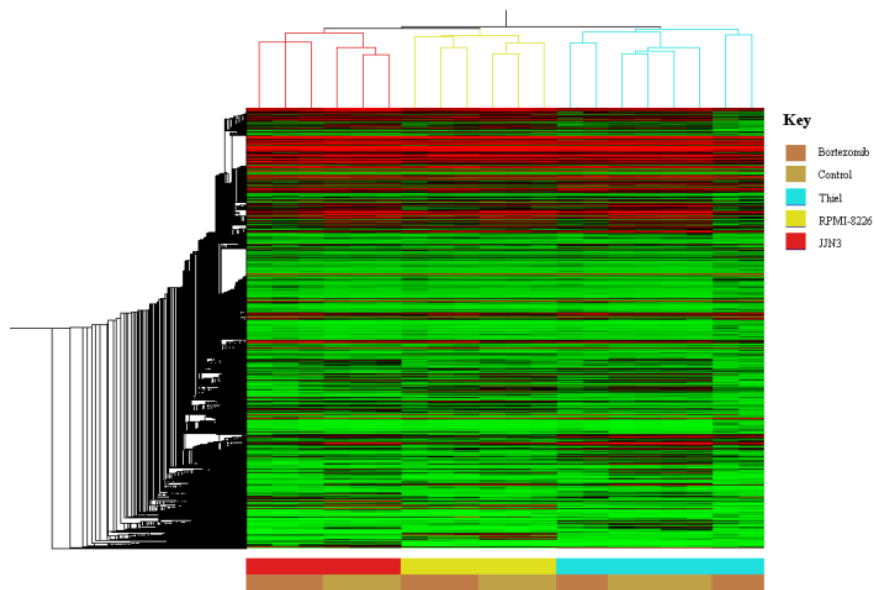
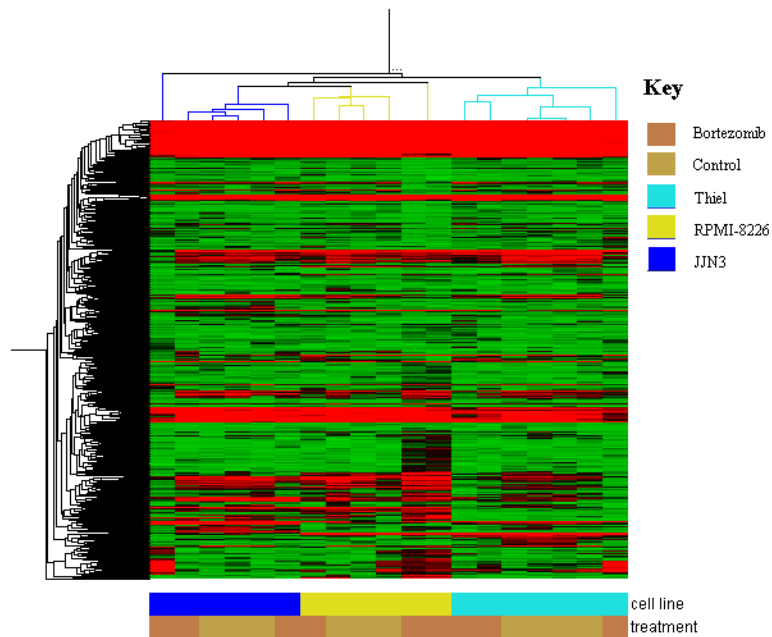
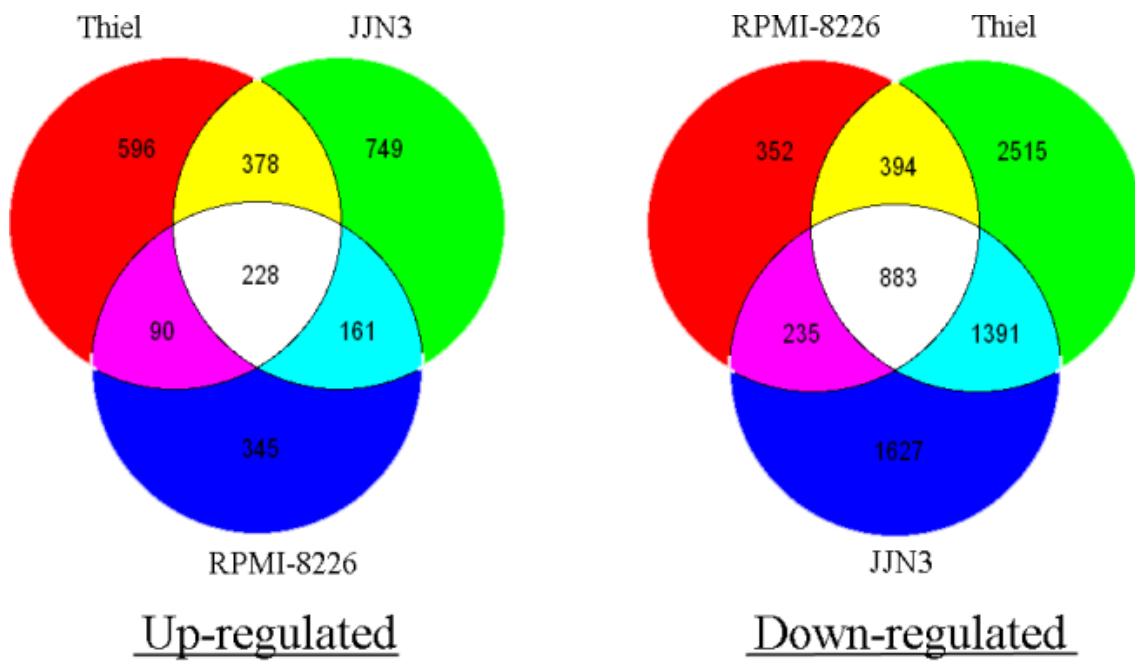
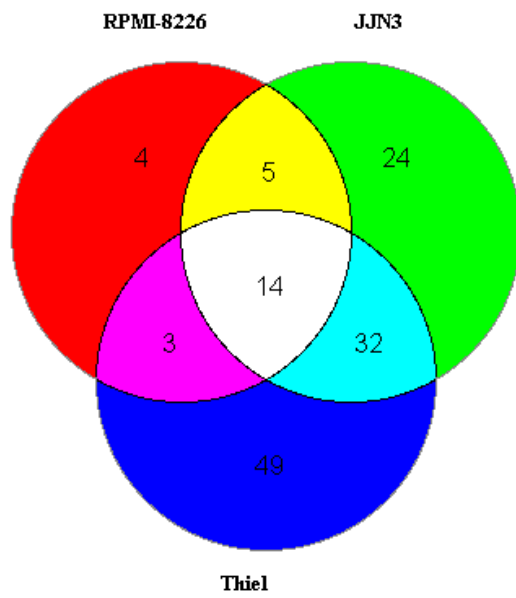


