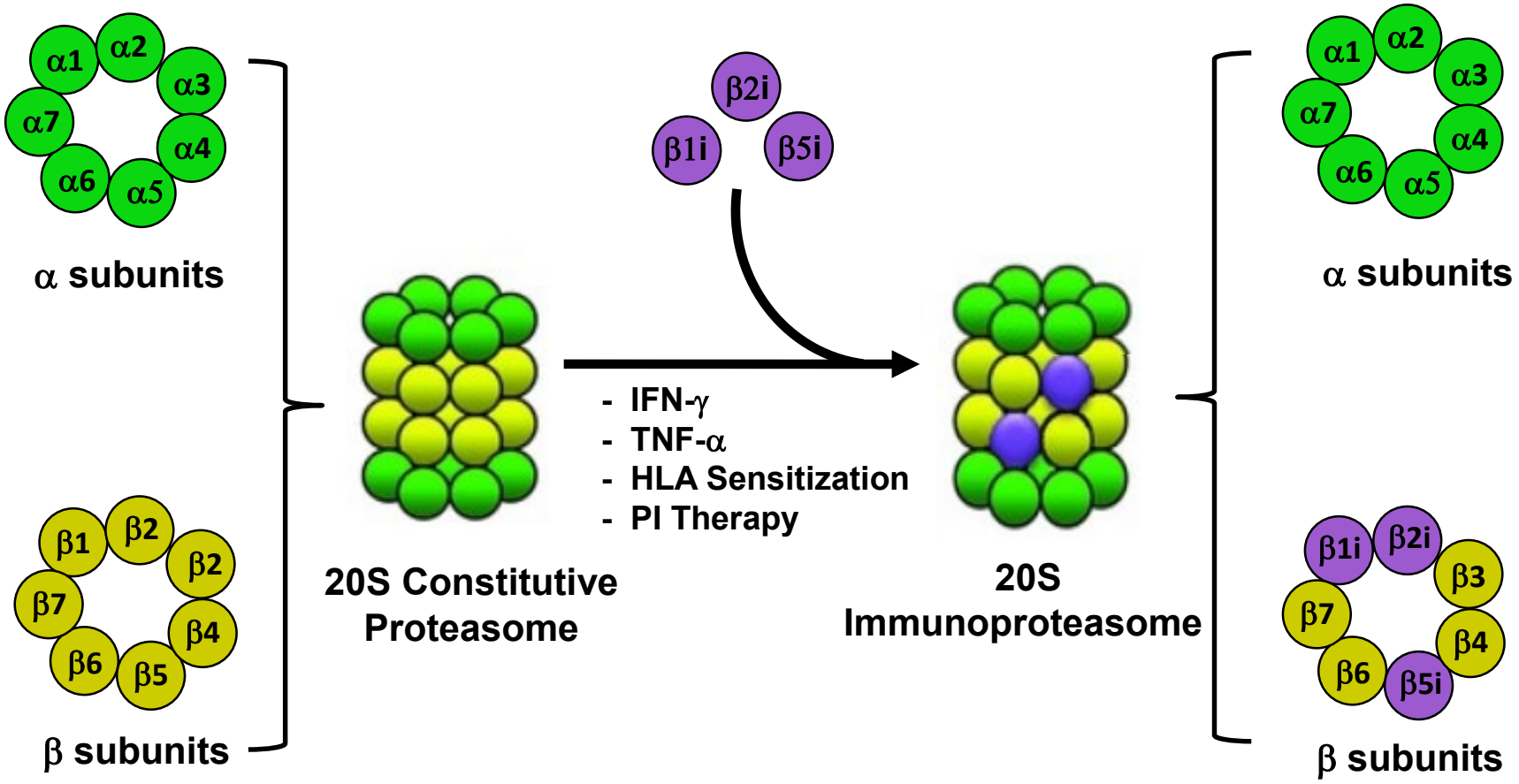
Supplementary Figure 1



Gene	Subunit	Catalytic Activity	Substrate Selectivity
PSMB5	β5	Chymotrypsin-like	Small hydrophobic
PSMB6	β1	Caspase-like	Acidic
PSMB7	β2	Trypsin-like	Basic, neutral
PSMB8	β5i, LMP7	Chymotrypsin-like	Bulky hydrophobic
PSMB9	β1i, LMP2	Chymotrypsin-like	Small hydrophobic
PSMB10	β2i, MECL1	Trypsin-like	Basic, neutral

