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A retained transcriptomic profile characterizes CD138+ cells in the short time progression from smoldering to active multiple myeloma

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A retained transcriptomic profile characterizes CD138^{+} cells in the short time progression from smoldering to active multiple myeloma.

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Running head: Transcriptional profile in smoldering myeloma

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Smoldering myeloma (SMM) is a pre-malignant monoclonal gammopathy with about 10% annual risk to progress to active multiple myeloma (MM).[1] The International Myeloma Working Group (IMWG) has recently updated SMM diagnostic criteria.[2] The previously defined "ultra high-risk" SMM (characterized by specific biomarkers associated with upper than 80% risk of progression to symptomatic MM within 2 years) has been included among patients with active MM. SMM is biologically heterogeneous and encompasses patients with a very low rate of progression to symptomatic MM, similar to what occurs in patients with monoclonal gammopathy of uncertain significance (MGUS), as well as patients who acquired organ damage and progress to active MM within five years from diagnosis.[3]

The molecular mechanisms involved in the SMM-to-MM progression are still far to be fully understood. Genomic studies indicate that the genetic aberrations that characterize MM patients are already present in SMM ones,[1,4] who present similar mutational and copy number alteration load.[5] Moreover, a 4-gene score integrated with clinical features has been identified as a putative predictor of high-risk SMM.[6] However, few data are available on the transcriptional profiles of SMM patients in relationship to the progression to active MM,[7-9] overall indicating minimal differential expression either in coding or non-coding RNA fraction. To date, data are still lacking which describe the transcriptional profiles of plasma cells (PCs) from paired samples obtained at the time of SMM and at MM onset.

Herein, for the first time we compared the transcriptome of purified bone marrow (BM) $CD138^+$ PCs from paired samples of SMM patients progressed to active MM (P-SMM), aimed at describing any possible common transcriptional discrepancy that may help to understand the *intra*-patient disease evolution; at the same time, we investigated the transcriptional differences between P-SMM and a subset of non-progressed SMM (NP-SMM) for a median follow up of more than three times the time to progression of P-SMM.

To this aim a total number of 21 SMM patients (Table 1a-b), admitted to the Hematological Unit of the Parma Hospital over the last 11 years, were considered: 11 NP-SMM and 10 P-SMM for whom

paired active MM samples were available. SMM patients were diagnosed according to the International Myeloma Working Group (IMWG) revised criteria[2] and stratified by known risk factors of progression[3] as previously described.[10] All the patients enrolled in this study were anti-MM therapy naïve. The study was approved by the local Ethics Committee and written informed consent was obtained from all the patients involved in the study. Median age at diagnosis was 71 years (range 43-84) in P-SMM and 74 years (range 38-86) in NP-SMM. The median percentage of bone marrow plasma cells (BMPCs) at diagnosis in the 10 P-SMM was 27,5% (range 13-40%). One of 10 patient had monoclonal M component ≥ 3 g/dL, whereas 80% of patients presented with immunoparesis and high-risk cytogenetic features - either del(17p), or t(4;14) - were detected in 3 of 9 cases. The median time to progression was 15,5 months and all patients progressed with onset of CRAB features. The 11 NP-SMM patients had 12% median percentage of BMPCs (range 10-25%) and 82% of them presented with immunoparesis; high-risk cytogenetic features were detected in 5 of the 9 patients with enough BMPCs to allow examination. According to Mayo score[3], available in 8 NP-SMM, half patients were classified as intermediate-risk and the other half were low-risk. Median follow up in NP-SMM was 56 months. Primary $CD138^+$ PCs were purified by immunomagnetic method using anti-CD138 mAb-coated microbeads (MACS, Miltenyi Biotec, Bergisch-Gladbach, Germany) from BM aspirate. Total RNA was extracted using RNeasy kit (Qiagen, Hilden, Germany) and global expression profiles of 19012 protein-coding and 13972 long non-coding RNAs (lncRNAs) were extracted from GeneChip® ClariomD arrays (Affymetrix, Thermo Fisher Scientific, USA) analyzed using RMA normalization procedure[9] and annotations based on Gencode project (version 26) provided by the University of Michigan (http://brainarray.mbni.med.umich.edu/Brainarray/Database/CustomCDF/22.0.0/genecodeg.asp). Data are publicly available on NCBI GEO repository under accession GSE117847. Rank Product[9] and Gene Set Enrichment Analysis (GSEA) were used for differential and functional analyses.

