Supplementary Information-1

Additional information on generation of drug resistant cell lines

Oesophagogastric cancer cell lines were grown in incrementally increasing concentrations of cisplatin, oxaliplatin and docetaxel (µM range) over 24 months. Bars represent measurements of cell viability that were taken after every 4 passages. X-axis indicates various cell lines, Y-axis resistance index (RI) defined as a fold change of IC50 values between each pair of resistant versus parental line. Error bars were calculated for 3 independent replicates and defined as SEM.

Figure S1A-Cisplatin resistant cell lines

Figure S1B-Oxaliplatin resistant cell lines

Figure S1C-Docetaxel resistant cell lines
Details of sample preparation and gene expression profiling

RNA Extraction

Cells were grown in T75 flasks to 80–90% confluency and washed twice in PBS. 1 ml of TRIzol (Invitrogen, Paisley, UK) reagent was added per flask and then lysates were transferred into 1.5 ml eppendorf tube and passed through a 20 gauge needle (0.9 mm diameter) at least 5-6 times. Samples were centrifuged at 1200g for 10 minutes at 4 °C and supernatants were collected and transferred into fresh tubes and incubated for 5 minutes at room temperature (RT). 200 µl of chloroform (Sigma Aldrich) was added and tubes were inverted several times and incubated for 3 minutes at RT. Tubes were centrifuged at 12000 g for 15 minutes at 4 °C. Supernatants were collected and transferred into new eppendorf tubes. 500 µl of 100 % isopropanol was added, mixed and incubated for 10 minutes at RT. Samples were centrifuged at 12000 g for 10 minutes at 4 °C. Supernatants were removed and pellets washed with 1ml of 75 % ethanol, vortex and centrifuged at 9500 rpm for 5 minutes at 4 °C. Remaining supernatants were removed, pellets briefly air-dried and resuspended in 30 µl of RNase free water. RNA was quantified spectrophotometrically (Nanodrop 1000 Spectrophotometer, Thermo Scientific, Loughbourough, UK). Both A260/280 and A260/230 ratios were determined and all samples were in the range 1.9- 2.3. Furthermore samples were purified on the Mini columns (Qiagen). Quality was assessed by electrophoresis on Tapestation (Lab901 Limited, Peqlab, UK) and QC was determined by SDV (Screen Tape degradation value) that represents RNA integrity. Values 0-5 represent high quality RNA, 5-14 - partially degraded RNA and ≥ 15 degraded RNA. All RNA samples had SDV values between 0.3 and 2.6. All analyses used 3 independent replicates per cell line from three different passages.

Sample preparation for Gene expression profiling and hybridisation

500 ng of total RNA was reverse transcribed into cDNA and further amplified in vitro into cRNA using Ambion WT Expression kit (Austin, TX, USA). The quality of cRNA was determined by electrophoresis (Tapestation, Lab901 Limited, Peqlab, UK). The A260/280 and A260/230 ratios, concentration and yield were determined on a spectrophotometer (Nanodrop 10000 spectrophotometer, Thermo Scientific, Loughborough, UK). cRNA (10µg) was reverse transcribed into cDNA (Ambion WT Expression Kit, Ambion) and its quantity and quality was determined as above. Subsequently, cDNA samples (5.5µg) were fragmented and biotin labelled (WT terminal labelling and controls kit, Affymetrix, Santa Clara, CA), and 5.5 µg hybridised to Human Exon 1.0 ST GeneChip microarrays (Affymetrix, Santa Clara, CA) at 45 °C for 17 hours at 45 rpm in a hybridization oven.
Supplementary Information-3

Gene expression Data

Quality assessment(QA) of Gene expression data

QA data for the profiling of drug resistant and parental cell lines is provided in table S4.1 and figure S4.1 below.

Core probe sets on the Human Exon 1.0 ST array were processed using a modified robust multiarray analysis (RMA16) algorithm (Affymetrix, Santa Clara, CA) that employs a non-linear per chip background correction with addition of 16 to the expression values to attain variance stabilisation of low level signals, quantile normalisation and summarisation of multiple probe sets per transcript using median polishing of log2 transformed data. Data were transformed to the median of all samples. QA was performed by examining signal intensity (PM_mean), background signal detection (Bgrd_mean), detection of outliers followed by analysis of hybridization and labelling controls. Further determination of outlier samples was performed by analysis of probe set summarization metrics such as Pos_vs_neg_auc and All_Probe_Set_RLE_Mean.