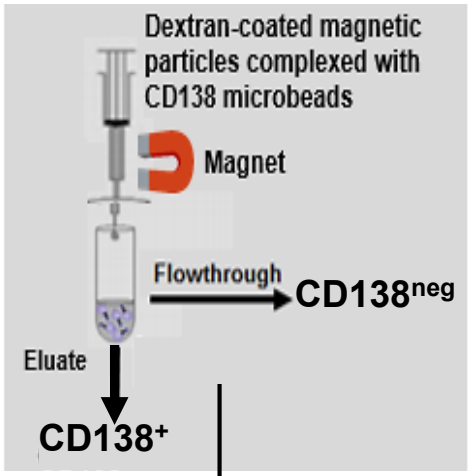
Supplementary Figure 2

HLA-Sensitized Patient Bone Marrow Aspirate and Biopsy

↓ RBC Removal
↓ Ficoll-Density Gradient Centrifugation

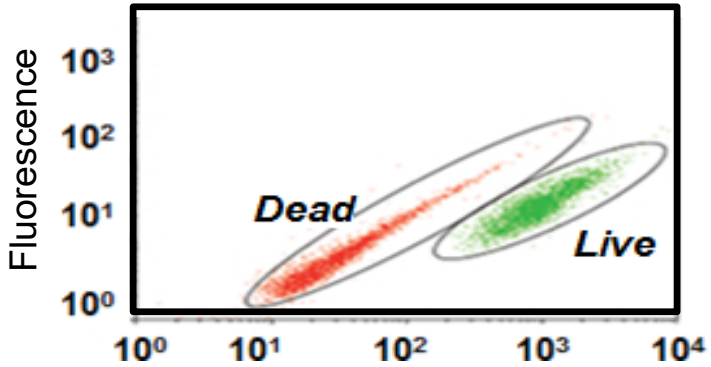
Bone Marrow Mononuclear Cell Fraction

↓ Immunomagnetic Positive Selection of CD138+ Cells

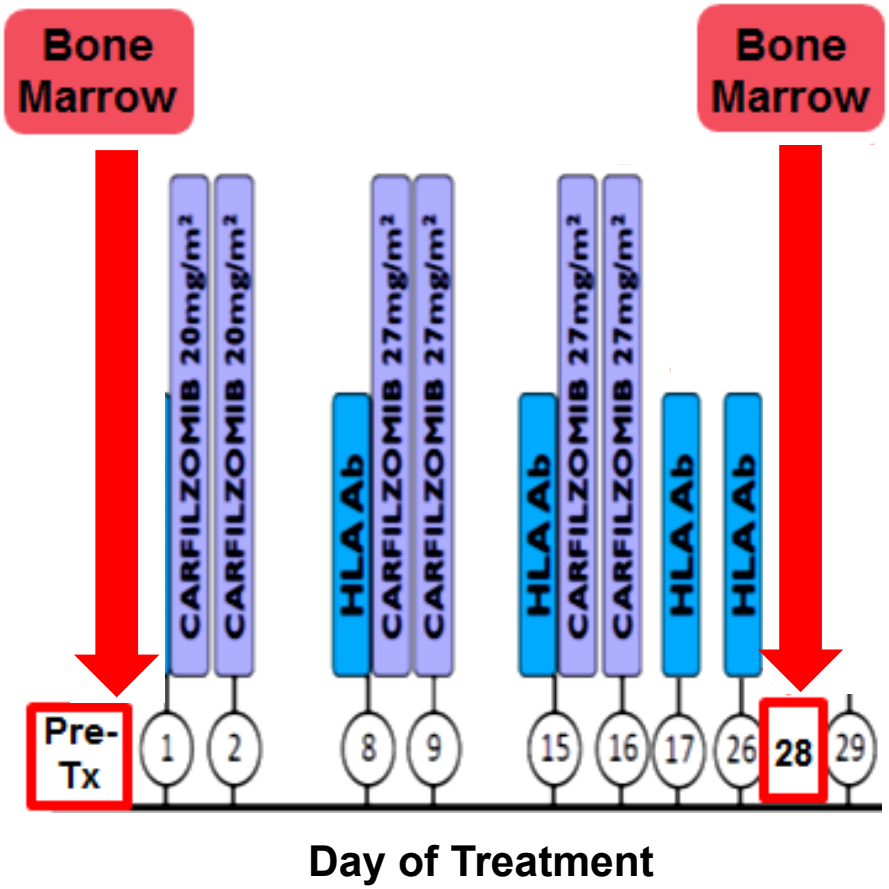


↓

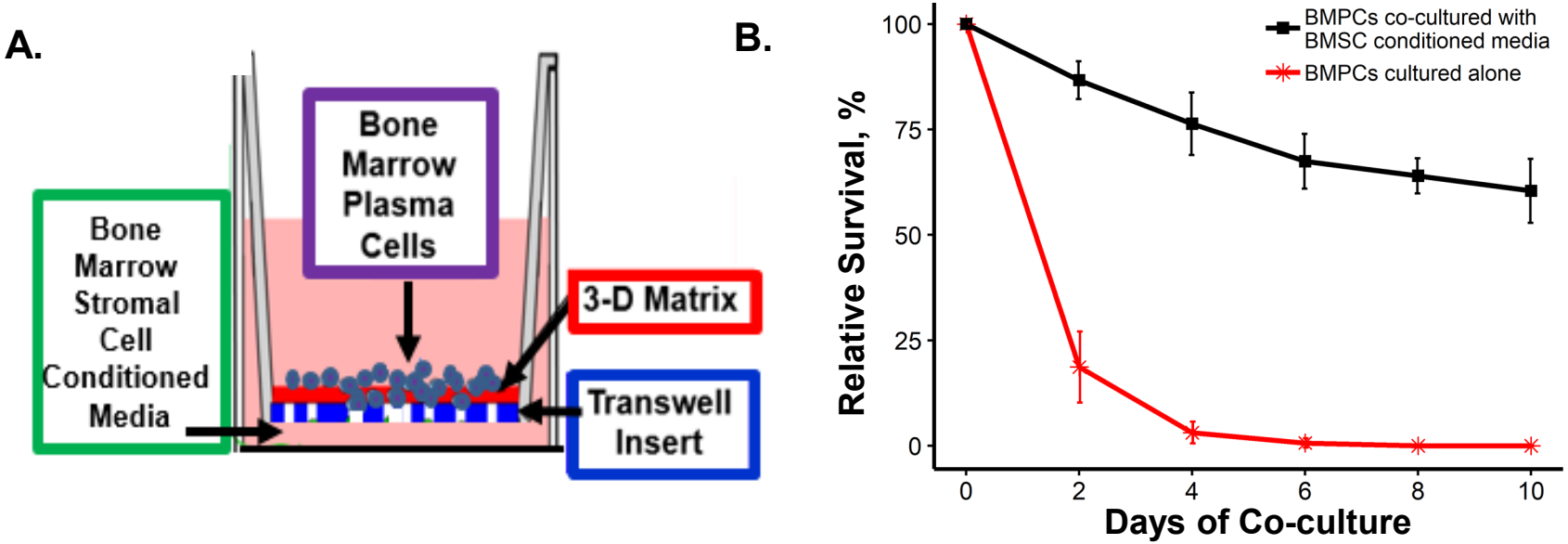
Live Cell Selection by Flow Cytometry



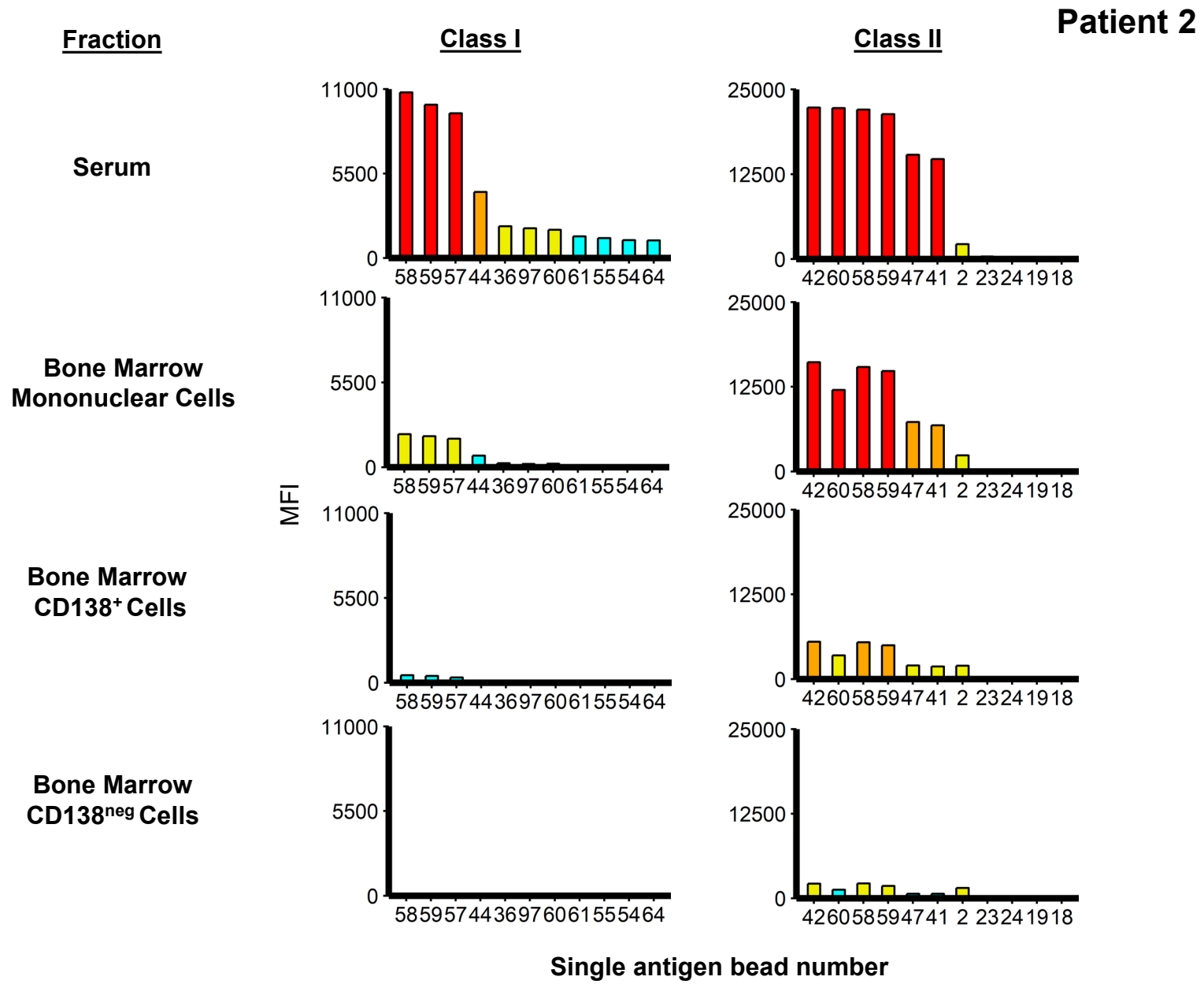
Supplementary Figure 3



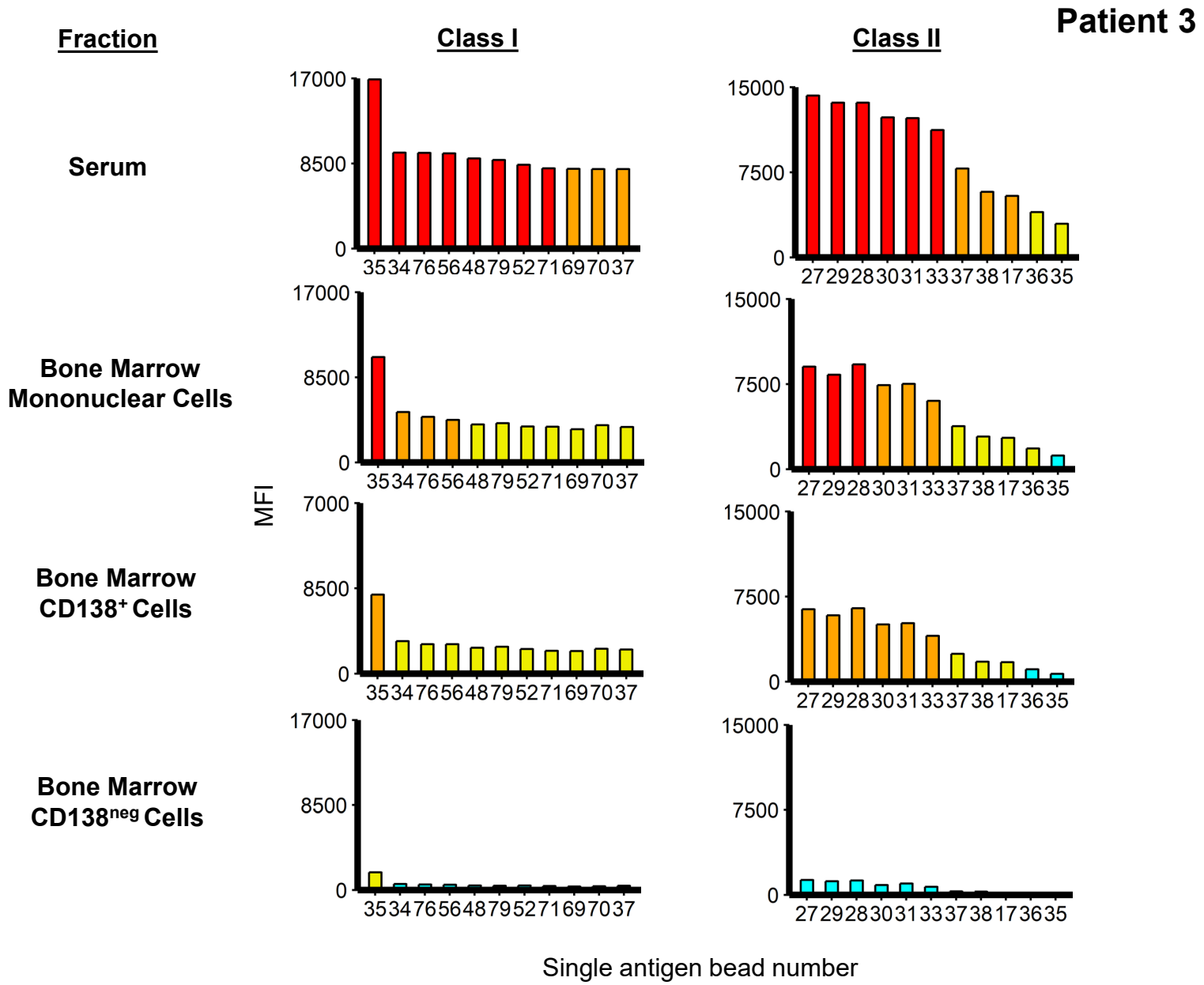
Supplementary Figure 4



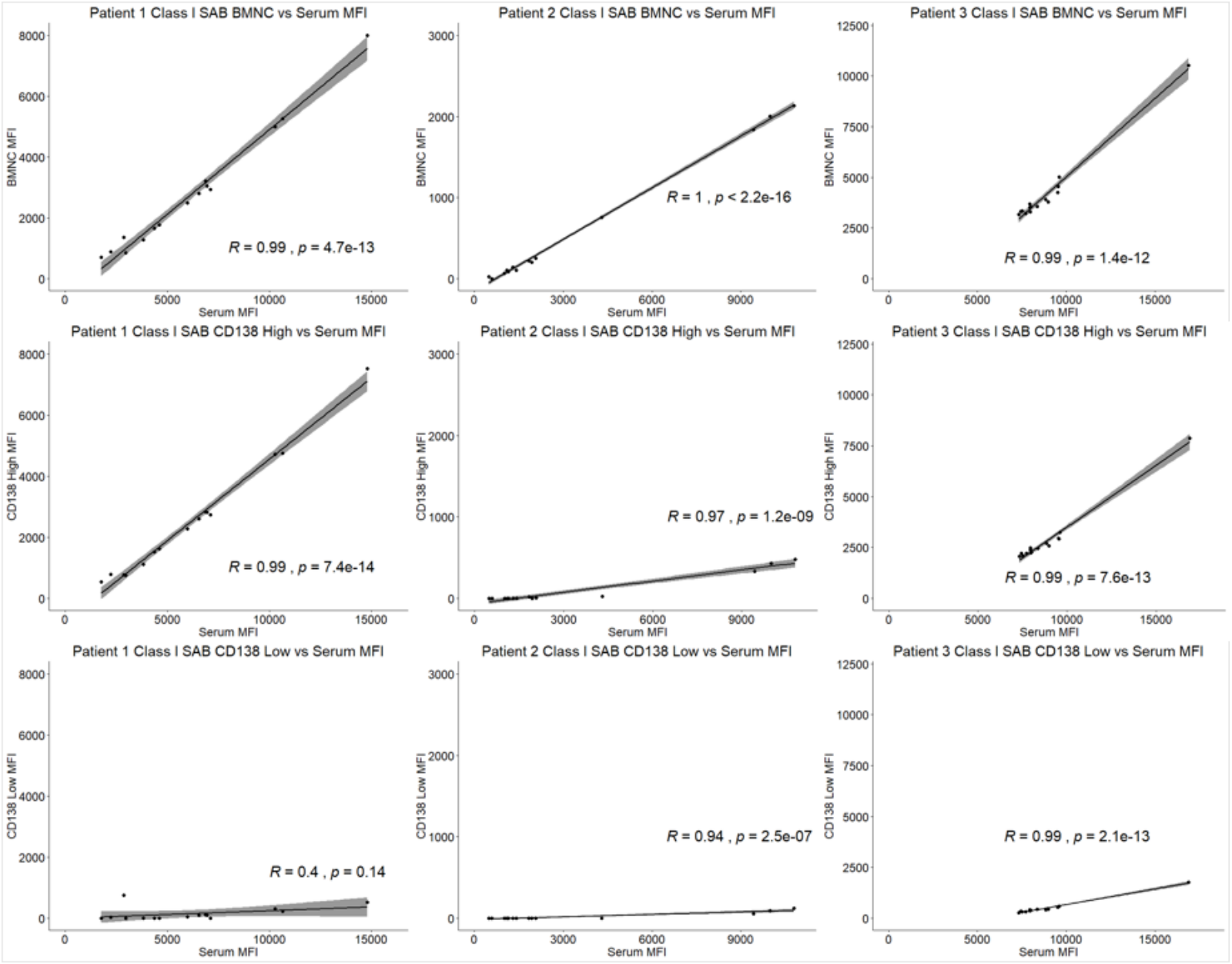
Supplementary Figure 5A



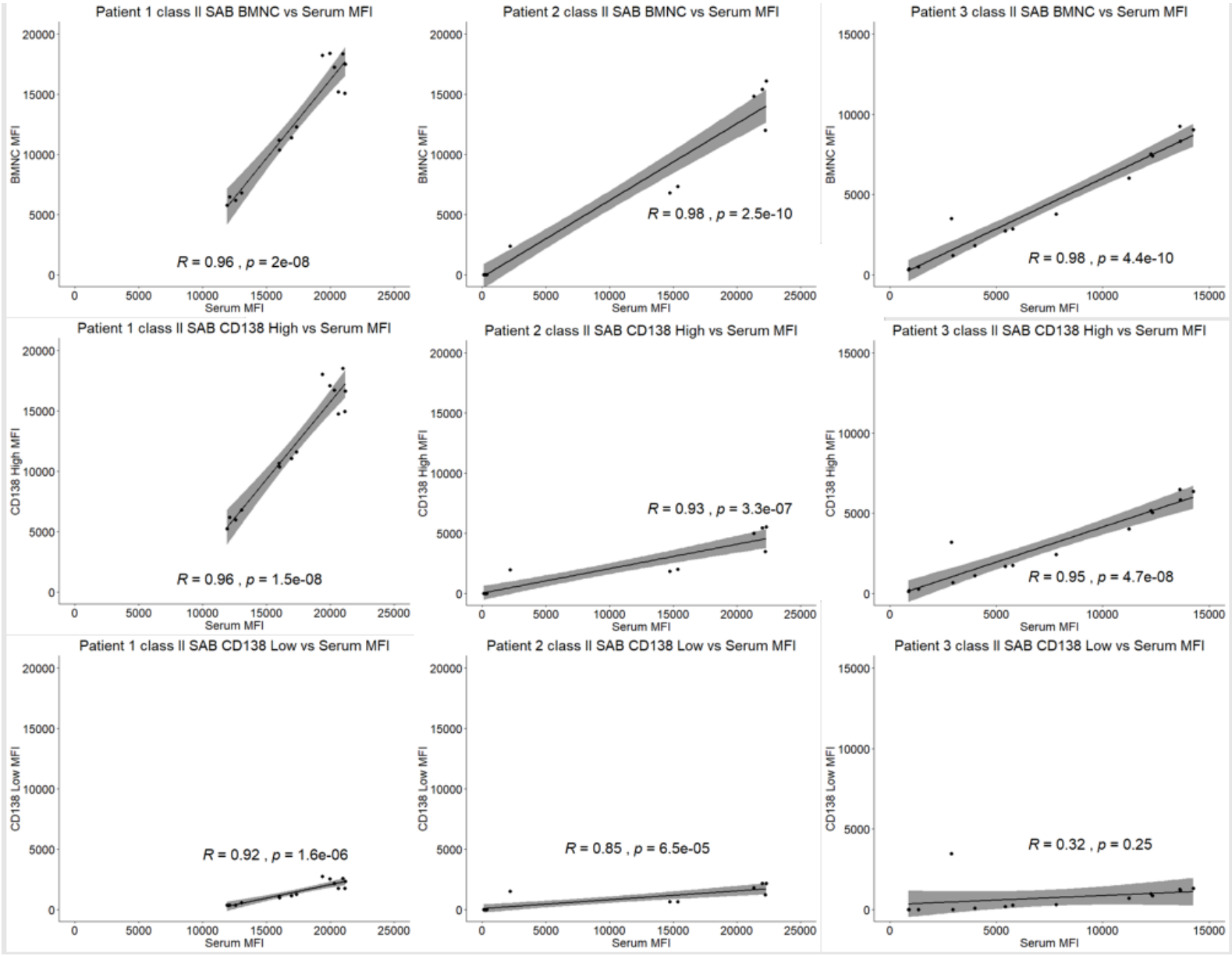
