member 3 peroxisome protiferator-activated receptor alphaa geroxisome protiferator-activated receptor agmama calcium/calmodulin-dependent protein in anclear receptor subfamily 1, group 0, member 3 peroxisome proliferator-activated receptor agmama calcium/calmodulin-dependent protein in peroxisome proliferator-activated receptor agmama calcium/calmodulin-dependent protein in peroxisome proliferator-activated receptor gamma calcium/calmodulin-dependent protein in peroxisome proliferator-activated receptor gamma calcium/calmo	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002489.2:35 NM_002489.2:35 NM_002480.2:33 NM_00546.2:230 NM_00546.2:230 NM_002492.3:115 NM_001199987.1:9 NM_0020492.3:125 NM_002920.3:2055 NM_00220.3:2055 NM_00220.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_002920.3:2055 NM_00161778.1:950 NM_00161778.1:950 NM_001632.7:355 NM_001614.7:435 NM_001636.2:640 NM_001634.2:315 NM_00293.2:225 NM_001634.2:3150 NM_0029542.3:150 NM_0029542.3:150 NM_001928.2:520 NM_0029542.3:150 NM_001928.2:520 NM_0029542.3:150 NM_001928.2:520 NM_0029542.3:150 NM_001928.2:520 NM_0029542.3:150 NM_001928.2:520 NM_0029542.3:150 NM_005693.3:150 NM_001928.2:520 NM_001928.2:520 NM_005693.3:150 NM_00233.3:150 NM	Hs00190006_m1 Hs00159582_g1 Hs00159582_g1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00125832_m1 Hs001258_g1 Hs001258_g1 Hs001258_g1 Hs00105856_m1 Hs00065866_m1 Hs000583166_m1 Hs000583166_m1 Hs0015833_m1 Hs001583_m1 Hs001583_m1 Hs001583_m1 Hs01582_m1 Hs001582_m1 Hs001
Oxidative activity Oxidative stress Oxidative stress Regulator of metabolism Serine/glycine synthesis	ME2 ME3 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB5 NDUFB9 NDUFC2 OGOH PC PD1 PD1 PD2 PD1 PD2 SD4A SLC25A13 SLC25A13 SLC25A14 SLC25A14 SLC25A14 SLC25A14 SLC25A15 SLC25A15 SLC25A15 SLC25A15 SLC25A16 SLC25A16 SLC25A16 SLC25A16 SLC25A17 SLC25A17 SLC25A17 SLC25A17 SLC25A16 SLC25A17 S	malic enzyme 2, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial malic enzyme 3, NAD(+)-dependent, mitochondrial NADH dehydrogenase (ubiquinone] 1 Jahpa subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 16KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 17KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 9, 25KDa NADH dehydrogenase (ubiquinone] 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcamplex unknown, 2, 14.5KDa oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide) privvate dehydrogenase (progenase complex, subunit 1, grouporter), member 10 solute carrier family 25 (mitochondrial carrier, dicarboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier, oxoglutarate carrier), member 10 solute carrier family 25 (mitochondrial carrier, oxoglutarate carrier), member 10 solute carrier family 25 (mitochondrial carrier, and 2) superoxide dismutase 1, soluble superoxide dismutase 2, anticohondrial superoxide dismutase 3, apha (glycogen synthase kinase 3 bata (gl	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002482.2:35 NM_002482.3:35 NM_002482.3:15 NM_002492.3:115 NM_002492.3:115 NM_002920.3:2055 NM_002104054.1:235 NM_002920.3:205 NM_002920.3:205 NM_002920.3:205 NM_002920.3:205 NM_002921.3:205 NM_002921.3:213 NM_002921.3:213 NM_002921.3:213 NM_002921.3:213 NM_00293.1:1575 NM_00293.1:1575 NM_00293.3:1705 NM_00293.3:1705 NM_00293.3:1705 NM_00293.3:1705 NM_00293.3:1705 NM_001216.3:1300 NM_001215.3:1442 NM_001253.3:1900 NM_001215.3:1445 NM_00293.3:1205 NM_001215.3:1445 NM_00293.3:1205 NM_001215.3:1445 NM_001215.3:1445 NM_001215.3:1445 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00253.3:1505 NM_001215.3:1445 NM_00253.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255.3:1505 NM_001215.3:1445 NM_00255 NM_00255 NM_00255 NM_00255 NM_00255 NM_00255 NM_00255 NM_0025 N	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs000159582_m1 Hs000159582_m1 Hs0007565_f1 Hs00172581_m1 Hs00172581_g1 Hs001860_m1 Hs0018662_m1 Hs0018662_m1 Hs0018662_m1 Hs0018662_m1 Hs0018663_m1 Hs0018633_m1 Hs001953166_m1 Hs001953166_m1 Hs001953136_m1 Hs0019533_m1 Hs0019533_m1 Hs0019533_m1 Hs00195417_s1 Hs00195417_s1 Hs00195417_s1 Hs00195417_s1 Hs00195417_m1 Hs0019562_m1 Hs001056647_m1