GSEA analyses on the global gene expression profiles of P-SMM compared to NP-SMM cases revealed a down-regulation of antigen processing gene set (Supplementary Figure 1A), whereas genes specifically associated with MM proliferation and hyperdiploidy were positively modulated in P-SMM cases (Supplementary Figure 1B). Interestingly, this observation was consistent with

previously published data showing that, among the gene expression-based molecular subtypes,[11] the proliferation (PR) subtype significantly correlates with progression in asymptomatic myeloma patients.[12] Additionally, we found 273 genes significantly modulated in P-SMM compared to NP-SMM (Supplementary Table 1). Specifically, among the 30 genes with at least a 2-fold change in expression levels, the Wnt inhibitors *FRZB* and *DKK1,* the adhesion molecule *CDH2* and the pro-angiogenic *CTGF* were up-regulated in association with progression to MM (Figure 1A). Subsequently, we confirmed the significant up-regulation of *DKK1* (Hs00183740_m1)*, FRZB* (Hs00173503_m1)*, CDH2* (Hs00983056_m1) and *CTGF* (Hs00170014_m1) mRNA in BM CD138+ cells of P-SMM compared to NP-SMM by quantitative real-time PCR (TaqMan Assay, Life Technology, USA) performed on Light Cycler 480 (Roche Diagnostics, Italy) following a standard protocol. In these experiments, GAPDH (Hs99999905_m1) was used as housekeeping gene and $2^{-\Delta\Delta Ct}$ method was applied to calculate the mRNA fold change variation (Supplementary Figure 2). Moreover, ELISA assays for FRZB protein (Abbexa, UK), namely Secreted Frizzled Related Protein (sFRP)-3, were performed on frozen BM plasma of the same patients' cohort, where available, and indicated that median sFRP-3 levels in NP-SMM patient was significantly lower than in P-SMM group, as well (p=0.032, Supplementary Figure 3). Accordingly, we have recently demonstrated that BM DKK-1 protein levels were significantly higher in SMM patients who progress to active MM, in comparison with those non-progressed.[10] Additionally, specific expression pattern of 65 lncRNAs (7 higher than 2 fold-change) was observed in the comparison between P- and NP-SMM cases (Supplementary Table 2), as also recently reported.[9] Among the most differentially expressed lncRNAs, the most part of them have still an unknown function in the MM cell biology and pathophysiology, and still few evidences have been provided in literature. Modulation of the lncRNA AC092611.2 (antisense to the proximal *GATB* gene) has been described in juvenile myelomonocytic leukemia,[13] whereas AL138899.1 was reported as downregulated in T-cells acute lymphoblastic leukemia tumors compared with immature thymocytes[14]. Major evidences are related to XIST, whose involvement in progression and poorer outcome has been reported in several tumors.[15]

Conversely, the major finding of our analysis was that very similar expression profiles were observed between the 10 paired SMM - MM samples. In fact, no significant differentially expressed coding genes and lncRNAs were observed in the comparison between paired cases, thus suggesting that the progression of SMM to active MM was not associated to significant modification of the transcriptional profiles of PCs. A general portrait was offered by Principal Component Analysis of the most variable protein-coding genes and lncRNAs throughout the entire dataset, which evidenced that NP-SMM agglomerated in a somehow distinguishable cloud from P-SMM patients, who conversely tended to aggregate according to patient's source (Figure 1B). Of note, in the paired P-SMM and MM samples any further deregulation was not observed in the gene expression levels of the previously described 30 genes, including the Wnt inhibitors *FRZB* and *DKK1* differentially expressed between P-SMM and NP-SMM.

