Supplementary Figure 1

Enrichment of CD138+ cells from patient BM cells
by anti-CD138 magentic beads

↓

Single-cell sort

↓

RT-PCR

↓

PCR amplification of the heavy and
light chain cDNA

Purification of
PCR products

Sequencing

↓

Cloning PCR product
into expression vectors
containing human **Igγ1,
Igκ1 or Igλ2 constant regions**

↓

Transformation

DNA purification

Colony PCR

↓

Transfection

Sequencing

↓

Ab purification

Supplementary Figure 1. Schematic of the workflow for generation of recombinant clonal Ig from single cell sorted human plasma cells

Supplementary Figure 2
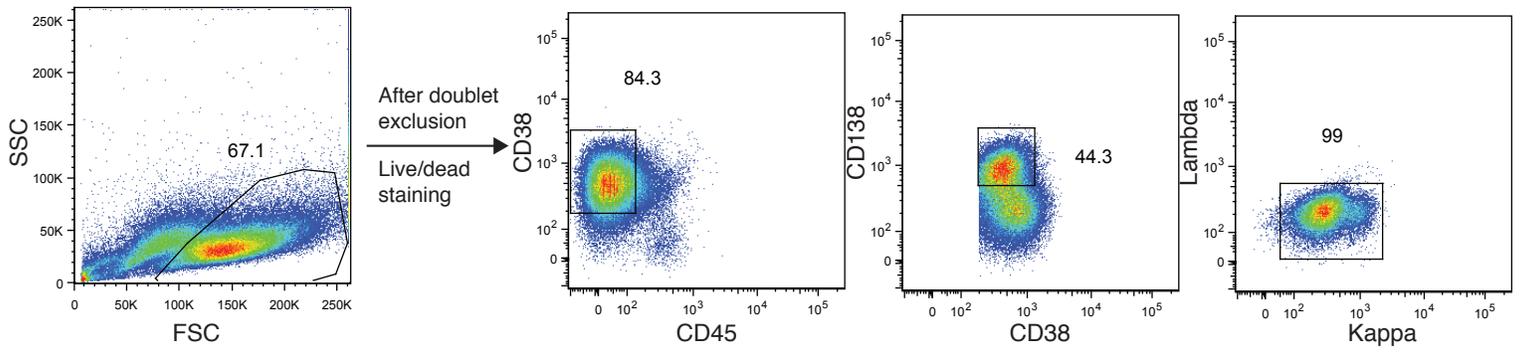
Supplementary figure 2. Representative FACS profile and gating strategy for single sorted plasma cells using IgA kappa patient's BM pre-enriched with anti-CD138 magnetic beads. Almost all of the clonal plasma cells were kappa positive.

Supplementary Figure 3

	FWR1	CDR1	FWR2	CDR2	FWR3

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                    FWR1                  CDR1        FWR2            CDR2        FWR3

IGHV3-48*03        EVQLVESGGGLVQPGGSLRLSCAAS GFTFSSYE MNWVRQAPGKGLEWVSY ISSSGSTI YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC
640:Clone 2        --------------------T-TV- -----N-- --------------A-- ----D--- ------------------A----L----V--------
640:Clones 6,11,15 --------------------T-TV- -----N-- ---------------- ----D--- ------------------A----L----V--------


IGHV1-69-2*01      QVQLVQSGAEVKKPGATVKISCKVS GYTFTDYY MHWVQQAPGKGLEWMGL VDPEDGET IYAEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYC
P008:Clones 29,36  --------------G---L----- -HP-S--- -Q--R---------V-- --TR---I M---S----L--------E-T----------------
Clone 30           --------------G---L----- -HP-S--- -Q-ARR--------V-- --TR---I M---SL---L--------E-T----------------


IGHV3-30*03        QVQLVESGGGVVQPGRSLRLSCAAS GFTFSSYG MHWVRQAPGKGLEWVAV ISYDGSNK YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC
P030: All Clones   --------------T-------V- ASN-N--- --------------A-- --H--TK- ------------------M------------------


IGHV1-3*01         QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYA MHWVRQAPGQRLEWMGW INAGNGNT KYSQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYC
637: All Clones    ----------------------- -------- ---------------- -------- -------------------------------------