**A****B**

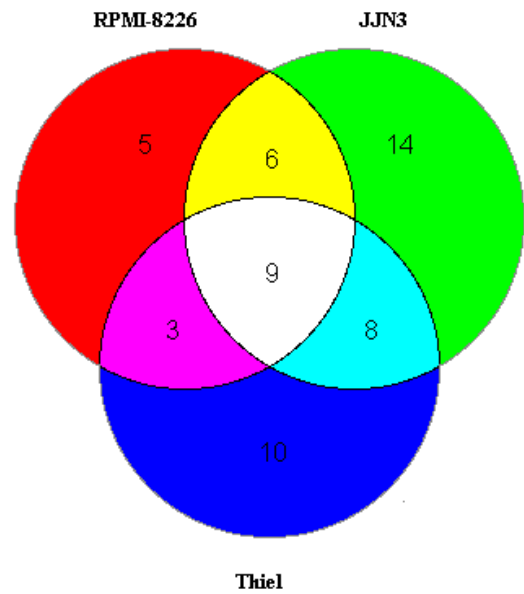
**Supplementary Figure S1. Unsupervised cluster analysis depicted as heat map showing relationship between (A) whole transcriptome and (B) miRnome with MM cell lines treated and untreated with bortezomib.** For U133plus2.0 arrays the raw data was RMA normalized and probes filtered to remove those with low intensity (>20 in >1 sample) resulting in 35,110 probes. For miRNA analysis raw data was normalised using the miQCtool software followed by filtering the human probe set to remove miRNAs of low intensity (i.e. filtered on 'present' flag >1/20 samples) resulting in 534 out of the original 847 human miRNA probe set. Analysis was carried out in Agilent Genespring GX software (Agilent Technologies, Palo Alto, CA).



**Supplementary Figure S2** Venn diagram showing relationship between genes up-regulated and down-regulated in the three MM cell lines (>2-fold median (n=3) change of untreated cells).