Overall, our findings on the up-regulation of Wnt inhibitors, such as DKK1 and FRZB by $CD138^+$ MM cells, in P-SMM patients sustains the hypothesis that high levels of these molecules produced by MM cells[16] and also BM mesenchymal stromal cells[17, 18] may influence the microenvironment, exerting a possible immunosuppressive effect[19] that leads to the progression of SMM towards active MM. Moreover, our data in a cohort of SMM with a short time to progression indicates that the transcriptome of the PCs of SMM patients who progressed to MM did not significantly change throughout the progression. Albeit a larger study cohort and longer follow up would be undoubtedly desirable for confirmation, our data strongly suggested that the transcriptional alterations of PCs observed in MM patients are indeed already present at the stage of smoldering disease. This prompts to support the notion that the alterations in the microenvironment cells could be critical in the progression from SMM to active MM.[3]

Supplementary information is available at Haematologica website.

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Table 1a: Clinical characteristics of the patients enrolled in the study.

	NP-SMM (n°11)	P-SMM (n°10)	MM (n°10)	*p* value (P-SMM vs MM)	*p* value (P-SMM vs NP-MM)
AGE at diagnosis (yrs)					
Median (range)	74 (38-86)	71 (43-84)	72 (46-86)	0,77	0,79
SEX					
Male	9 (81,8%)	4 (40%)	4 (40%)		
Female	2 (18,2%)	6 (60%)	6 (60%)		
ISOTYPE					
k	7 (63,6%)	9 (90%)	9 (90%)		
l	4 (36,4%)	1 (10%)	1 (10%)		
HEAVY CHAIN					
IgG	9 (81,8%)	8 (80%)	8 (80%)		
IgM	2 (18,2%)	2 (20%)	2 (20%)		
ISS					
I	/	/	4 (40%)		
II	/	/	4 (40%)		
III	/	/	2 (20%)		
R-ISS					
I	/	/	1 (10%)		
II	/	/	6 (60%)		
III	/	/	1 (10%)		
N.D.	/	/	2 (20%)		
CRAB					
Yes	/	/	10 (100%)		
No	/	/	0		
slim CRAB					
Yes	0	0	/		
No	11 (100%)	10 (100%)	/		
IMMUNOPARESIS					
Yes	9 (81,8%)	8 (80%)	10 (100%)		
No	2 (18,2%)	2 (20%)	0		
BMPCs %					
Median (range)	12 (10-25)	27,5 (13-40)	35 (20-80)	0,054167	0,00102
MONOCLONAL COMPONENT (g/dL)					
Median (range)	1,6 (0,5-2,9)	2,45 (1-4,5)	3,4 (1,4-7,4)	0,064973	0,37854
CYTOGENETICS					
High Risk	5 (45,4%)	3 (30%)	4 (40%)		
Low Risk	4 (36,4%)	6 (60%)	5 (50%)		
N.D.	2 (18,2%)	1 (10%)	1 (10%)		
FOLLOW UP (months)					
Median (range)	56 (9-132)		/		
TTP (months)					
Median (range)	/	15,5 (5-44)	/		

Abbreviations: yrs, years; BMPCs, bone marrow plasma cells; ISS; International staging system; R-ISS, revised international staging system, N.D, not determined; TTP, time to progression.

Table 1b: Individual clinical characteristics of the patients enrolled in the study.

