**SUPPLEMENTARY FIGURES.**

**Supplementary Figure 1**

A) 1H NMR spectra (CPMG) of conditioned medium from human U266 MMC cells upon

incubation for 0 (bottom), 4 (middle) or 18 (top) hours with 10 mM acetate. t-But= t-butanol

standard, Lac= lactate (1.31-1.32 ppm), A= alanine (3-position at 1.5 ppm), Acetate=acetate (1.91

ppm), Glu=glutamate (2.34-2.38 ppm), Glc = glucose (5.24 ppm).

B-D) Normalized 1H NMR peak integrals for Acetate (B, 1.91 ppm), glucose (C, 5.24 ppm) and

lactate (D, 1.31-1.32 ppm), normalized to alanine (1.5 ppm), relative to time 0 in the extracellular

media of 5TGM1, OPM2, and U266 human MMC, plated at different concentrations (x axis), plot

of representative experiments.

E) 13C-enrichment in intracellular glutamate upon incubation of U266 and OPM2 cells with 10mM

13C-Acetate for 0 vs. 16 h, measured as a ratio of HSQC and CPMG measurements on the same

samples. Mean and standard deviation of two biological replicates increase over time by two-way

ANOVA p<0.001.

F) 2D 1H-13C HSQC of 5TGM1 and OPM2 chloroform extraction (membranes) after 70 hours

incubation with 10mM 13C-Acetate (chemical assignment in main figure 1)

**Supplementary Figure 2**

A) 1H NMR analysis in CPMG (top) and gHSQC (bottom) sequences of intracellular extracts from

U266 upon 8h incubation with 13C-Acetate 10mM with CHC 2.5 mM (left) or vehicle (DMSO,

right). Arrows: acetate peak (1.91 ppm) in HSQC sequences (13C-labeled).

B-C) (B) Cell death of MMC lines measured as % PI+ cells by flow cytometry in U266, OPM2,

and 5TGM1 upon with different doses (20-500 μM) of orlistat for 24h, (B) at different time-points

(0, 24, 48h) with 50 μM orlistat. Average and standard deviation of 2 to 8 biological replicates per

dose, per line (two-way ANOVA p<0.0001).

D) Oil-red-O positive adipocytes per well upon 14 d of culture of primary BMSC from three

representative mice in the presence of 0-100 μM orlistat. b6: black-6, kj: KaLwRij, F female, M

male. Average and standard deviation of quadruplicates, two-way ANOVA p<0.01.

E) Apoptosis induction upon 72h treatment with orlistat of 5TGM1 MMC vs. primary BMSC from

black 6 (b6) or KaLwRij (K) mice and stromal cell lines ST2 and MC3T was measured by

AnnexinV-staining and flow cytometry

F-H) MM cell death upon combined treatment with CHC (0-5 mM) and orlistat (20 to 200 μM)

measured by flow cytometry upon staining with propidium iodide of U266 (F), 5TGM1 (G), or

OPM2 (H) cells (one representative experiment per cell line).

**Supplementary Figure 3**

A) Optical (GFP) and 11C-Acetate PET/CT in KaLwRij mice with bi-lateral flank subcutaneous

5TGM1 tumors (T1 and T2): imaging (i) and TAC (ii) of tumors vs. muscle, p<0.01 by ANOVA.

B) Measured tumor areas by GFP, 18F-FDG PET, and 11C-Acetate PET in subcutaneous 5TGM1

PCT in KaLwRij mice imaged within 12h with the three modalities.

C) Bio-distribution of 11C-Acetate in a bi-lateral OPM2 PCT compared to muscle.

D) *Ex vivo* optical imaging of femurs from a non-tumor bearing KaLwRij mouse (left) vs. 3 weeks

after 5TGM1 injection (right), showing GFP in bone lesions (arrows).

E) Differential involvement of bones from 5TGM1 implanted subcutaneously (left) or injected

i.v., measured by flow cytometry for GFP+ viable cells (PI negative) in the bone marrow \*\* p<0.

01

F) Correlation between bone marrow GFP+ viable cells (PI negative, x axis) and bone 11C-Acetate

uptake by biodistribution (y axis), (Spearman’s rs=0.63, p<0.05).

**Supplementary Figure 4**

A) Percentage of dead cells (7-AAD positive) in tissue homogenates from subcutaneous MM

tumors of bortezomib-treated mice relative to vehicle-treated tumors or non-tumor-bearing tissues

of both treatment groups (ANOVA, Tuckey’s multiple comparison test, \*\* p<0.01)

B) Correlation between 11C-acetate uptake by biodistribution, measured as tissue/blood ID%/g (x

axis) and percentage of viable tumor cells (GFP+ 7AAD-) by flow cytometry. rs= 0.7, p=0.02

C) Quantification of dead cells (7AAD+) in tumor tissue homogenates from vehicle vs. melphalantreated

(right) KaLwRij mice

D) 11C-Acetate average SUV over time in mice treated with melphalan (grey) vs. Vehicle (black)

at the tumor ROI (full line) vs. Muscle (dashed).

E-F) Tumor burden in KaLwRij mice 27 days after 5TGM1 I.v. on day 5 of treatment with saline

or bortezomib i.v. measeured as % viable (GFP+ PI-) tumor cells in the bone marrow (E) of gamma

globulin by SPEP (F)

\*p<0.05, \*\* p<0.01 columns: mean, error bars: standard deviation