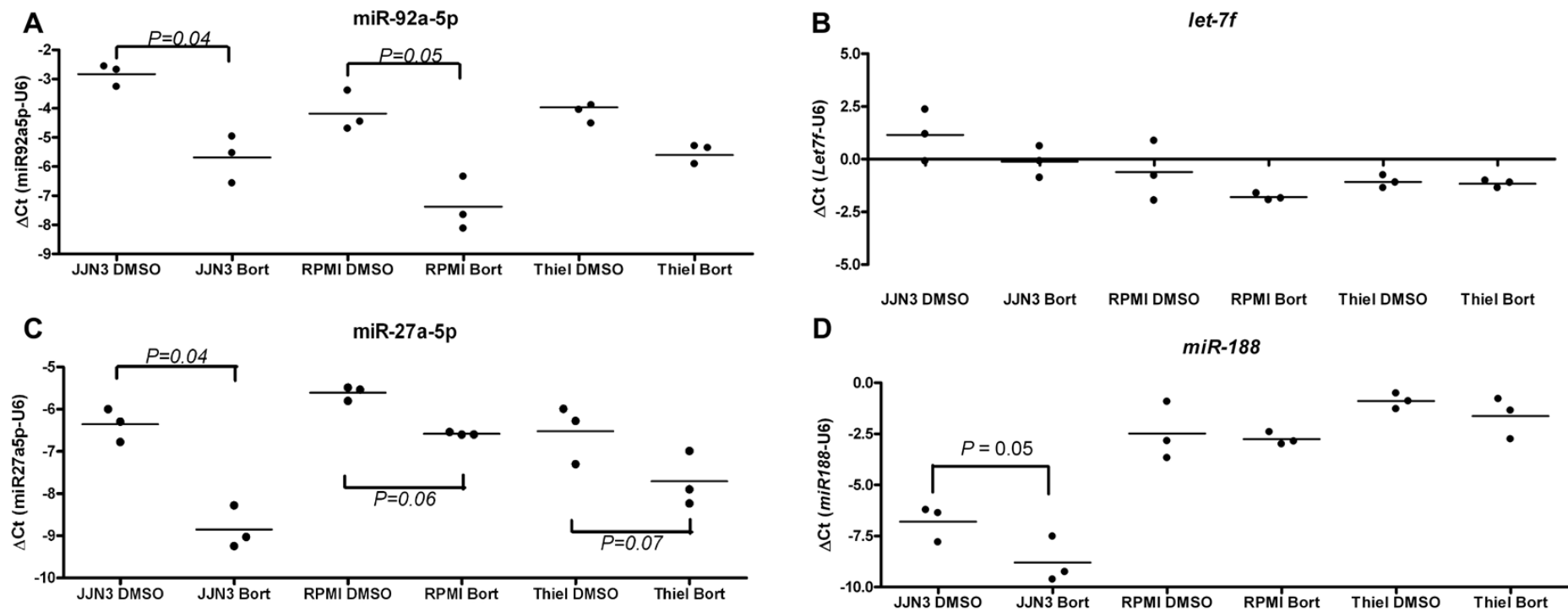


**Down-regulated**



**Up-regulated**

**Supplementary Figure S3** Venn diagram showing relationship between miRNAs up-regulated and down-regulated in the three MM cell lines (>2-fold median (n=3) change of untreated cells).



**Supplementary Figure S4.** Levels of (A) *miR-92a-5p*, (B) *let-7f* (C) *miR-27a-5p* and (D) *miR-188* in MM cell lines ±bortezomib treatment measured by Taqman probe qRT-PCR (Applied Biosystems, Warrington, UK). Expression levels are depicted as ΔCt (mean Ct of miRNA of interest – mean of control U6 snRNA). *P* values were calculated by Mann-Witney independent t-test (Graphpad Prism 4.0).

| <b>Cell line</b>                        | <b>Canonical Pathway</b>                  | <b>P-value</b>                          | <b>molecules</b>      |
|---|---|---|-----------------------|
| <i>Thiel</i>                            | Role of BRCA1 in DNA damage response      | $5 \times 10^{-8}$                      | 30/61 (0.492)         |
|   | Methionine metabolism                     | $1.31 \times 10^{-6}$                   | 17/78 (0.218)         |
|   | NRF2-mediated oxidative stress response   | $3.51 \times 10^{-6}$                   | 63/192 (0.328)        |
|   | Hereditary breast cancer signalling       | $6.17 \times 10^{-6}$                   | 44/129 (0.341)        |
|   | Molecular mechanisms of cancer            | $8.65 \times 10^{-6}$                   | 104/379 (0.274)       |
|   | <b>Protein ubiquitination pathway</b>     | <b><math>9.13 \times 10^{-6}</math></b> | <b>82/274 (0.299)</b> |
|   | ATM Signaling                             | $1.29 \times 10^{-5}$                   | 25/59 (0.463)         |
|   | Role of CHK Proteins in Cell Cycle        | $2.43 \times 10^{-5}$                   | 18/35 (0.514)         |
|   | Mitotic Roles of Polo-Like Kinase         | $4.09 \times 10^{-5}$                   | 26/65 (0.400)         |
| Mismatch Repair in Eukaryotes           | $5.35 \times 10^{-5}$                     | 11/24 (0.458)                           |                       |
| <i>JJN3</i>                             | Role of BRCA1 in DNA Damage Response      | $5.68 \times 10^{-11}$                  | 32/61 (0.525)         |
|   | Hereditary Breast Cancer Signaling        | $1.25 \times 10^{-9}$                   | 48/129 (0.372)        |
|   | Purine Metabolism                         | $1.47 \times 10^{-6}$                   | 79/398(0.198)         |
|   | Pyrimidine Metabolism                     | $2.11 \times 10^{-6}$                   | 48/217 (0.221)        |
|   | Role of CHK Proteins in Cell Cycle        | $3.40 \times 10^{-6}$                   | 18/35 (0.514)         |
|   | <b>Protein Ubiquitination Pathway</b>     | <b><math>5.25 \times 10^{-6}</math></b> | <b>75/274 (0.274)</b> |
|   | One Carbon Pool by Folate                 | $2.50 \times 10^{-5}$                   | 12/37 (0.324)         |
|   | Mismatch Repair in Eukaryotes             | $1.19 \times 10^{-4}$                   | 10/24 (0.417)         |
|   | NRF2-mediated Oxidative Stress Response   | $1.78 \times 10^{-4}$                   | 52/192 (0.271)        |
|   | Molecular Mechanisms of Cancer            | $1.90 \times 10^{-4}$                   | 88/379 (0.232)        |
| <i>RPMI-8226</i>                        | <b>Protein Ubiquitination Pathway</b>     | <b><math>2.55 \times 10^{-6}</math></b> | <b>45/274 (0.164)</b> |
|   | NRF2-mediated Oxidative Stress Response   | $2.90 \times 10^{-6}$                   | 35/192 (0.182)        |
|   | Interferon Signaling                      | $8.36 \times 10^{-6}$                   | 12/36 (0.336)         |
|   | Aldosterone Signaling in Epithelial Cells | $6.36 \times 10^{-5}$                   | 29/174 (0.167)        |
|   | Cyclins and Cell Cycle Regulation         | $2.95 \times 10^{-4}$                   | 17/89 (0.191)         |
|   | Mitotic Roles of Polo-Like Kinase         | $3.77 \times 10^{-4}$                   | 14/65 (0.215)         |
|   | Cell Cycle: G1/S Checkpoint Regulation    | $6.20 \times 10^{-4}$                   | 13/61 (0.213)         |
|   | Role of BRCA1 in DNA Damage Response      | $7.48 \times 10^{-4}$                   | 13/61 (0.213)         |
|   | B Cell Receptor Signaling                 | $1.19 \times 10^{-3}$                   | 24/156 (0.154)        |
|   | Methionine Metabolism                     | $1.26 \times 10^{-3}$                   | 8/78 (0.103)          |
|   | <i>All cell lines</i>                     | One Carbon Pool by Folate               | $9.06 \times 10^{-5}$ |
| Role of BRCA1 in DNA Damage Response    |   | $1.39 \times 10^{-4}$                   | 10/61 (0.164)         |
| Methionine Metabolism                   |   | $8.24 \times 10^{-4}$                   | 6/78 (0.077)          |
| Mitotic Roles of Polo-Like Kinase       |   | $8.77 \times 10^{-4}$                   | 9/64 (0.141)          |
| NRF2-mediated Oxidative Stress Response |   | $8.97 \times 10^{-4}$                   | 18/193 (0.093)        |
| Cyclins and Cell Cycle Regulation       |   | $2.16 \times 10^{-3}$                   | 10/89 (0.112)         |
| Cell Cycle: G2/M DNA Damage Checkpoint  |   | $2.71 \times 10^{-3}$                   | 7/49 (0.143)          |
| Hereditary Breast Cancer Signaling      |   | $3.93 \times 10^{-3}$                   | 12/129 (0.093)        |
| <b>Protein Ubiquitination Pathway</b>   |   | <b><math>4.12 \times 10^{-3}</math></b> | <b>21/274 (0.077)</b> |
| Granzyme B Signaling                    |   | $4.66 \times 10^{-3}$                   | 4/16 (0.25)           |