IGHV3-23*01        QVQLVQGGLVQPGGSLRLSCAAS  GFTFSSYA MSWVRQAPGKGLEVSA  ISGSGGST YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC
GD1: All Clones    --------CSSLA----------  --P--T-- ------P---------- -----ET- ----------------EA--F--VD---P--------
```

FWR1,2 and 3 - Framework region 1, 2 and 3
CDR1 and 2 - Complementary determining region 1 and 2

Supplementary figure 3. Heavy chain amino acid sequence alignment for plasma cells from MM and GD patients.
The germline amino acid sequence is shown at the top for each sequence while subsituted residues are in black and dash indicates identity to germline line

Supplementary Figure 4
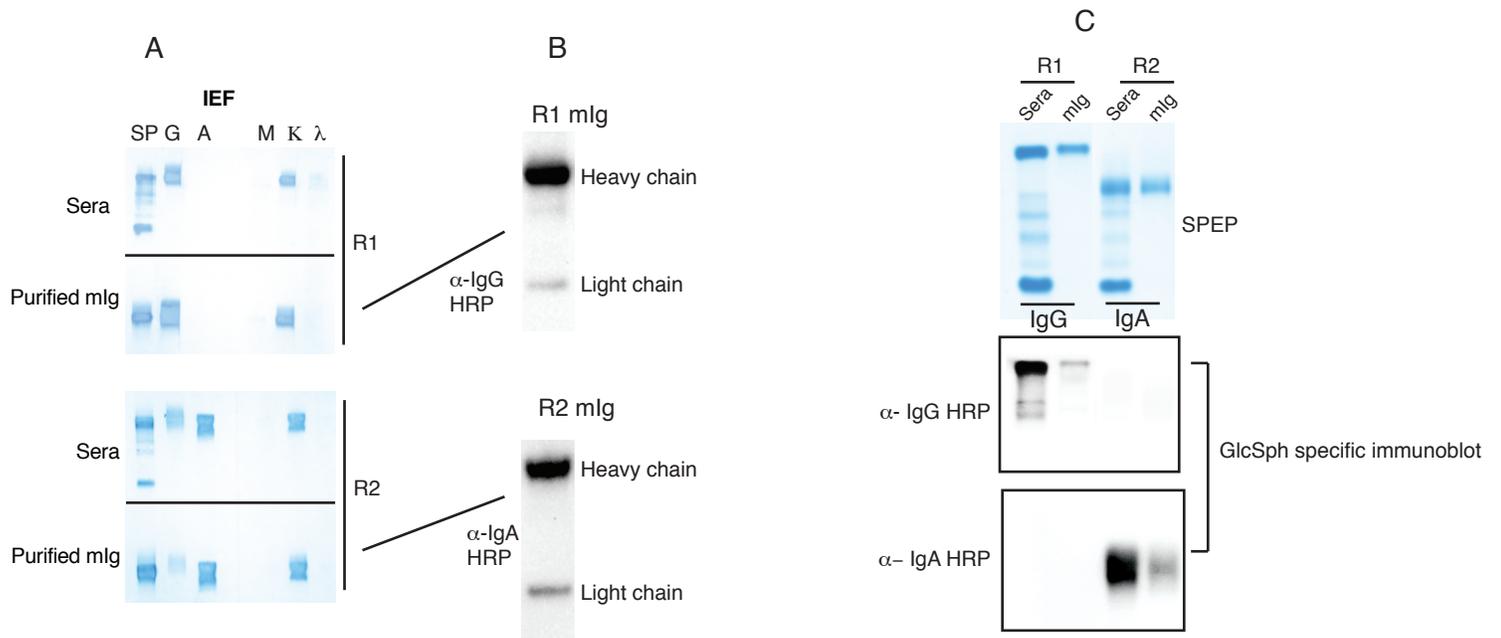
Supplementary figure 4. Purification monoclonal Ig (mIg) from patient sera and verification of purity of isolated mIgs

mIgs were affinity purified from the sera of lipid reactive patients and the purity of mIgs were verified using isoelectric focusing (IEF) **(A)**, the mIgs were run on SDS PAGE followed by immunoblotting using specific heavy chain antibody **(B)**.**(C)** Purified mIg show similar position and GlcSph reactivity to that of the corresponding serum paraprotein in SPEP (top panel) and GlcSph specific immunoblot (bottom panel) respectively. Representative blots for patients with mIgG (R1) and mIgA (R2) are shown.

Supplementary Figure 5
