**Regulation of Metabolism by LSR**

20 breast cancer cell pellets from four cell lines [MCF7 parental (LSR+), MCF7 Crisper (LSR-), Hs578t parental (LSR-) and Hs578t (LSR++)], with five replicate samples for each cell line were stored at -80˚ until sample preparation.

Cell pellets were resuspended in volume of ice cold Lipid Extractions Solvent (50 µg/mL) based on biomass. Contents were transferred to new, pre-labeled 2.0 mL LoBind tube with 10-15 ceramic beads, and homogenized using 2 pulses at 2,000 rpm for 30 sec on a MagNA Lyser. Volume of HPLC-grade water (with 0.02 mg/mL Tryptophan-d5 in water) was added based on biomass. Samples were allowed to sit at room temperature for 10 minutes, then centrifuged at 16,000 rcf for 10 min at 10˚C. For lipidomics, transferred the maximum clean volume of the lower lipid-rich DCM layer to a new, pre-labeled LoBind tube and a 375 µL aliquot was then transferred to a new 1.5 mL, LoBind tube for analysis.

An additional 125 µL aliquot of each study sample was transferred to a 7.0 mL glass vial to make a QC pool, which was vortexed for 30 sec and aliquoted into 5 Total Pool samples (375 µL each), and the remaining was used for 1 Equilibrium sample (column conditioning). Samples were frozen at -80˚C for 60 mins and lyophilized to dryness. Samples were reconstituted in ACN/IPA/H2O (65:30:5 v/v/v), vortexed at 4,000 rpm for 2 mins and centrifuged at 16,000 rcf for 4 min. 225 µL of the supernatant was transferred to pre-labeled autosampler vials and 10 µL was injected into OrbiTrap Velos.

Samples were randomized and pooled quality control samples were interspersed throughout the analysis sequence. A mixture of five lipid standards was used to check the system suitability, and the column was equilibrated with repeat injections of QC samples immediately prior to data acquisition. A Waters Acquity UPLC was used to inject samples (10 µL) on an Acquity CSH C18 column (2.1 X 100 mm 1.7 µm) at 50°C. Separation was accomplished using a gradient comprised of a three solvent system (mobile phase A: 10mM Ammonium Formate in 60:40 H2O/ACN with 0.1% formic acid, and mobile phase B: 10mM Ammonium Formate in 90:10 IPA/ACN with 0.1% formic acid) at a flow rate of 0.250 mL/min and directed to a LTQ Orbitrap Velos-ETD (Thermo Scientific, CA). Mass spectra (120-2000 m/z) were collected for all samples in positive mode and in negative mode with a resolution of 30,000. Five data dependent scan events utilizing dynamic exclusion were completed at a resolution of 7,500 in the FT to fragment the top five most intense ions from a given MS spectrum.

Progenesis QI software (Nonlinear Dynamics, UK) was used to pick, align, and assign peaks. LIPIDBLAST, LIPIDMAPS, and HMDB databases were used to match spectra and tentatively identify compounds. Multivariate Analysis (MVA) was performed using SIMCA 14.1 (Umetrics, Umeå, Sweden). Significant metabolites will be reported based on Variable Influence on Projection (VIP) criteria and statistical measures.