**Supplementary Table S1.** Top ten most significant canonical pathways for genes up- or down- regulated >2-fold in response to bortezomib treatment. Results for each individual cell line and those genes commonly deregulated in all three MM cell lines. Analysis implemented in Ingenuity Pathway Analysis software suite (Ingenuity, CA). 156 different canonical pathways were present in the database.

**Supplementary Table S2. Top 30 up- regulated genes in response to bortezomib treatment (median >2-fold in all three MM cell lines)**

| <b>Fold change*</b> | <b>Gene</b>          | <b>Name</b>  | <b>Canonical pathway†</b>   |
|---------------------|----------------------|--|---|
| 55.006              | <i>NCK1</i>          | NCK adaptor protein 1  | Actin Nucleation by ARP-WASP Complex; Angiopoietin Signaling; Axonal Guidance Signaling; Ephrin Receptor Signaling; ErbB Signaling; Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes; GDNF Family Ligand-Receptor Interactions; Insulin Receptor Signaling; Integrin Signaling; Natural Killer Cell Signaling; Netrin Signaling; PAK Signaling; Paxillin Signaling |
| 45.786              | <i>HSPA6</i>         | heat shock 70kDa protein 6 (HSP70B')                           | Aldosterone Signaling in Epithelial Cells; eNOS Signaling; Glucocorticoid Receptor Signaling; Huntington's Disease Signaling; <b>Protein Ubiquitination Pathway</b>   |
| 35.242              | <i>CLU</i>           | clusterin  | Atherosclerosis Signaling; Clathrin-mediated Endocytosis Signaling; IL-12 Signaling and Production in Macrophages; LXR/RXR Activation; Production of Nitric Oxide and Reactive Oxygen Species in Macrophages  |
| 27.665              | <i>HSPA1A/HSPA1B</i> | heat shock 70kDa protein 1A                                    | Aldosterone Signaling in Epithelial Cells; eNOS Signaling; Glucocorticoid Receptor Signaling; Huntington's Disease Signaling; <b>Protein Ubiquitination Pathway</b>   |
| 21.129              | <i>ZFAND2A</i>       | zinc finger, AN1-type domain 2A                                | -   |
| 18.750              | <i>HMOX1</i>         | heme oxygenase (decycling) 1                                   | Acute Phase Response Signaling; Endothelin-1 Signaling; Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes; Glycerophospholipid Metabolism; IL-10 Signaling; IL-8 Signaling; mTOR Signaling; NRF2-mediated Oxidative Stress Response; Pancreatic Adenocarcinoma Signaling; Phospholipase C Signaling; Phospholipid Degradation; Xenobiotic Metabolism Signaling      |
| 18.014              | <i>MLLT11</i>        | myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, | -   |

