**Supplementary figure legends**

**Figure S1, related to Figure 1** Representative IHC analysis in patient samples and normal healthy donors. Bone marrow biopsies from MM patients and normal healthy donors were sectioned and stained with USP14 and UCHL-5 antibodies. Immunostained samples were imaged using microscopy (Zeiss AxioImager M1 Microscope, Oberkochen, Germany). The scale bar is 20µM. Red arrowheads indicate USP14/UCHL5-positive cells (brown color).

**Figure S2, related to Figure 2** b-AP15 targets USP14 and UCHL-5 in MM. (A) RPMI8226 or KMS11 cells were treated with DMSO or indicated concentration of b-AP15 for 3 hrs. Proteasome activity was determined by monitoring the cleavage of LLVY-AMC substrate (B) RPMI8226 or KMS11 cells were treated with DMSO or b-AP15 (1000nM) for 3 hrs. Total DUB activity was measured using cleavage of ubiquitin-AMC. (C) RPMI8226 cells were treated as in (B). Protein lysates were incubated with the active site probe Ub-VS for indicated time points. Note the decrease in active USP14 and UCHL5 compared with the non-proteasomal DUBs USP7 and UCHL3. (Note a lot of non-specific bands are present from the UCHL5 antibody. The (*) denotes the increase in the inactive form of UCHL5 following b-AP15 treatment). (D) RPMI8226 or KMS11 cells were treated with DMSO or b-AP15 (1000nM) for 3 hrs and analyzed for DUB activity using Ub-VS as in (C). (E) RPMI8226 cells were treated with DMSO or b-AP15 for 3 hrs and total DUB activity analyzed using HA tagged Ub-VS (HA-UbVS).

**Figure S3, related to Figure 3** Cytotoxicity of b-AP15 in solid tumor cell lines. Solid tumor cell lines: colon cancer cell lines (colo320, DLD1, LS174), neuroblastoma cell line SHSY5Y, renal cell carcinoma cell line 7860 and osteosarcoma U2OS cell line were
treated with DMSO or b-AP15 at different concentrations for 48h, followed by measurement of cell viability with MTT assay.

**Figure S4, related to Figure 4** Mechanisms of b-AP15-Induced MM cell death (A) MM.1S cells were treated with DMSO or b-AP15 for 24h and then protein lysates were subjected to IB with anti-cyclinD1, cyclinE1, P21 or beta-actin antibodies. (B) ANBL6 and ANBL6-V5R cells were treated with b-AP15 (300nM) or bortezomib (2.5nM) for 8h and then protein lysates were subjected to IB with anti-p-eIF2α, CHOP or beta-actin antibodies.
Supplementary Figure 1

Normal donor

MM patient

USP14

UCHL5
Supplementary Figure 4

A

B