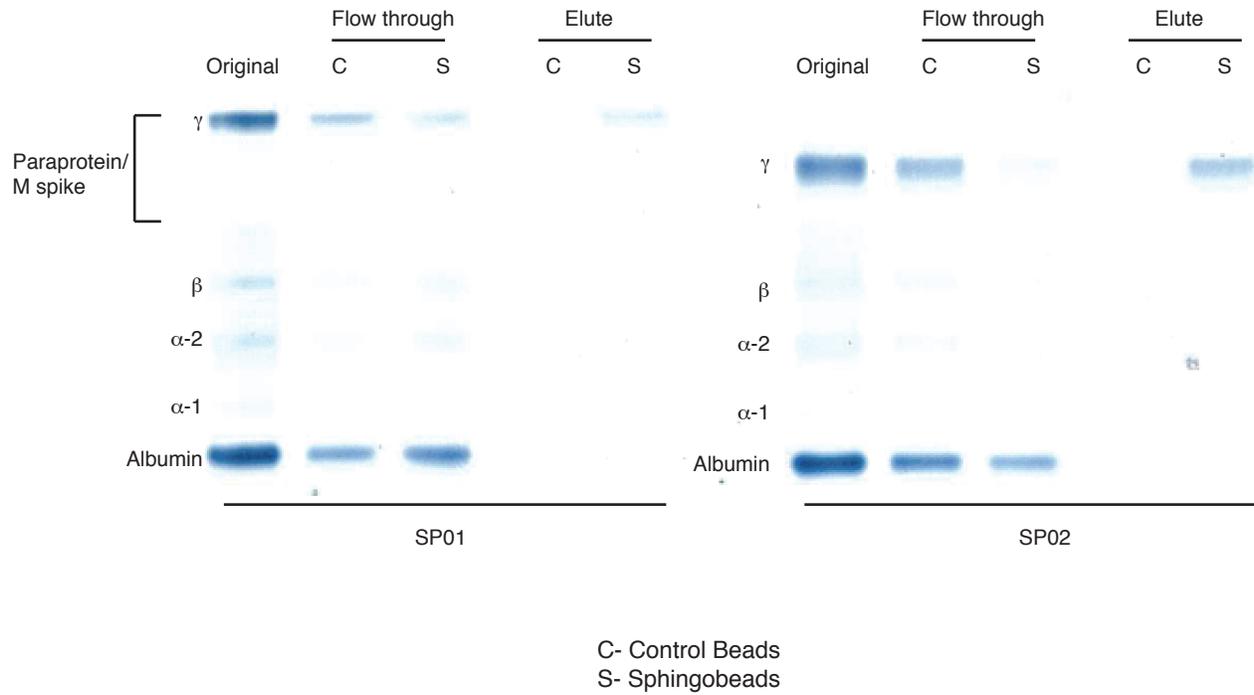
Supplementary Figure 5. Binding of paraprotein / M spike to sphingosine beads.

Plasma from 2 patients (SP01 and SP02) with lipid reactive gammopathies (1:50 dilution) were incubated with control or sphingosine beads and the flow through (FT) and elute (E) were analyzed by serum electrophoresis. Data are representative of similar data obtained independently in two labs (M.C./L.B. and M.T.F./N.M).

Supplementary Figure 6
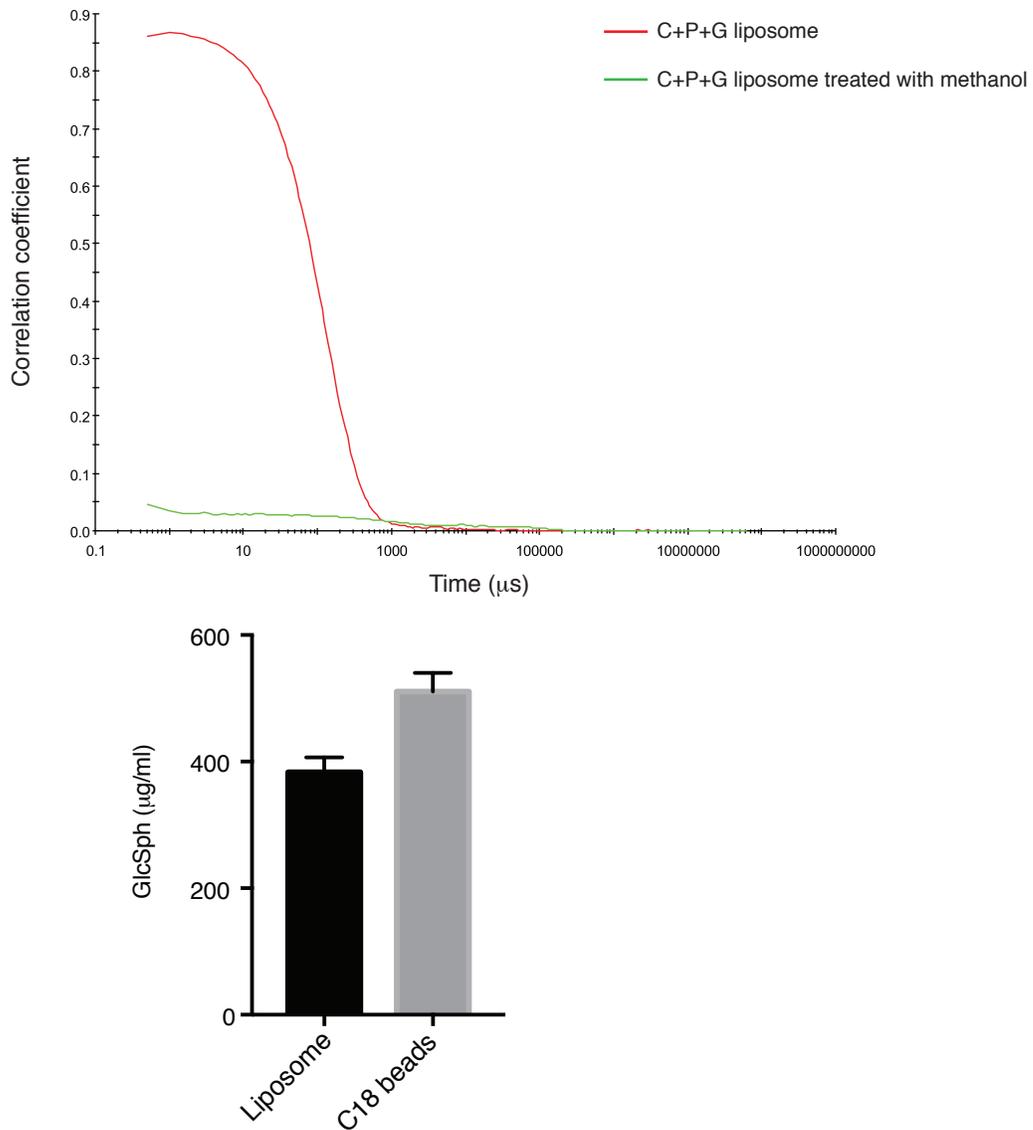
Supplementary Figure 6. Characterization of Glucosylsphingosine (GlcSph) containing liposomes and C18 beads

Dynamic light scatter (DLS) analysis of extruded liposome (C+P+G) before and after disruption with methanol (10 μg/ml) upper panel; Concentration of GlcSph detected by LC/MS/MS of methanol disrupted C+P+G (2:6:2) liposomes and C+P+G (2:6:2) coated C18 beads both containing 5mg/ml of total lipids (lower panel).
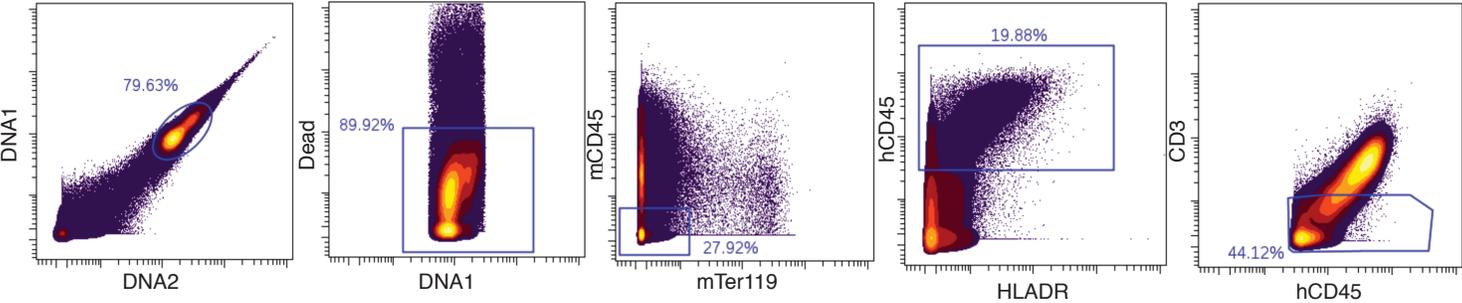
Gating strategy used to define human CD38$^+$CD138$^+$plasma cell from bone marrow mononuclear cells obtained from tumor engrafted MIS$^{(KI)}$TRG6 mice for Mass cytometry (CyTOF) analysis.

Supplementary Table 1

Ig gene sequence analysis by IgBLAST identify identical germline V(D)J gene segments and complementarity determining region (CDR)3 sequence between different clones from the same donor and somatic mutation present in the heavy and light chain Ig sequences.