Quality control of hybridization and labelling was determined by analysis of bacterial (bac_spike) and polyadenylated (polyA_spike) controls and polyadenylated RNA spikes such as Lys, Phe, Thr and Dap were analyzed independently.

Table S4.1 Quality assessment measures from Affymetrix 1.0ST Exon arrays for all cell line samples

| Signal detection      | Range      | Detected across all samples |
|-----------------------|------------|-----------------------------|
| PM_mean               | 200-400    | Within the range            |
| Bgrd_mean             | 200-550    | Within the range            |
| Summarization metrics |            |                            |
| Pos_vs_neg_auc        | 0.8-0.9    | Within the range            |
| All_Probe_Set_RLE_mean| Close to the median | -2.67 - 1.41 |
| Hybridization QC      |            |                            |
| PolyA                 | 4-5        | Within the range            |
| Lys, Phe, Thr, Dap    | 7-8        | Within the range            |
Figure S4.1 Box plots represent the relative log expression for all the probe sets analyzed. The mean absolute RLE is proportional to the width of the box plots, or the inter-quartile range of RLE values and whiskers are 1.5x IQR.

Analysis of gene expression data

Gene expression data analysis was performed in GeneSpring GX v 11.5 using RMA16 normalization, log transformation and baseline to median of all samples. Core gene sets were analysed and entities with normalised expression levels between the 20th and 100th percentiles in at least 1 sample were included with 16939 out of 17881 genes meeting this filter. Unpaired t-test, with Benjamini and Hochberg MTC corrected $p \leq 0.05$ was performed to identify discriminatory gene profiles of each pair of drug resistant versus parental lines.

Pathway analysis

Gene set enrichment analysis using gene ontologies and mapping of gene sets of interest onto biological pathways was performed using DAVID v 6.7 (Function Annotation Bioinformatics Microarray Analysis), Bioinformatic Resources, NIAID, NIH Significantly enriched GO terms, functional networks or pathways were determined using gene set enrichment analysis (EASE score, DAVID v 6.7) and genes were visualised on BioCarta and KEGG pathways. Data was pre-processed in DAVID bioinformatics database to provide the link between probe IDs and Entrez Gene Symbols. Probe sets with multiple Entrez IDs and those which could not be found in Ensembl/Entrez ID were excluded from further analysis.
Supplementary information -4

PCR primer sequences

| Primer Name   | Length | Sequence (5’-3’)                  |
|--------------|--------|-----------------------------------|
| SPHK1 Forward| 20     | ATCCAGAAAGCCCTGTGTAG              |
| SPHK1 Reverse| 19     | TGGTGACCTGTCATAGCC                |
| SGPL1 Forward| 19     | GGGTCCCATTGACGAAGAT               |
| SGPL1 Reverse| 20     | TGGCAGTGTTCCTGGAGATA              |
| GAPDH Forward| 19     | AGCCACATCGCTCAGACAC               |
| GAPDH Reverse| 19     | GCCCAATACGACCAAATCC               |
Supplementary Information-5

Additional details of analysis and quantification of sphingosine-1-phosphate from cell lines using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)

Equipment used for Tandem mass spectrometry (MS/MS): Thermo Fisher TSQ Quantum (Thermo Fisher Scientific); HPLC analysis: Agilent-1100 (Agilent Technologies); column: Spectra C8SR (Peeke Scientific, Redwood City, CA) 150 x 3.0 mm, 3-µm particle size.

For cell pellet preparation and lipid extraction for analysis, cells were washed 3 times in ice cold phosphate buffered saline (PBS), pH 7.4, scraped on ice in 10 ml of ice cold PBS using a cell scraper (Corning, UK) and centrifuged at 500 x g for 5 minutes at 4°C. PBS was removed and cell pellets were fortified with 50 µl (1nmole/ml) internal standard solution.