Supplementary Figure 5B



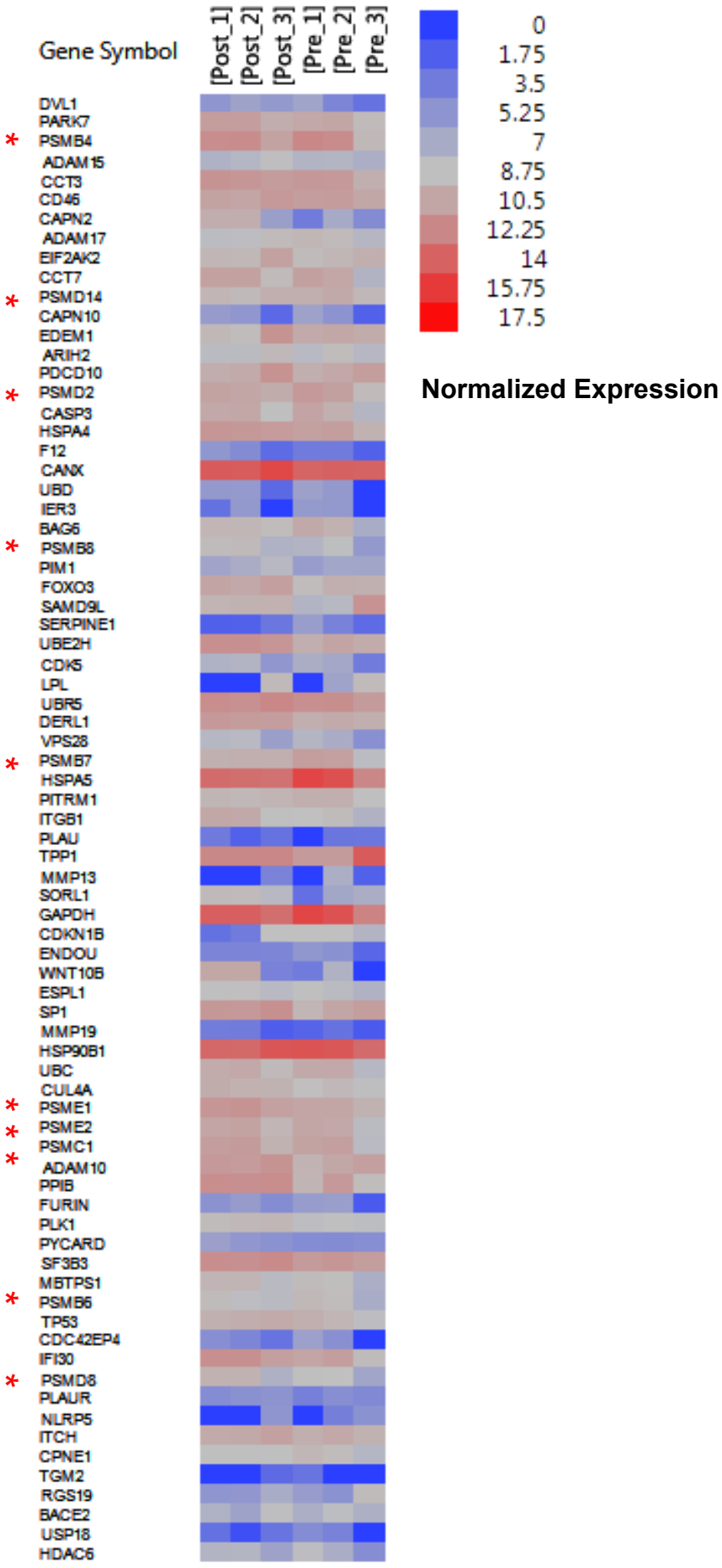
Supplementary Figure 6A



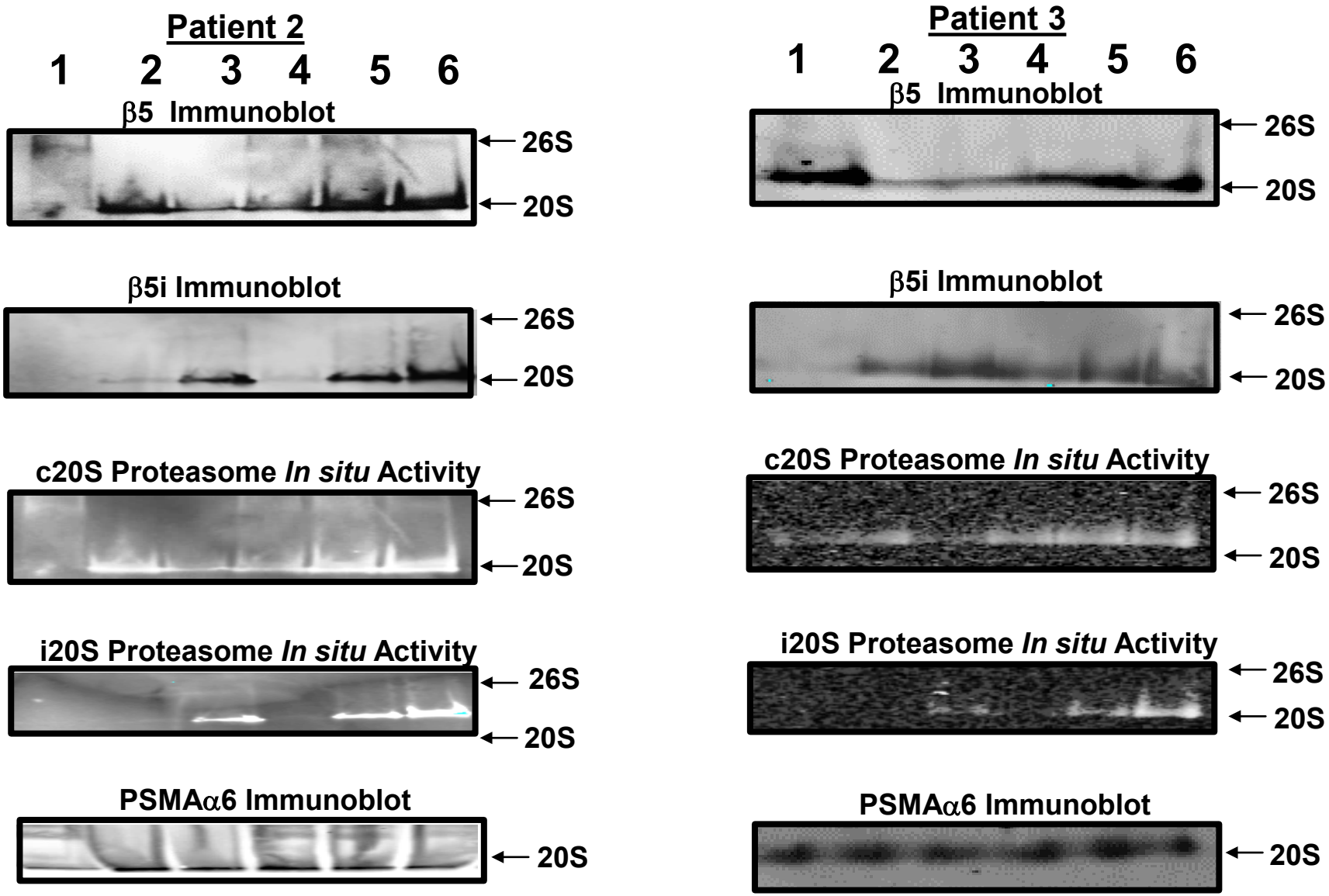
Supplementary Figure 6B



Supplementary Figure 7



Supplementary Figure 8



SUPPLEMENTARY INFORMATION

Supplementary Figure 1. Schematic representation of IFN-γ-induced conversion of c20S proteasomes to i20S proteasomes. IFN-γ and other activators, e.g., IFN-γ, TNF-α, trigger transcriptional increases in at least five proteasome catalytic and activator subunits which cooperate to form an i20S proteasomes. New catalytic subunits (β1i, β2i, β5i) and activator subunits (PA28α and PA28β) are incorporated