Oxidative activity Oxidative stress Regulator of metabolism Serine/glycine synthesis	ME2 ME3 ME3 NDUFA4 NDUFA5 NDUFB2 NDUFB5 NDUFB5 NDUFB6 NDUFB9 NDUFC2 OGOH PC PDH8 PCP1 PDF1 PDF2 SDHA SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A11 SLC25A13 SLC25A11 SLC25A13 SLC25A13 SLC25A13 SLC25A14 SLC25A14 SLC25A14 SLC25A15 SLC25A15 SLC25A15 SLC25A15 SLC25A15 SLC25A15 SLC25A16 SLC25A16 SLC25A16 SLC25A17 S	malic enzyme 2, NAD(-)-dependent, mitochondrial malic enzyme 3, NADP(-)-dependent, mitochondrial MaDH dehydrogenase (ubiquinone] 1 alpha subcomplex, 4, 9KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 14KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 4, 15KDa NADH dehydrogenase (ubiquinone] 1 beta subcomplex, 5, 13KDa NADH dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutaret) ehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutaret) ehydrogenase (lipoamide) privvate dehydrogenase (ubiquinone] 1 subcomplex unknown, 2, 14.5KDa oxoglutareta (alpha-ketoglutaret) ehydrogenase (lipoamide) privvate dehydrogenase complex, subunit 1 privvate dehydrogenase complex, subunit 1, flavoprotein (fp) solute carrier family 25 (mitochondrial carrier; claraboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; claraboxylate transporter), member 10 solute carrier family 25 (mitochondrial carrier; claraboxylate transporter), member 10 subuter arrier family 25 (mitochondrial carrier; claraboxylate transporter) and muclear factor (erythrolid-derived 2)-like 2 superoxide dismutase 2, nutochondrial superoxide dismutase 2, attacellular glycogen synthase kinase 3 beta phosphatidylethanolamine binding protein 1 insulin induced gene 1 insulin induced gene 2 MuX interacting protein 1 sunclear receptor subfamily 1, group 0, member 1 nuclear receptor subfamily 1, group 0, member 2 nuclear receptor subfamily 1, group 0, member 3 peroxisome proliferator-activated receptor gamma calclum/calmodulin-dependent protein kinase kinase 2, beta cAMP responsive element binding protein 1 peroxisome proliferator	NM_002395.3:1405 NM_002395.3:1405 NM_0010481.1:1080 NM_002480.2:33 NM_004546.2:330 NM_004546.2:330 NM_005456.2:33 NM_005462.2:30 NM_002492.3:115 NM_002902.3:2055 NM_002104054.1:1235 NM_002920.3:2055 NM_00293.2:925 NM_00293.2:925 NM_00293.2:925 NM_00293.2:1350 NM_00293.2:3130 NM_002542.3:1300 NM_002542.3:1300 NM_00293.2:575 NM_001928.2:5200 NM_00293.3:1900 NM_002543.3:1900 NM_002543.3:1900 NM_00257.3:225 NM_005693.3:1505 NM_00257.3:225 NM_00297.3:255 NM_00297.3:2555 NM_00297.3:2555 NM_00297.3:255 NM_00297.3:2555 NM	Hs00190006_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00159582_m1 Hs00129582_m1 Hs00129582_m1 Hs0027581_g1 Hs0027511_g1 Hs0102152_g1 Hs0102152_g1 Hs0102582_m1 Hs00105862_m1 Hs0098566_m1 Hs0098166_m1 Hs00191582_s1 Hs00191582_s1 Hs00191582_s1 Hs00191782_s1 Hs00191782_s1 Hs0019510_s1 Hs0019510_s1 Hs0019510_s1 Hs00195279_m1 Hs00156276_m1 Hs00156276_m1 Hs00156276_m1 Hs001562776_m1 Hs001562776_m1 Hs00156277_m1 Hs00156277_m1 Hs0015627_1_m1 Hs0015627_1_m1 Hs0015627_1_m1 Hs0015627_1_m1 Hs0015627_1_m1 Hs001628_5_1 Hs001628_5_1 Hs001628_5_1

Pommier et al. Table S3 (Related to Figure 5) List, abbreviations, accession numbers and Applied Biosience references of the genes analyzed by Taqman assays in xenograft models.