Lipids were extracted from cell pellets by adding 2ml of iso-propanol-water-ethyl acetate (30:10:60 vol), sonication for 30 sec, vortexing and centrifugation for 6 minutes at 3000 x g. Organic upper phase was transferred into a new tube and the remaining sample was re-extracted as previous. The new organic phase was combined with the previous supernatant and 1ml of lipid extract was dried down to determine phosphorus concentration (Pi). The remaining organic phase was evaporated under Nitrogen to dryness. Dry residue were reconstituted in 150 µl of the mobile phase “B” containing 2mM ammonium formate solution in methanol containing 0.2 % formic acid, then centrifuged for 5 minutes at 3000 x g. Samples (200 µl) were transformed to an auto-sampler HPLC vial and 10 µl were injected into the HPLC system. The phosphate content was measured with a standard curve and a colorimetric assay of ashed phosphate.
Supplementary Information-6

Additional details of chemotherapy treatment of patients

Neoadjuvant chemotherapy was with Epirubicin, Cisplatin, and capecitabine (epirubicin 50mg/m² intravenous day 1, cisplatin 60mg/m² intravenous day 1 and capecitabine 1250mg/m²/day in 2 divided doses orally day 1-21, with a 21 day cycle). Radiological response was assessed by CT chest and abdomen pre-therapy and after 3 (neoadjuvant) or 4 (palliative) cycles of chemotherapy according to RECIST criteria v1.1. If the absence of progressive disease on CT scan, patients receiving neoadjuvant chemotherapy proceeded to surgical resection after 3 cycles and also 3 cycles of post-operative/adjuvant chemotherapy with the same regimen if the treating oncologist considered them fit enough to begin this treatment within 12 weeks of the resection.
Supplementary Information-7: Pathways identified in Gene enrichment analysis (DAVID v6.7) of resistant cell lines

The following tables show the pathways and genes were identified as over-represented from the lists of genes with significantly different expression (student’s t-test \( p < 0.05 \)) between resistant daughter cell line and parental wild type cell line using DAVID v6.7, \( p < 0.05 \) with Benjamini and Hochberg correction used for multiple testing.

**AGSCis5 versus AGS**

| Term | Genes | \( p \) values |
|------|-------|---------------|
| Lysosome | ARSB, GM2A, HEXA, LGSN, AD3S2, CTSA, GLB1, CD66, TPPL1, LIPA, PI4P, GUSB, ATP6V1H, CD65, FUCAL1, GNS, LAMPI, LAMP3, GJA1, IGBP3, GAA, CTD8, CTSB, CTNS, GGA2, CTSH | 7.23E-06 |
| Base excision repair | POLD4, POLE1, UNG1, POLG1, POLQ1, PARP1, XRCC1, APEX1, FEN1 | 0.000718 |
| DNA replication | POLD4, MCM7, POLE3, RFC2, LIL1, POLC, MCM2, MCM4, FEN1, MCM5 | 0.000126 |
| p55 signaling pathway | STEAP3, PMAIP1, SFN, CCNG2, GSK3E, CCNE1, TP53D, D4DAH, TNFRSF10B, CD82, SREPIN1, DDB1, THBS1, GADD45A | 0.000634 |
| Pyrimidine metabolism | POLR3D1, POLE, POLB1A, CAF1, POLR3G, TK2, POLR3D, TYMS, POLE2, ENTPD5, CDA, TNND1, UCK2, DPD, DUT | 6.0218725 |
| Proteasome | PSMA6, PSMD6, PSME1, PSMD4, PSMB2, PSMD2, PSMB6, PSMB8, PSMD9 | 0.00475293 |
| ECM-receptor interaction | HS1SP2, DAG1, ITG5, ITG4, ITG3, SDC4, LAM3, LAMB2, LAMC3, CD44, ITG5, ITGAM, THBS1, SPP1 | 0.0040959 |
| Fatty acid metabolism | ACCADV1, ACACA2, CPT2, ACSL1, ALDH5B1, ACAT2, PECLIS, ACSL5 | 0.0049097 |
| Glutathione metabolism | GSTM1, G6PD2, G6PD1, GSTM4, SREMB, GSTF2, GPX1, TXN2, MT1G2 | 0.00497152 |
| Glycolytic metabolism | GLA, PGM1, GAA, HKII, PFKM, GLN1 | 0.00555363 |
| Systemic lupus erythematosus | HIST1H2A, HIST1H2D, HIST2AB, HIST2AB, HIST3H1C, HIST3H2B, HIST3H2D, HIST3H3E, HIST3H3F, HIST3H4E, HIST3H4F, HIST3H4H, HIST3H4I, HIST3H4J, HIST3H4K, HIST3H4L, HIST3H4M | 0.00515149 |
| Amyloid processing and presentation | HSISP90A1, PSME2, TAP1, TAP2, GMN, TAP1, CTSB, CTSB, HLA-DMA, TAPBP, B2M | 0.00641706 |
| Glycosphingolipid degradation | ARSB, GNS, HEX, GUSB, GLB1 | 0.00795848 |
| Sphingolipid metabolism | SGPL1, GLA, SGPP1, SGPP2, PA2P2, SMPD4, GLB1 | 0.00964488 |