into i20S proteasomes. **C**. Genes that encode c20S and i20S proteasomes catalytic subunits, activities and substrate specificities.

Supplementary Figure 2. Scheme to isolate $CD138^{+}$ cells from BM of HLA-sensitized patients.

Supplementary Figure 3. Carfilzomib treatment schedule for HLA-sensitized renal transplant candidates. Transplant candidates were enrolled in IRB-approved clinical trial NCT02442648 to determine the effect of *in vivo* carfilzomib therapy on HLA and iAb levels (*24)*.

Supplementary Figure 4. Semi-permeable transwell device to co-culture BMPCs (upper chamber) with BMSCs or BMSC-conditioned media (lower chamber). **B.** Effect of BMSCs, BMSC-conditioned media or individual growth factors on the relative survival of patient BMPCs in the co-culture system. Patient BMPCs (5,000 cells) were co-cultured with BMSCs, BMSC-conditioned media or individual growth factors and the relative number of cells that survived counted. Assays were performed in triplicate and viability was determined by trypan blue staining. Shown is a representative experiment using cells from a single patient. Similar results were observed using cells from three different patients.

Supplementary Figure 5. Class I and II Ab levels were determined in the serum from HLA-sensitized patients using the SAB assay and BMPCs from two additional patients as in Fig. 1. BM mononuclear cells (20,000 cells/assay), $CD138^{+}$ (100,000 cells/assay) and $CD138^{neg}$ PCs (100,000 cells/assay) from that same patient were incubated in 100uL BMSC media at 37^{o}C for 72 h.

Culture supernatants were then removed and used for SAB assays. Histograms of luminex™ SAB assays to determine class I and II HLA levels in patient serum and cell fractions are shown. Supp. Fig 5A represents results for patient 2 and Supp. Fig 5B represents patient 3.

Supplementary Figure 6. A. Plots to correlate class I levels in patient serum with class I levels detected in supernatants from $CD138^+$ cells of that same patient BM using the SAB assay. **B.** Plots to correlate class II SAB levels in patient serum with class II SAB levels detected in supernatants from $CD138^+$ cells of that same patient BM using the SAB assay. (N=3 patients).

Supplementary Figure 7. Heat map for supervised analysis of UPS genes most differentially expressed in BMPCs isolated from individual transplant candidates following *in vivo* carfilzomib therapy relative to their expression in BMPCs isolated prior to treatment. Hierarchical clustering was performed by Ward's method using Euclidean distance metrics. Red asterisks indicate proteasome and immunoproteasome-specific genes.