Pt-Clone #	# of single cells sorted	# of clones obtained after PCR and sequencing	Lipid Reactivity	HEAVY CHAIN							LIGHT CHAIN				
				VH	D	RF	JH	CDR3(aa)	Length	Mutations	Vk	Jk	CDR3(aa)	Length	Mutations
MM patient with MG															
640-2	24	4	Yes	3-48	3-10	2	3	DLCYYGSGRCYNDDAFDI	18	8	3-15	5	QQYNIWPPIT	10	7
640-6				3-48	3-10	2	3	DLCYYGSGRCYNDDAFDI	18	8	3-15	5	QQYNIWPPIT	10	7
640-11				3-48	3-10	2	3	DLCYYGSGRCYNDDAFDI	18	8	3-15	5	QQYNIWPPIT	10	7
640-15				3-48	3-10	2	3	DLCYYGSGRCYNDDAFDI	18	8	3-15	5	QQYNIWPPIT	10	7
P008-29	24	3	Yes	1-69-2	1-26	1	3	DSRWEDDAFDI	11	18	1-5	2	HQYNSYSYA	9	6
P008-30				1-69-2	1-26	1	3	DSRWEDDAFDI	11	19	1-5	2	HQYNSYSYA	9	6
P008-36				1-69-2	1-26	1	3	DSRWEDDAFDI	11	17	1-5	2	HQYNSYSYA	16	6
P030-50	24	4	No	3-30	4-4	2	5	DFHGESFGKYSNEPLGP	17	12	1-5	2	QQYYSYLYT	9	10
P030-52				3-30	4-4	2	5	DFHGESFGKYSNEPLGP	17	12	1-5	2	QQYYSYLYT	9	10
P030-61				3-30	4-4	2	5	DFHGESFGKYSNEPLGP	17	12	1-5	2	QQYYSYLYT	9	10
P030-64				3-30	4-4	2	5	DFHGESFGKYSNEPLGP	17	11	1-5	2	QQYYSYLYT	9	10
637-80	24	3	No	1-3	4-4	3	5	DRTTVTTINWFDP	13	2	1-33	5	QQYDNLPIT	9	4
637-82				1-3	4-4	3	5	DRTTVTTINWFDP	13	2	1-33	5	QQYDNLPIT	9	4
637-83				1-3	4-4	3	5	DRTTVTTINWFDP	13	1	1-33	5	QQYDNLPIT	9	4
GD patient with MG															
GD-1	24	2	Yes	1-23	1-15	2	3	AKALFPVSATDDAFDN	16	16	1-4	4	QRYNSFPLT	9	16