	Sex	Age (yrs)	Isotype	Heavy Chain	BMPCs (%)	MC (g/dL)	Immunoparesis (Y/N)	High-risk FISH (Y/N)	HY	Progression (Y/N)	Time to progression /Follow-up (months)	CRAB criteria at progression			
												Anemia (Y/N)	Renal insufficiency (Y/N)	Bone disease (Y/N)	Hypercalcemia (Y/N)
P-SMM1	F	84	k	IgG	25	2.6	Y	Y	N	Y	8	Y	N	Y	Y
P-SMM2	M	69	k	IgG	30	1.4	Y	N	N	Y	16	Y	N	N	N
P-SMM3	F	79	k	IgG	35	2.9	Y	N	Y	Y	5	N	N	Y	N
P-SMM4	M	83	k	IgG	30	2.1	N	N	Y	Y	42	N	N	Y	N
P-SMM5	F	69	k	IgG	30	2.9	Y	N	N	Y	13	Y	N	Y	N
P-SMM6	M	73	l	IgG	20	4.5	Y	N	Y	Y	16	Y	N	N	Y
P-SMM7	F	43	k	IgA	20	1.0	Y			Y	44	N	N	Y	N
P-SMM8	M	58	k	IgG	13	1.5	N	N	Y	Y	34	Y	N	Y	N
P-SMM9	F	60	k	IgG	25	2.3	Y	Y	Y	Y	15	Y	N	Y	N
P-SMM10	F	74	k	IgA	40	2.6	Y	Y	N	Y	12	Y	N	N	N
NP-SMM11	M	76	k	IgG	20	2.5	Y	Y	Y	N	77				
NP-SMM12	M	38	k	IgG	12	2.9	Y	N	Y	N	65				
NP-SMM13	M	86	k	IgG	10	2.7	Y	Y	N	N	132				
NP-SMM14	M	58	k	IgG	25	2.5	Y	Y	N	N	54				
NP-SMM15	M	74	l	IgG	15	2.3	Y			N	61				
NP-SMM16	M	76	l	IgA	20	1.6	Y	N	Y	N	56				
NP-SMM17	M	72	l	IgG	12	0.6	N			N	56				
NP-SMM18	M	76	k	IgG	16	2.8	Y	Y	N	N	9*				
NP-SMM19	F	76	l	IgA	12	0.5	Y	N	N	N	90				
NP-SMM20	M	73	k	IgG	12	2.6	Y	Y	N	N	42				
NP-SMM21	F	38	k	IgG	11	1.2	N	N		N	49				

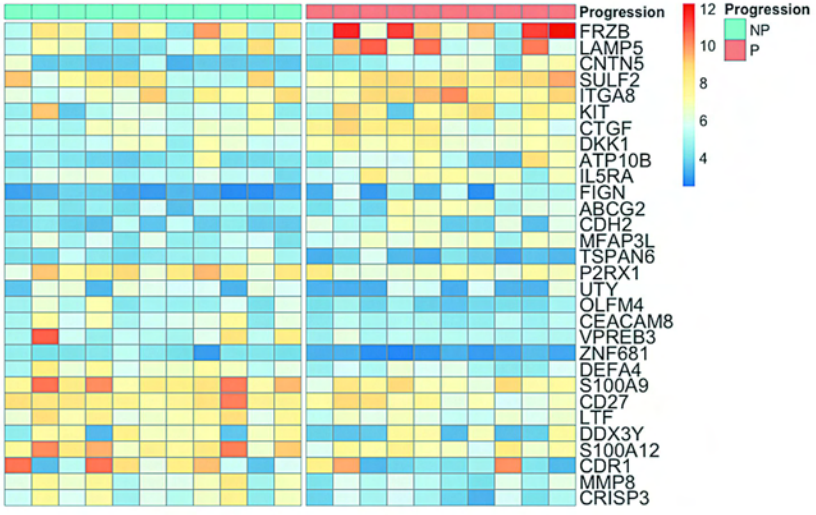
Abbreviations: yrs, years; BMPCs, bone marrow plasma cells; FISH, fluorescence in situ hybridization; HY: hyperdiploid; MC, monoclonal component; Y, yes; N, no.