|        |                   |  |  |
|--------|-------------------|--|--|
|        |                   | Drosophila); translocated to, 11                               |  |
| 15.602 | <i>GABARAP L1</i> | GABA(A) receptor-associated protein like 1                     | -  |
| 14.362 | <i>ATF3</i>       | activating transcription factor 3                              | PI3K Signaling in B Lymphocytes  |
| 13.307 | <i>NEAT1</i>      | nuclear paraspeckle assembly transcript 1 (non-protein coding) | -  |
| 12.648 | <i>JUN</i>        | jun proto-oncogene   | 14-3-3-mediated Signaling; 4-1BB Signaling in T Lymphocytes; Activation of IRF by Cytosolic Pattern Recognition Receptors; Acute Phase Response Signaling; Agrin Interactions at Neuromuscular Junction; Androgen Signaling; April Mediated Signaling; Aryl Hydrocarbon Receptor Signaling; ATM Signaling; B Cell Activating Factor Signaling; B Cell Receptor Signaling; BMP signaling pathway; Cardiac Hypertrophy Signaling; CCR5 Signaling in Macrophages; CD27 Signaling in Lymphocytes; CD28 Signaling in T Helper Cells; CD40 Signaling; Cdc42 Signaling; Ceramide Signaling; Chemokine Signaling; Cholecystokinin/Gastrin-mediated Signaling; Colorectal Cancer Metastasis Signaling; Corticotropin Releasing Hormone Signaling; CXCR4 Signaling; EGF Signaling; Endothelin-1 Signaling; ErbB2-ErbB3 Signaling; ErbB Signaling; Erythropoietin Signaling; Estrogen-Dependent Breast Cancer Signaling; GDNF Family Ligand-Receptor Interactions; Glucocorticoid Receptor Signaling; GNRH Signaling; Ga12/13 Signaling; Hepatic Cholestasis; HGF Signaling; HIF1 $\alpha$ Signaling; HMGB1 Signaling; Huntington's Disease Signaling; Hypoxia Signaling in the Cardiovascular System; IGF-1 Signaling; IL-10 Signaling; IL-12 Signaling and Production in Macrophages; IL-17A Signaling in Fibroblasts; IL-17A Signaling in Gastric Cells; IL-17 Signaling; IL-1 Signaling; IL-2 Signaling; IL-3 Signaling; IL-6 Signaling; IL-8 Signaling; ILK Signaling; Inhibition of Angiogenesis by TSP1; iNOS Signaling; LPS/IL-1 Mediated Inhibition of RXR Function; LPS-stimulated MAPK Signaling; MIF Regulation of Innate Immunity; |

|        |                |  |   |
|--------|----------------|--|---|
|        |                |  | Molecular Mechanisms of Cancer; Neurotrophin/TRK Signaling; NRF2-mediated Oxidative Stress Response; OX40 Signaling Pathway; P2Y Purigenic Receptor Signaling Pathway; p53 Signaling; PDGF Signaling; PI3K Signaling in B Lymphocytes; PKC $\theta$ Signaling in T Lymphocytes; PPAR Signaling; PPAR $\alpha$ /RXR $\alpha$ Activation; Production of Nitric Oxide and Reactive Oxygen Species in Macrophages; Prolactin Signaling; Rac Signaling; RANK Signaling in Osteoclasts; RAR Activation; Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes; Relaxin Signaling; Renal Cell Carcinoma Signaling; Renin-Angiotensin Signaling; Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis; Role of NFAT in Regulation of the Immune Response; Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis; SAPK/JNK Signaling; Sertoli Cell-Sertoli Cell Junction Signaling; Signaling by Rho Family GTPases; Systemic Lupus Erythematosus Signaling; T Cell Receptor Signaling; TGF- $\beta$ Signaling; Thrombopoietin Signaling; Tight Junction Signaling; TNFR1 Signaling; TNFR2 Signaling; Toll-like Receptor Signaling; Wnt/ $\beta$ -catenin Signaling |
| 11.385 | <i>DDIT3</i>   | DNA-damage-inducible transcript 3                                      | p38 MAPK Signaling  |
| 10.812 | <i>ID2</i>     | inhibitor of DNA binding 2, dominant negative helix-loop-helix protein | Mouse Embryonic Stem Cell Pluripotency  |
| 9.807  | <i>MIR22HG</i> | MIR22 host gene (non-protein coding)                                   | -   |
| 9.711  | <i>TMEFF2</i>  | transmembrane protein with EGF-like and two follistatin-like domains 2 | Neuregulin Signaling  |
| 9.614  | <i>SQSTM1</i>  | sequestosome 1   | NRF2-mediated Oxidative Stress Response   |
| 8.939  | <i>ANXA1</i>   | annexin A1   | Glucocorticoid Receptor Signaling   |
| 8.285  | <i>AIM2</i>    | absent in melanoma 2   | -   |
| 7.529  | <i>SAT1</i>    | spermidine/spermine N1-acetyltransferase 1                             | Arginine and Proline Metabolism; Polyamine Regulation in Colon Cancer   |
| 7.311  | <i>TUSC3</i>   | tumor suppressor candidate 3   | N-Glycan Biosynthesis   |