**AGSOX8 versus AGS**

**AGSDOC6 versus AGS**
## AGSDOC6 versus AGS (continued)

| Term                                | Genes                                      | p values   |
|-------------------------------------|--------------------------------------------|------------|
| Prostate cancer                     | EGRF, FGFR2, HS96AB1, E2F2, GRB2, ERBB2, RELA, CREBBP, AKT1, CCNE1, IGFR1, CCND1, CDKN1B, CAPS9, INS, POGFRA, MDM2, AKT2 | 0.0316127  |
| Sphingolipid metabolism             | SGP1, SPTLC2, SGP1P, KDS, BAG6, ATP2A2, PPAP2D1, SPO2D2, ASAP1, DEGS1 | 0.062435   |
| Colorectal cancer                    | EGFR, DVL3, GRB2, CYCS, MEF, BIRC5, FZD9, TGFBI, AKT7, ACVR1B, IGFR1, CCND1, CAPS9, PDGFRB, AKT2 | 0.0732152  |
| Pancreatic metabolism               | POLE17, G6A, POLεL1, ADCAV, ZNRF1, RBMD2, POLR2A, POLR2E, PEEG, POLC3, ATC, ETPN5, INPDH2, NTC, NUDT22, POL51D1, POL51E1, POL51H1, NUP4, PDE4D, SMT6, NME4, NME5, PSM2, POLD1, POLD2 | 0.0754299  |
| RNA polymerase                      | POL2, POLR1E, POLR1D, POLR1A, POLR1C, POLR1G1, ZNRF1, POLR2A | 0.04116694 |
| Parkinson’s disease                 | ND1, DEFB32, SNCAP1, UQCR11, CCNH, NDUFA3, ATP5J, CVCS, NDUFS1, ATP6K1A, ATP8A2, NDUFA3, ATP5A1, ND5, ATP5F1 | 0.0473522  |
| Base excision repair                | POLE4, POL51, UMG, POL1, LRG1, POL51D2, POL51E, ZNRF1, POLR1C | 0.0349588   |
| Non-small cell lung cancer          | PRKCA, EGFR, AKT1, E2F2, CCND1, CASP9, GRB2, RXRB, ERBB2, CDK4, STK4, AKT2 | 0.0594121  |
| Chronic myeloid leukemia             | E12, CBP1, OR2K, RELA, BCL2, CDK4, TGFBI1, AKT1, ACVR1B, CCND1, CDKN1B, MDM2, ABL1, RUNX1, AKT2 | 0.0569907  |
| Cell cycle                          | E2F1, RB1L1, CREBBP, PTMY1, CDC26, MCM2, CDK4, CDC25C, MCM5, TGFBI1, CDC5, ACE1, CCND1, CCNB3, MCMT, CDKN1B, CDKN2B, PLK1, TDP2, MDM2, ABL1, GADD45A | 0.0534759  |
| Pancreatic cancer                    | EGFR, E2F2, RB1L1, CREBBP, PTMY1, CDC26, MCM2, CDK4, CDC25C, MCM5, TGFBI1, CDC5, ACE1, CCND1, CCNB3, MCMT, CDKN1B, CDKN2B, PLK1, TDP2, MDM2, ABL1, GADD45A | 0.0334759  |
| Adipocytokine signaling pathway     | TRAP2, RXRB, LEF1, RELA, XPC, PTMY1, PRKCA, PRKAC2, ESR1, AKT1, AKT2, ESR1, AKT1, AKT2, ESR1, AKT1 | 0.0395522  |
| Lysosome                            | LIPA, CLTB, LAMPT, GM2A, PSAP, HEXA, LUMN, CTSA, ACP2, AP4M1, AP4S1, FUC1A, GNS, LAMPI, CD69, FP1, IGFR2, ATPI6, ACP1, CTSL, GGA3 | 0.0762497  |