***** The patient died for other cause than myeloma.

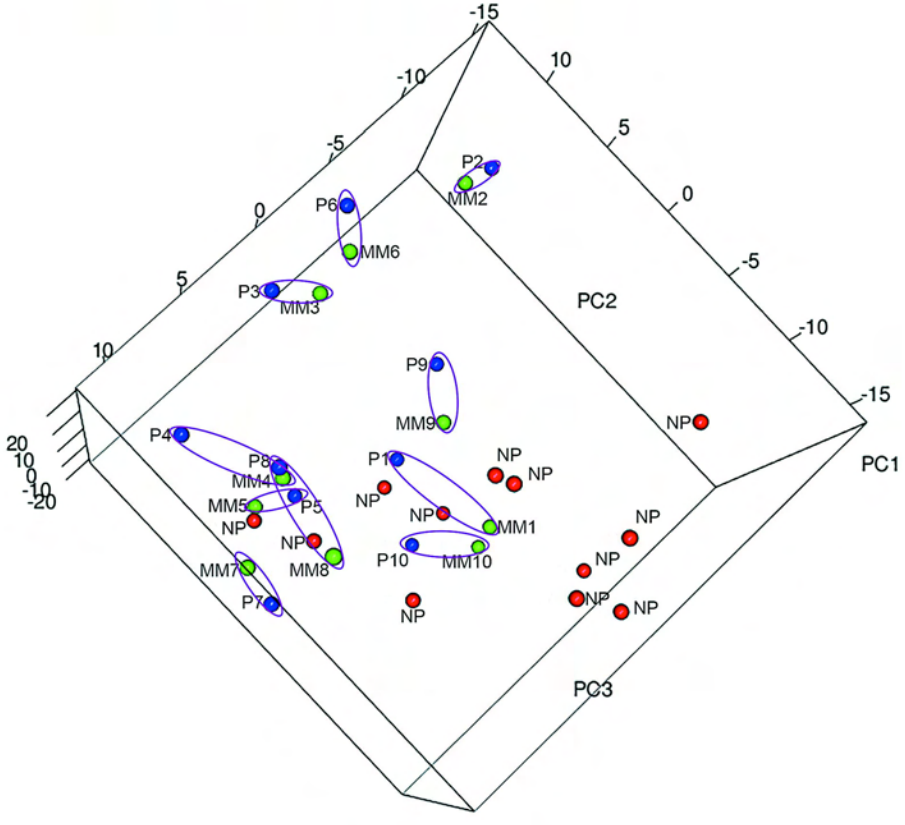
FIGURE LEGEND

Figure 1. Differential transcriptomic profile between not progressed and progressed smoldering and paired myeloma samples. A) Heatmap of the 30 most variable coding genes (highlighted in light blue in Supplementary Table 1) with at least 2-fold change in expression levels in 10 P-SMM samples versus 11 NP-SMM samples (Prog: progression; NP: not progressed SMM; P: progressed SMM); **B)** 3D visualization of Principal Component (PC) Analysis on the most variable transcripts across the whole dataset. NP-SMM (red dots) agglomerated distinguishable cloud from P-SMM patients (blue dots), who conversely tended to aggregate with their MM (green dots) paired sample. The P-SMM and MM from the same patient' origin shares the same number and they are highlighted by a purple circle. (NP: non-progressed SMM, P: progressed SMM; MM: myeloma).

A)


Progression
FRZB
LAMP5
CNTN5
SULF2
ITGA8
KIT
CTGF
DKK1
ATP10B
IL5RA
FIGN
ABCG2
CDH2
MFAP3L
TSPAN6
P2RX1
UTY
OLFM4
CEACAM8
VPREB3
ZNF681
DEFA4
S100A9
CD27
LTF
DDX3Y
S100A12
CDR1
MMP8
CRISP3
12
10
8
6
4
Progression
NP
P

B)


PC1
PC2
PC3
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
MM1
MM2
MM3
MM4
MM5
MM6
MM7
MM8
MM9
MM10
NP

Supplementary Table 1: 273 differentially expressed genes between NP-SMM and P-SMM CD138+ samples. In the table, the 30 most variable genes with a least 2 absolute fold change expression variation are highlighted in light blue (pfp: percentage of false prediction using RankProd package for Bioconductor).