Supplementary Figure 8. Native gel electrophoresis to detect structural and functional changes within proteasomes isolated from patient BMPCs. A**.** Samples were run on 3-8% Bis-Tris protein gels (Invitrogen) for 45 V at 4°C overnight Western blot using proteasomes isolated from human erythrocytes, liver or spleen (lanes 1-3). Samples from the PCs of a healthy adult (lane 4) or from a single HLA-sensitized patient prior to and after *in vivo* carfilzomib therapy (lanes 5 and 6). Samples (5ug each) were loaded onto native gels and electrophoresed as above. **A.** Western blot using a proteasome β5-specific Ab with the same samples electrophoresed as above. **B**. Western blot using a proteasome β5i (PSMB8) subunit-specific Ab with the same samples electrophoresed as above. **C.** Activity overlay assay using the pan-proteasome fluorogenic substrate Suc-LLVY-MCA. **D.** Activity overlay assay using the i20S proteasome substrate Ac-ANW-AMC. **E.** Western blot using proteasome subunit alpha6 as loading control.

Supp. Table 1. Patient demographic features and clinical characteristics of patients included in the current study.

	Overall
N (number of patients)	3
Age (mean (sd))	40.78 (17.84)
Time on dialysis (years, mean (sd))	7.42 (1.33)
African American (%)	1 (33.3)
Female (%)	2 (66.7)
Hypertension	2 (66.7)
Diabetes	1 (33.3)
Etiology of ESRD (%)	
Hypertension	1 (33.3)
Alports syndrome	1 (33.3)
Dysplastic Kidneys	1 (33.3)
Hemodialysis (%)	3 (100.0)
Prior transplant(s) (%)	3 (100.0)
Number of prior transplants (median [IQR])	1.00 [1.00, 1.00]
Etiology of prior transplant failure (%)	
Chronic rejection	1 (33.3)
Polyoma (BK) nephropathy	1 (33.3)
Acute Rejection	1 (33.3)
Previous transplant nephrectomy (%)	0 (0)
History of pregnancy (%)	0 (0)
History of blood transfusion	2 (66.7)
UNOS cPRA (%, mean (sd))	99.85 (0.14)
UNOS cPRA (% median [IQR])	99.89 [99.80, 99.93]

Supp. Table 2. The top ten genes up- or down regulated in patient BMPCs following *in vivo* carfilzomib therapy.

Gene	Fold Change ([Post/Pre])	Log Fold Change ([Post/Pre])
MUC17	30.72	4.94
ZNF645	25.09	4.65
VN1R1	24.33	4.60
JAKMIP3	23.06	4.53
SH3TC2	21.17	4.40
MUC4	20.05	4.33
MAPT-IT1	19.49	4.28
SMCO3	18.79	4.23
NMNAT2	18.19	4.18
MSL3P1	16.61	4.05

Gene	Fold Change ([Post/Pre])	Log Fold Change ([Post/Pre])
SATL1	-68.67	-6.10
PYGM	-24.04	-4.59
RPRM	-14.64	-3.87
ARHGEF25	-13.56	-3.76
SYNC	-12.58	-3.65
ABO	-11.63	-3.54
NPIPA2	-11.59	-3.54
C2orf71	-10.15	-3.34
SH3RF1	-9.49	-3.25
C3orf65	-9.37	-3.23

A p-value cutoff of 0.05 was considered statistically significant (Fisher's exact test).

Supp. Table 3. The top ten genes with the UPS up- or down regulated in patient BMPCs following *in vivo* carfilzomib therapy.

Gene	Fold Change ([Post/Pre])	Log Fold Change ([Post/Pre])
HSPA2	13.8	3.79
HSP18	6.16	2.62
HSPB7	4.59	2.20
ISG15	4.42	2.14
RNF138P1	4.31	2.11
UBALD2	3.56	1.83
N4BP3	3.31	1.73
DCAF15	2.46	1.30
PSMB8	1.96	0.97
PSMB7	1.95	0.96

Gene	Fold Change ([Post/Pre])	Log Fold Change ([Post/Pre])
CCNB3	-6.34	-2.66
YAP1	-5.48	-2.46
RNF148	-4.25	-2.09
CCNJL	-4.01	-2.00
RNF113B	-3.90	-1.96
ZNF137P	-2.57	-1.36
CDKN2B	-2.32	-1.21
PSMD6-AS2	-2.23	-1.16
DNAJB7	-2.11	-1.08
UBLCP1	-1.80	-0.85

A p-value cutoff of 0.05 was considered statistically significant (Fisher's exact test).

Supp. Table 4. GSEA for proteasome and immunoproteasome-associated genes.

Gene	Fold Change ([Post/Pre])	Log Fold Change ([Post/Pre])
PSMB8	1.96	0.97
PSMB7	1.95	0.96
PSMC1	1.74	0.80
PSMB6	1.74	0.80
PSME2	1.67	0.80
PSME1	1.63	0.71
PSMD2	1.56	0.64
PSMB4	1.52	0.61
PSMD8	1.50	0.59
PSMD13	1.50	0.59

A p-value cutoff of 0.05 was considered statistically significant (Fisher's exact test).

Supp. Table 5. Cytokines, chemokines and cell surface receptors deregulated in BMPCs following *in vivo* carfilzomib therapy.

	Fold Change in Expression ([Post]/[Pre])
G-protein receptor	8.24
IFN-induced protein with tetratricopeptide repeats 3	3.66
Chemokine (C-X-C motif)	3.09
Guanylate binding protein 1, IFN-inducible	3.06
Growth factor receptor-bound protein 7	2.29
IFN, gamma-inducible protein 30	1.73
IFN-induced protein with tetratricopeptide repeats 5	1.72
Leptin receptor	1.52

A p-value cutoff of 0.05 was considered statistically significant (Fisher's exact test).