## OX33CIS4 versus OE33

| Term                                | Genes                                      | p values   |
|-------------------------------------|--------------------------------------------|------------|
| Lysosome                            | ARSB, SG5H, CLTB, LOMN, ATP6API, HHEX, AP352, AP351, ABCA2, CLTC, ATP6V0B, ORL1B, AP153, AP151, CD8S, AP152, AP152, AP152, GALC | 0.01224-05 |
| Ribosome                            | RPL18, RPL15, RPL35, RPL36, RPL10L, RPL32, RPS29L, RPL6, EPSAP58, RPL1P, RPL1L, RPL4, RPS24, RPL5A, RPSAP15, RPL7, RPL24, RPS8, RPS7, RPL29, RPS19, RPL18A, RPS15, RPL11, UBAP2 | 0.00048637 |
| Ubiquitination mediated proteolysis  | UBE2C1, UBE2C2, UBE2D1, UBE2C2, UBE2D3, CDA4, ANAPC11, UBE3C, CUL4, WWF1, ITCH, TRAF6, TRIP2, UAPC2, VHL, FZD2, BIRC6, UBE1L6, CDC25, MID1, CDC26, UBE1L3, CDC27, BRC1, TRIM7B, UBE2O, PSM4 | 0.01957259 |
| Adenosine metabolism                | P1P1G1, P1P2D3, PPPEF, BALAP2, NLR, ERBB2, LEF1, CTNND1, SMAD2, ACPI, TFC1, TCV, CSN2A2, TRTL4 | 0.00261459 |
| Neurotrophic signaling pathway      | GRB2, BRCA1, CD42, MAP2K5, KRAS, MAP3K5, BCL2, RHOA, RAF1, PAK1, PI3K, PDK1, IRAK1, IRAK3 | 0.0016653 |
| Epithelial cell signaling in Heelcabin pylou infection | GITH1, ATP6V0E1, ADAM10, LYN, ATP6V0A1, ATP6V0G1, ATP6V0B2, ATP6V0B, ATP6V0F, ATP6V0A1, CDCR3, PLGC1, MAPK13, MAPK14, ATP6V0D1, HBEF, IKBK, ATP6V0D1 | 0.0160035 |
| Gp1 signaling pathway               | STEAP1, TP53, CDK6, ERBB2, SFN, CCNG1, PTK1, ATM, CCNE1, CCND1, PPK1, CDK1, LAMA1, CDK1, CDK1 | 0.0160035 |
| Colorotic cancer                     | DVL2, MSHE, ORP2, TPS1, LEF1, RAF1, SMAD2, FZD3, BIRC3, FZD5, TCF7L2, RALGPS, FZD8, MAPK1, ACVR1B, CCND1, KRAS, BCL2, PDK1, AKT2, AKT2 | 0.0162505 |
| Neurotrophic signaling pathway      | PRRCC, PARPS2, CLDN9, ZAR, GNA1, CLDN5, ASH1L, PTEN, LNLICL2, CSNK2A2, CD42, KRAS, CSNK2A1, RIBOA, EXOC4, YES1, MLLT4, PPP2R2D, PRR1C, PRRG1, MYC, PSA, PDKC, PRCDC, PRKACQ, RAB4B, TPR3 | 0.0167832 |
| Amino sugar and nucleotide metabolism | UAP1, CYST1R1, GSPD1A1, GNE1, CMAS, HAD2, HEC1, USNI, GALK2, PGM2, MPI, G5P1, GTP72 | 0.0065077 |
| Cell cycle                          | CDC14A, DPB4, SFN, ANAPC11, CCNE1, ORC1L, MCM7, ORC1L, BUB1B, BUB1B, STAG2, ANAPC2, TP3, CDC3, CDK6, SMAD2, CDC26, CDC27, WTAH1A, AMAP1, RPS6KE1, WEE1, MCM8, CDKN1A, CCND1, CDKN2B, EP300, HDAC1 | 0.00111571 |
| Viroc Cholerae Infection            | ATP6V0E1, SLCA2, ATP6V0A1, PRRG1, ATP6V0G1, ATP6V0B, ATP6V0B, ATP6V0A1, CSK, PFC1, P1G1, ATP1L1, ATP1L1, ATP1L1, P1G1, SECL1A2 | 0.00755081 |
| Prostate cancer                     | GEF2, CEBEB, GRB2, ERBB2, PC3, LEF1, RAF1, TCF7L2, PTEN, CCNE1, MAPK1, CDK4A, CCND1, PDK1, KRAS, EP300, BCT1, TGF1, MTR, PIK1R3, IKBK | 0.0295084 |
| Fc gamma R Mediated                | LYN, LIMK1, SPOH1, ASAP1, ASAP2, RAF1, PRKCG, ARPC5, PRKCE, PRKCD, TLL1, ARPC1A, CD42, MAPK1 | 0.00519584 |
| Term | Genes | p values |
|------|-------|----------|
| ox33cis4 versus oe33 (continued) | | |
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OE33OX4 versus OE33 (continued)