Gene symbol- ENSG	Fold Change (SMM-P vs SMM-NP)	Pfp (<1%)	Approximate P.value
FRZB ENSG00000162998	3,080714726	$<1x10^4$	$<1x10^4$
LAMP5 ENSG00000125869	3,056234719	$<1x10^4$	$<1x10^4$
CNTN5 ENSG00000149972	2,790178571	$<1x10^4$	$<1x10^4$
SULF2 ENSG00000196562	2,683843264	$<1x10^4$	$<1x10^4$
ITGA8 ENSG00000077943	2,610966057	$<1x10^4$	$<1x10^4$
KIT ENSG00000157404	2,569373073	$<1x10^4$	$<1x10^4$
CTGF ENSG00000118523	2,44977952	$<1x10^4$	$<1x10^4$
DKK1 ENSG00000107984	2,447381302	$<1x10^4$	$<1x10^4$
ATP10B ENSG00000118322	2,411963338	$<1x10^4$	$<1x10^4$
IL5RA ENSG00000091181	2,283105023	$<1x10^4$	$<1x10^4$
FIGN ENSG00000182263	2,239641657	2,00E-04	$<1x10^4$
ABCG2 ENSG00000118777	2,220741728	$<1x10^4$	$<1x10^4$
CDH2 ENSG00000170558	2,212389381	$<1x10^4$	$<1x10^4$
MFAP3L ENSG00000198948	2,071680133	2,00E-04	$<1x10^4$
TBCEL ENSG00000154114	1,992428771	2,00E-04	$<1x10^4$
BTBD3 ENSG00000132640	1,977066034	2,00E-04	$<1x10^4$
CADM1 ENSG00000182985	1,940993789	1,00E-04	$<1x10^4$
NEB ENSG00000183091	1,939111887	2,00E-04	$<1x10^4$
KIAA1217 ENSG00000120549	1,913509376	3,00E-04	$<1x10^4$
MORC1 ENSG00000114487	1,904761905	2,00E-04	$<1x10^4$
ADGRB3 ENSG00000135298	1,887504719	2,00E-04	$<1x10^4$
TMPRSS11E ENSG00000087128	1,879699248	0,0081	$<1x10^4$
USH2A ENSG00000042781	1,865671642	0,0044	$<1x10^4$
LSAMP ENSG00000185565	1,848770568	2,00E-04	$<1x10^4$
SAMD9L ENSG00000177409	1,807664497	2,00E-04	$<1x10^4$
ELOVL7 ENSG00000164181	1,795009873	6,00E-04	$<1x10^4$
STK17A ENSG00000164543	1,766472355	5,00E-04	$<1x10^4$
RSAD2 ENSG00000134321	1,759943682	2,00E-04	$<1x10^4$
RASSF6 ENSG00000169435	1,759633996	3,00E-04	$<1x10^4$
PDE3A ENSG00000172572	1,749475157	0,006	$<1x10^4$
HGF ENSG00000019991	1,743679163	5,00E-04	$<1x10^4$
DCLK1 ENSG00000133083	1,737619461	0,0012	$<1x10^4$
IFI6 ENSG00000126709	1,735809755	2,00E-04	$<1x10^4$
MAGEC1 ENSG00000155495	1,730702665	2,00E-04	$<1x10^4$
AC024940.1 ENSG00000177359	1,726221302	0,0014	$<1x10^4$
QPCT ENSG00000115828	1,715265866	2,00E-04	$<1x10^4$
ISLR ENSG00000129009	1,677008217	0,0024	$<1x10^4$
HERC5 ENSG00000138646	1,671681712	7,00E-04	$<1x10^4$
LGR4 ENSG00000205213	1,642305797	0,002	$<1x10^4$