GD-2				1-23	1-15	2	3	AKALFPVSATDDAFDN	16	16	1-4	4	QRYNSFPLT	9	16

Supplementary Table 2

Table compares the percentages of different molecular classification (MC) subgroups between lipid non-reactive and lipid reactive patients. Data shown are cumulative data from cohort 1(n=76) and 2 (n=274), (***, p<0.001, *p<0.05, Fisher's exact test)

Factor	All patients	Lipid non-reactive (n=255)	Lipid reactive (n=95)	P-value
CD1	5/350 (1.43%)	5/255 (2.0%)	0/95 (0%)	0.329
CD2	57/350 (16.3%)	35/255 (13.7%)	22/95 (23.2%)	0.0496*
HY	134/350 (38.6%)	113/255 (44.3%)	22/95 (23.2%)	0.0003***
LB	64/350 (18.3%)	39/255 (15.3%)	25/95 (26.3%)	0.0203*
MF	23/350 (6.6%)	19/255 (7.5%)	4/95 (4.2%)	0.3394
MS	35/350 (10.0%)	19/255 (7.5%)	16/95 (16.8%)	0.0149*
PR	31/350 (8.90%)	25/255 (9.8%)	6/95 (6.3%)	0.3991

Supplementary Table 3

Table shows comparison of percentage of patients based on the detection of high risk GEP signatures and cytogenetics in tumor cells between lipid reactive and non-reactive patients. Data shown is from patients in cohort 2 (n=274) with available cytogenetics and GEP signatures (**, $p<0.01$, *$p<0.05$, Fisher's exact test).

	Factor	Lipid reactive	Lipid non-reactive	P-value
GEP Signatures	UAMS70 High risk	16/79 (20.3%)	47/195 (24.1%)	0.53
	IFM 15 High risk	18/79 (22.8%)	26/195 (13.3%)	0.0686
	EMC/SKY92 High risk	5/79 (6.3%)	16/195 (8.2%)	0.802