|       |               |  |  |
|-------|---------------|--|--|
| 7.297 | <i>DNAJB1</i> | DnaJ (Hsp40) homolog, subfamily B, member 1            | Aldosterone Signaling in Epithelial Cells; Androgen Signaling; Huntington's Disease Signaling; NRF2-mediated Oxidative Stress Response; <b>Protein Ubiquitination Pathway</b>  |
| 7.184 | <i>RPS11</i>  | ribosomal protein S11                                  | EIF2 Signaling; mTOR Signaling; Regulation of eIF4 and p70S6K Signaling  |
| 7.098 | <i>IL8</i>    | interleukin 8  | Airway Pathology in Chronic Obstructive Pulmonary Disease; Atherosclerosis Signaling; Bladder Cancer Signaling; Communication between Innate and Adaptive Immune Cells; Glucocorticoid Receptor Signaling; Hematopoiesis from Pluripotent Stem Cells; Hepatic Cholestasis; Hepatic Fibrosis / Hepatic Stellate Cell Activation; HMGB1 Signaling; IL-17A Signaling in Gastric Cells; IL-17 Signaling; IL-6 Signaling; IL-8 Signaling; Role of Cytokines in Mediating Communication between Immune Cells; Role of IL-17A in Arthritis; Role of IL-17F in Allergic Inflammatory Airway Diseases; Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis; Role of Tissue Factor in Cancer; TREM1 Signaling |
| 6.998 | <i>RBM11</i>  | RNA binding motif protein 11                           | -  |
| 6.982 | <i>MALAT1</i> | metastasis associated lung adenocarcinoma transcript 1 | -  |
| 6.9   | <i>BAG3</i>   | BCL2-associated athanogene 3                           | -  |
| 6.677 | <i>TUBB2A</i> | tubulin, beta 2A                                       | 14-3-3-mediated Signaling; Axonal Guidance Signaling; Breast Cancer Regulation by Stathmin1; Gap Junction Signaling; Germ Cell-Sertoli Cell Junction Signaling; Sertoli Cell-Sertoli Cell Junction Signaling   |
| 6.185 | <i>PALLD</i>  | palladin, cytoskeletal associated protein              | -  |
| 5.956 | <i>YPEL5</i>  | yippee-like 5 (Drosophila)                             | -  |
| 5.09  | <i>DNAJB4</i> | DnaJ (Hsp40) homolog, subfamily B, member 4            | Aldosterone Signaling in Epithelial Cells; NRF2-mediated Oxidative Stress Response; <b>Protein Ubiquitination Pathway</b>  |

\*Average fold change between three cell lines. †Canonical pathways listed in Ingenuity analysis suite.

**Supplementary Table S3. Top 30 down- regulated genes in response to bortezomib treatment (median >2-fold in all three MM cell lines)**

| <b>Fold change*</b> | <b>Gene</b>      | <b>Name</b>  | <b>Canonical pathway†</b>  |
|---------------------|------------------|--|--|
| -12.522             | <i>UNC13C</i>    | unc-13 homolog C (C. elegans)                          | -  |
| -12.056             | <i>KISS1R</i>    | KISS1 receptor   | G-Protein Coupled Receptor Signaling   |
| -10.499             | <i>MYB</i>       | v-myb myeloblastosis viral oncogene homolog (avian)    | -  |
| -10.404             | <i>GAS2</i>      | growth arrest-specific 2                               | Apoptosis Signaling  |
| -9.16               | <i>LOC730101</i> | hypothetical LOC730101                                 | -  |
| -8.862              | <i>METTL7A</i>   | methyltransferase like 7A                              | -  |
| -8.484              | <i>IMPA2</i>     | inositol(myo)-1(or 4)-monophosphatase 2                | Inositol Phosphate Metabolism  |
| -7.454              | <i>AKAP2</i>     | A kinase (PRKA) anchor protein 2                       | cAMP-mediated signaling; Cardiac $\beta$ -adrenergic Signaling; Protein Kinase A Signaling |
| -7.374              | <i>BCL11A</i>    | B-cell CLL/lymphoma 11A (zinc finger protein)          | -  |
| -7.108              | <i>SULF2</i>     | sulfatase 2  | Androgen and Estrogen Metabolism; Glycosaminoglycan Degradation; Sphingolipid Metabolism   |
| -6.77               | <i>STS</i>       | steroid sulfatase (microsomal), isozyme S              | Androgen and Estrogen Metabolism   |
| -6.678              | <i>DUT</i>       | deoxyuridine triphosphatase                            | Pyrimidine Metabolism  |
| -6.589              | <i>PKP2</i>      | plakophilin 2  | -  |
| -6.513              | <i>KCTD12</i>    | potassium channel tetramerisation domain containing 12 | -  |
| -6.388              | <i>MZB1</i>      | marginal zone B and B1 cell-specific protein           | -  |
| -6.067              | <i>MORC1</i>     | MORC family CW-type zinc finger 1                      | -  |