CHSY3 ENSG00000198108	1,623903865	0,0012	<1x10^4
GPRIN3 ENSG00000185477	1,623376623	4,00E-04	<1x10^4
SMAD1 ENSG00000170365	1,619433198	0,0043	<1x10^4
IFI44 ENSG00000137965	1,605651895	0,006	<1x10^4
PCDHB14 ENSG00000120327	1,601281025	0,0045	<1x10^4
MX1 ENSG00000157601	1,595659805	0,0029	<1x10^4
TNFSF10 ENSG00000121858	1,593879503	0,0022	<1x10^4
TOX ENSG00000198846	1,589319771	0,0028	<1x10^4
PDCD4 ENSG00000150593	1,587805653	0,0012	<1x10^4
BTAF1 ENSG00000095564	1,587301587	0,0051	<1x10^4
SAMD9 ENSG00000205413	1,583782072	0,0024	<1x10^4
GRIA3 ENSG00000125675	1,580527896	0,0046	<1x10^4
UBE2Q2 ENSG00000140367	1,580028441	0,0027	<1x10^4
GOLGA8S ENSG00000261739	1,573316551	0,0014	<1x10^4
FGD6 ENSG00000180263	1,569119724	0,0045	<1x10^4
RNF168 ENSG00000163961	1,568135487	0,0029	<1x10^4
PARP14 ENSG00000173193	1,562988434	0,006	<1x10^4
GBP1 ENSG00000117228	1,557147306	0,0053	<1x10^4
LTBP1 ENSG00000049323	1,552553951	0,0019	<1x10^4
FAM13A ENSG00000138640	1,546072975	0,0038	<1x10^4
TECTA ENSG00000109927	1,545117429	0,0064	<1x10^4
IFI27 ENSG00000165949	1,542971764	0,0052	<1x10^4
HERC6 ENSG00000138642	1,538224888	0,0052	<1x10^4
PEAK1 ENSG00000173517	1,536334306	0,0064	<1x10^4
NPY4R2 ENSG00000264717	1,535626536	0,0063	<1x10^4
IFIT5 ENSG00000152778	1,531862745	0,0063	<1x10^4
RNF144B ENSG00000137393	1,530456076	0,0025	<1x10^4
EPSTI1 ENSG00000133106	1,522533496	0,0044	<1x10^4
FUT8 ENSG00000033170	1,520218912	0,0063	<1x10^4
ETV1 ENSG00000006468	1,507386192	0,0025	<1x10^4
AP003108.2 ENSG00000256591	1,506931887	0,006	<1x10^4
CPED1 ENSG00000106034	1,505570611	0,0056	<1x10^4
MTX3 ENSG00000177034	1,503307276	0,0076	<1x10^4
PCDHGA9 ENSG00000261934	1,502178158	0,0036	<1x10^4
TLR10 ENSG00000174123	1,501050736	0,0048	<1x10^4
SLC44A5 ENSG00000137968	1,492760113	0,0045	<1x10^4
TRPM7 ENSG00000092439	1,492760113	0,01	<1x10^4
CPEB4 ENSG00000113742	1,488759863	0,0052	<1x10^4
LRRC70 ENSG00000186105	1,487652484	0,0069	<1x10^4
BTLA ENSG00000186265	1,485001485	0,0044	<1x10^4
LAP3 ENSG00000002549	1,484340211	0,008	<1x10^4
DDX58 ENSG00000107201	1,484340211	0,009	1,00E-04
JCHAIN ENSG00000132465	1,484119917	0,008	<1x10^4
RNPC3 ENSG00000185946	1,476668636	0,01	1,00E-04
ZNF215 ENSG00000149054	1,466705779	0,0071	<1x10^4
STAP1 ENSG00000035720	1,442793248	0,0018	<1x10^4