	MYC-activation index >1	34/79 (43.0%)	84/195 (43.0%)	1
Cytogenetics	gain 1q21	39/79 (49.3%)	70/195 (36.0%)	0.042*
	del 8p21	25/79 (31.6%)	54/195 (27.7%)	0.557
	del 13q14	36/79 (45.6%)	80/195 (41.0%)	0.502
	del 17p13	9/79 (11.4%)	27/195 (13.8%)	0.694
	t(4;14)	12/79 (15.2%)	14/195 (7.2%)	0.0426*
	t(11;14)	16/79 (20.3%)	27/195 (13.8%)	0.201
	Percentage of aberrant plasma cell >95%	41/79 (52%)	93/195 (47.7%)	0.594

n/N (%): n-Number with factor, N-Number with valid data for factor

Supplementary table: Antibodies

Antibody	Source	Clone
CD117 (c-kit)	Biolegend	104D2
CD11b	Fluidigm	ICRF44
CD11c	Fluidigm	Bu15
CD138	BD Biosciences	MI15
CD14	Fluidigm	RM052
CD152 (CTLA4)	Fluidigm	14D3
CD16	Fluidigm	3G8
CD185 (CXCR5)	Fluidigm	RF8B2
CD19	Fluidigm	HIB19
CD197 (CCR7)	Fluidigm	G043H7
CD200	Fluidigm	Ox-104
CD25	Fluidigm	2A3
CD27	Fluidigm	L128
CD272 (BTLA)	Fluidigm	MIH26
CD274 (PDL1)	eBioscience	MIH1
CD276 (B7H3)	Biolegend	MIH42
CD3	Fluidigm	UCHT1
CD33	Fluidigm	WM53
CD34	Biolegend	581
CD38	Fluidigm	HIT2
CD4	Fluidigm	RPAT4
CD45	Fluidigm	HI30
CD45RO	Fluidigm	UCHL1
CD56	Fluidigm	HCD56
CD69	Fluidigm	FN50
CD8	Fluidigm	RPAT8
CD95	Fluidigm	DX2
FOXP3	Fluidigm	259D/C7
Granzyme	Fluidigm	GB11
HLADR	Biolegend	L243
KAPPA	Fluidigm	MHK-49
Ki67	Fluidigm	Ki-67
LAMBDA	Fluidigm	MHL-38
mCD45	Fluidigm	30-F11
TER119	Fluidigm	TER-119
TIGIT	Biolegend	A15153G