|        |                 |  |  |
|--------|-----------------|--|--|
| -6.016 | <i>ALDH5A1</i>  | aldehyde dehydrogenase 5 family, member A1     | Aryl Hydrocarbon Receptor Signaling; Butanoate Metabolism; GABA Receptor Signaling; Glutamate Metabolism; LPS/IL-1 Mediated Inhibition of RXR Function; Xenobiotic Metabolism Signaling  |
| -5.947 | <i>RCSD1</i>    | RCSD domain containing 1                       | -  |
| -5.941 | <i>FAM171A1</i> | family with sequence similarity 171, member A1 | -  |
| -5.868 | <i>BIRC5</i>    | baculoviral IAP repeat containing 5 (survivin) | Angiopoietin Signaling; Colorectal Cancer Metastasis Signaling; p53 Signaling; Pancreatic Adenocarcinoma Signaling   |
| -5.839 | <i>KLF13</i>    | Kruppel-like factor 13                         | -  |
| -5.74  | <i>DEPDC1B</i>  | DEP domain containing 1B                       | -  |
| -5.727 | <i>SIGMAR1</i>  | sigma non-opioid intracellular receptor        | -  |
| -5.659 | <i>TOP2A</i>    | topoisomerase (DNA) II alpha 170kDa            | Cell Cycle: G2/M DNA Damage Checkpoint Regulation  |
| -5.635 | <i>NFE2L3</i>   | nuclear factor (erythroid-derived 2)-like 3    | -  |
| -5.555 | <i>E2F5</i>     | E2F transcription factor 5, p130-binding       | Breast Cancer Regulation by Stathmin1; Cell Cycle: G1/S Checkpoint Regulation; Cell Cycle Regulation by BTG Family Proteins; Chronic Myeloid Leukemia Signaling; Cyclins and Cell Cycle Regulation; Estrogen-mediated S-phase Entry;; Molecular Mechanisms of Cancer; Pancreatic Adenocarcinoma Signaling; Role of BRCA1 in DNA Damage Response; Role of CHK Proteins in Cell Cycle Checkpoint |
| -5.532 | <i>CDCA7</i>    | cell division cycle associated 7               | -  |
| -5.502 | <i>MEX3D</i>    | mex-3 homolog D ( <i>C. elegans</i> )          | -  |
| -5.386 | <i>PTGER4</i>   | prostaglandin E receptor 4 (subtype EP4)       | cAMP-mediated signaling; Colorectal Cancer Metastasis Signaling; Eicosanoid Signaling; G-Protein Coupled Receptor Signaling  |
| -5.384 | <i>CD59</i>     | CD59 molecule, complement regulatory protein   | Complement System  |

\*Average fold change between three cell lines. †Canonical pathways listed in Ingenuity analysis suite.

| <b>MicroRNA ID</b>             | <b>Fold change</b> | <b>Map</b>      | <b>Up/down</b> |
|--------------------------------|--------------------|-----------------|----------------|
| <i>hsa-miR-548a-3p</i>         | 4.819              | 6p22.3          | Up             |
| <i>hsa-miR-149-3p</i>          | 4.426              | 2q37.3          | Up             |
| <b><i>hsa-miR-1225-5p</i></b>  | 3.976              | 16p13.3         | Up             |
| <i>hsa-miR-92b-5p</i>          | 3.599              | 1q22            | Up             |
| <i>hsa-miR-1228-5p</i>         | 3.423              | 12q13.3         | Up             |
| <b><i>hsa-miR-603</i></b>      | 3.378              | 10p12.2         | Up             |
| <b><i>hsa-miR-638</i></b>      | 3.281              | 19p13.2         | Up             |
| <b><i>hsa-miR-570</i></b>      | 3.067              | 3q29            | Up             |
| <i>hsa-miR-923<sup>1</sup></i> | 3.050              | -               | Up             |
| <i>hsa-miR-92a-1-5p</i>        | -25.368            | 13q31.3         | Down           |
| <i>hsa-miR-25-5p</i>           | -7.872             | 7q22.1          | Down           |
| <b><i>hsa-let-7f</i></b>       | -4.862             | 9q22.32/Xp11.22 | Down           |
| <b><i>hsa-miR-362-5p</i></b>   | -4.469             | Xp11.23         | Down           |
| <i>hsa-miR-551b-5p</i>         | -4.208             | 3q26.2          | Down           |
| <i>hsa-miR-193b-5p</i>         | -4.051             | 16p13.12        | Down           |
| <i>hsa-miR-30b-3p</i>          | -3.646             | 8q24.22         | Down           |
| <i>hsa-miR-29c-5p</i>          | -3.499             | 1q32.2          | Down           |
| <b><i>hsa-miR-27a-5p</i></b>   | -3.280             | 19p13.13        | Down           |
| <b><i>hsa-miR-500a</i></b>     | -3.116             | Xp11.23         | Down           |
| <b><i>hsa-miR-18a</i></b>      | -3.087             | 13q31.3         | Down           |
| <b><i>hsa-miR-188</i></b>      | -2.960             | Xp11.23         | Down           |
| <b><i>hsa-miR-296-3p</i></b>   | -2.859             | 20q13.32        | Down           |
| <b><i>hsa-miR-502-3p</i></b>   | -2.849             | Xp11.23         | Down           |

**Supplementary Table S4.** MiRNAs that underwent >2-fold median (n=3) expression change in response to bortezomib treatment in all three MM cell lines (see Supplementary Figure S3). <sup>1</sup>hsa-mir-923 has since been re-designated part of 28S RNA. MicroRNAs that have targeting information available in Ingenuity are shown in bold.