| Term                        | Genes                          | p values  |
|-----------------------------|-------------------------------|----------|
| N-glycan biosynthesis       | MGAT4B, MGAT1, NAGA, ST6GAL1, TUSC3, DAD1, DPM2, ALG6, MAN1A1, RPN2 | 0.0760523 |
| p53 signaling pathway       | ZMAT3, CDK6, SFN, ATB, REM2B, ATM, CCNE1, TP53I, CDKN1A, TSC2, MDM4, FAS, THBS1 | 0.0867645 |
| Insulin signaling pathway   | PIKCA2, PRKCE, PIK3CB, MAPK2, PIK3G, PIK3CA, FLOT1, SOCS1, PRKAB1, FOXO1, PP1ICB, NRAS, PPP1R4C, PTG1, STLE2, PRKARIA, CALM2, MAPK8, INPP5D, JNK1, KRAS, TRIP10, SMC4 | 0.0935216 |
| small cell lung cancer      | NTCH, PIK3CB, CDK5, ITGA5, RCL2L1, MAX, CCNE1, LAMB3, LAMB2, TRAF6, IKBKB, TRAF5, MYC, TRAF4, TRAF3 | 0.0991423 |

OE21OX4 versus OE21

| Term                        | Genes                          | p values  |
|-----------------------------|-------------------------------|----------|
| Lysosome                    | AGA, CTSL2, NPC1, SLC17A5, PSAP, IGF2R, CTSD, ACP2, CTSA, ATP6V0D1, ATP6V0B, CTSL1 | 0.0202848 |
| Gloma                       | PRKCA, E2F2, IGF1R, CAMK2G, ARAF, TP53, TGFA, CALM1 | 0.0267068 |
| Prior diseases              | NOTCH1, LAMC1, BSAFA5, PRS85, CCL5 | 0.0777872 |
| Pathways in cancer          | PRKCA, E2F2, DUS3, BNP2, AR, STK56, CDH1, TP53, ITGB1, MMP2, CTNNB1, FOS, IGF1R, WNT11B, LAMA3, LAMB2, LAMA5, ARAF, VEGFA, TGFA, LAMC2, LAMC3 | 0.0855966 |
| Tight junction              | PRKCA, EP340L2, CDKN7, RAB38, EPB41L1, CD44, CSNK2B, ECHOC5, AMOTL1, PRKCE, CTNNB1 | 0.0959217 |
| Small cell lung cancer      | E2F2, LAMA3, LAMB2, LAMA5, TP53, LAMC2, LAMC1, ITGB1 | 0.0966986 |