| Cell line                             | Canonical Pathway  | P-value                       | molecules             |
|---------------------------------------|--|-------------------------------|-----------------------|
| <i>Thiel</i>                          | Role of BRCA1 in DNA Damage Response                       | 1.14 x 10 <sup>-5</sup>       | 24/61 (0.394)         |
|                                       | DNA Double-Strand Break Repair by Homologous Recombination | 1.93 x 10 <sup>-5</sup>       | 10/17 (0.588)         |
|                                       | Molecular Mechanisms of Cancer                             | 3.83 x 10 <sup>-5</sup>       | 90/377 (0.239)        |
|                                       | Methionine Metabolism                                      | 4.54 x 10 <sup>-5</sup>       | 14/78 (0.179)         |
|                                       | One Carbon Pool by Folate                                  | 6.44 x 10 <sup>-5</sup>       | 11/36 (0.306)         |
|                                       | Glucocorticoid Receptor Signaling                          | 1.03 x 10 <sup>-4</sup>       | 71/295 (0.241)        |
|                                       | <b>Protein Ubiquitination Pathway</b>                      | <b>4.59 x 10<sup>-4</sup></b> | <b>67/274 (0.245)</b> |
|                                       | ATM Signaling  | 4.74 x 10 <sup>-4</sup>       | 20/54 (0.370)         |
|                                       | NRF2-mediated Oxidative Stress Response                    | 5.67 x 10 <sup>-4</sup>       | 50/193 (0.259)        |
| Hypoxia Signaling in Cardiovascular   | 9.18 x 10 <sup>-4</sup>                                    | 22/68 (0.324)                 |                       |
| <i>JJN3</i>                           | Role of BRCA1 in DNA Damage Response                       | 1.20 x 10 <sup>-8</sup>       | 24/61 (0.393)         |
|                                       | Hereditary Breast Cancer Signaling                         | 3.30 x 10 <sup>-6</sup>       | 33/129 (0.256)        |
|                                       | Molecular Mechanisms of Cancer                             | 2.02 x 10 <sup>-5</sup>       | 63/379(0.182)         |
|                                       | Cell Cycle Control of Chromosomal                          | 3.61 x 10 <sup>-5</sup>       | 12/31 (0.397)-        |
|                                       | Purine Metabolism  | 3.62 x 10 <sup>-5</sup>       | 57/398 (0.143)        |
|                                       | One Carbon Pool by Folate                                  | 7.96 x 10 <sup>-5</sup>       | 10/37 (0.270)         |
|                                       | Role of CHK Proteins in Cell Cycle                         | 7.96 x 10 <sup>-5</sup>       | 13/35 (0.371)         |
|                                       | Factors Promoting Cardiogenesis in                         | 1.01 x 10 <sup>-4</sup>       | 24/95 (0.253)         |
|                                       | <b>Protein Ubiquitination Pathway</b>                      | <b>1.73 x 10<sup>-4</sup></b> | <b>53/274 (0.193)</b> |
| Granzyme B Signaling                  | 2.78 x 10 <sup>-4</sup>                                    | 8/16 (0.500)                  |                       |
| <i>RPMI8226</i>                       | Aldosterone Signaling in Epithelial Cells                  | 7.75 x 10 <sup>-5</sup>       | 26/170 (0.153)        |
|                                       | NRF2-mediated Oxidative Stress Response                    | 1.94 x 10 <sup>-4</sup>       | 28/193 (0.145)        |
|                                       | Cell Cycle: G1/S Checkpoint Regulation                     | 6.98 x 10 <sup>-4</sup>       | 12/61 (0.197)         |
|                                       | Cyclins and Cell Cycle Regulation                          | 7.06 x 10 <sup>-4</sup>       | 16/89 (0.169)         |
|                                       | Role of BRCA1 in DNA Damage Response                       | 8.32 x 10 <sup>-4</sup>       | 12/61 (0.197)         |
|                                       | Molecular Mechanisms of Cancer                             | 1.10 x 10 <sup>-3</sup>       | 42/377 (0.111)        |
|                                       | One Carbon Pool by Folate                                  | 1.73 x 10 <sup>-3</sup>       | 6/36 (0.167)          |
|                                       | B Cell Receptor Signaling                                  | 2.73 x 10 <sup>-3</sup>       | 21/156 (0.135)        |
|                                       | Role of CHK Proteins in Cell Cycle                         | 3.01 x 10 <sup>-3</sup>       | 8/35 (0.229)          |
| <b>Protein Ubiquitination Pathway</b> | <b>4.89 x 10<sup>-3</sup></b>                              | <b>31/274 (0.113)</b>         |                       |
| <i>All cell lines</i>                 | NRF2-mediated Oxidative Stress Response                    | 1.56 x 10 <sup>-3</sup>       | 9/193 (0.046)         |
|                                       | Aldosterone signalling in epithelial cells                 | 2.50 x 10 <sup>-3</sup>       | 8/174 (0.046)         |
|                                       | One Carbon Pool by Folate                                  | 3.59 x 10 <sup>-3</sup>       | 3/36 (0.083)          |
|                                       | Aryl hydrocarbon receptor signalling                       | 4.53 x 10 <sup>-3</sup>       | 7/159 (0.044)         |
|                                       | Aminophosphate Metabolism                                  | 4.88 x 10 <sup>-3</sup>       | 3/57 (0.052)          |
|                                       | <b>Protein Ubiquitination Pathway</b>                      | <b>4.98 x 10<sup>-3</sup></b> | <b>10/274 (0.036)</b> |
|                                       | Glucocortoid receptor signalling                           | 6.16 x 10 <sup>-3</sup>       | 10/295 (0.034)        |
|                                       | Cyclins and Cell Cycle Regulation                          | 6.56 x 10 <sup>-3</sup>       | 5/89 (0.056)          |
|                                       | Purine Metabolism  | 7.73 x 10 <sup>-3</sup>       | 10/398(0.026)         |
| Phospholipase C signalling            | 8.27 x 10 <sup>-3</sup>                                    | 9/261 (0.035)                 |                       |

**Supplementary Table S5.** Top ten most significant canonical pathways for genes deregulated (>2-fold) in response to bortezomib treatment that are predicted targets (in opposite direction) of deregulated miRNAs. Results for each individual cell line and those genes commonly deregulated in all three MM cell lines. Analysis implemented in Ingenuity Pathway Analysis software suite (Ingenuity, CA).