GOLGA8A ENSG00000175265	1,440299582	0,0052	<1x10^4
EPHB1 ENSG00000154928	1,424907381	0,0074	<1x10^4
BIRC3 ENSG00000023445	1,419849496	0,006	<1x10^4
GCNT4 ENSG00000176928	1,408252359	0,0079	<1x10^4
EDNRB ENSG00000136160	1,398601399	0,0045	<1x10^4
CD200 ENSG00000091972	1,390820584	0,0066	<1x10^4
TMEM156 ENSG00000121895	1,387347392	0,0052	<1x10^4
KCNS3 ENSG00000170745	1,374381528	0,0073	<1x10^4
CTSW ENSG00000172543	1,372118551	5,00E-04	<1x10^4
CCR2 ENSG00000121807	1,320829481	0,007	<1x10^4
MAML2 ENSG00000184384	1,308557969	0,0063	<1x10^4
MT1X ENSG00000187193	1,299545159	0,0067	<1x10^4
FAM106A ENSG00000213077	1,251251251	3,00E-04	<1x10^4
RGS13 ENSG00000127074	1,246261216	0,0045	<1x10^4
AFF2 ENSG00000155966	1,160092807	0,0036	<1x10^4
PPBP ENSG00000163736	1,127649977	0,0067	<1x10^4
CD44 ENSG00000026508	1,118943717	0,009	1,00E-04
IFI44L ENSG00000137959	1,98019802	5,00E-04	<1x10^4
BVES ENSG00000112276	1,87899286	2,00E-04	<1x10^4
TRAT1 ENSG00000163519	1,75070028	0,0012	<1x10^4
SCYL2 ENSG00000136021	1,62999185	0,0015	<1x10^4
MMP16 ENSG00000156103	1,58755358	0,0078	<1x10^4
XAF1 ENSG00000132530	1,57480315	0,0039	<1x10^4
ME1 ENSG00000065833	1,52998776	0,0051	<1x10^4
MIOS ENSG00000164654	1,52998776	0,0075	<1x10^4
FAT4 ENSG00000196159	1,50466446	0,0023	<1x10^4
PRKD3 ENSG00000115825	1,50466446	0,0065	<1x10^4
STS ENSG00000101846	1,47080453	0,0043	<1x10^4
PPARGC1A ENSG00000109819	1,27420999	0,0097	1,00E-04
EDN1 ENSG00000078401	1,26246686	0,0052	<1x10^4
KIAA1324L ENSG00000164659	1,5211439	0,0045	<1x10^4
TREML2 ENSG00000112195	-1,88	<1x10^4	<1x10^4
CRISP3 ENSG00000096006	-2,82	<1x10^4	<1x10^4
RASGRP1 ENSG00000172575	-1,258	0,0078	1,00E-04
YBX3 ENSG00000060138	-1,356	0,0079	1,00E-04
GAGE12J ENSG00000224659	-1,462	0,0018	<1x10^4
ZNF675 ENSG00000197372	-1,477	0,0079	1,00E-04
ATF3 ENSG00000162772	-1,527	0,0018	<1x10^4
CST7 ENSG00000077984	-1,561	0,0033	<1x10^4
PGLYRP1 ENSG00000008438	-1,589	0,0034	<1x10^4
TGFB2 ENSG00000092969	-1,761	<1x10^4	<1x10^4
HBA1 ENSG00000206172	-1,823	<1x10^4	<1x10^4
FAM106A ENSG00000213077	-0,7992	0,0014	<1x10^4
VCAM1 ENSG00000162692	-1,0351	0,0064	<1x10^4
TIMD4 ENSG00000145850	-1,2227	0,0025	<1x10^4
C1QC ENSG00000159189	-1,2319	0,0093	1,00E-04

GPRC5D ENSG00000111291	-1,2571	0,0029	<1x10^4
RND3 ENSG00000115963	-1,2597	0,0048	<1x10^4
PRKG1 ENSG00000185532	-1,2762	0,0033	<1x10^4
HIST1H1C ENSG00000187837	-1,2879	0,009	1,00E-04
SLAMF1 ENSG00000117090	-1,3278	0,0048	<1x10^4
AC068896.1 ENSG00000258539	-1,3294	0,005	<1x10^4
EDEM3 ENSG00000116406	-1,3403	0,0058	<1x10^4
APP ENSG00000142192	-1,3467	0,0034	<1x10^4
USP9Y ENSG00000114374	-1,3477	0,0052	<1x10^4
NBPF6 ENSG00000186086	-1,3478	0,0018	<1x10^4
FAM129A ENSG00000135842	-1,3599	7,00E-04	<1x10^4
RHOB ENSG00000143878	-1,3605	0,009	1,00E-04
CD79A ENSG00000105369	-1,3773	<1x10^4	<1x10^4
OR2T2 ENSG00000196240	-1,3805	0,0091	1,00E-04
FCRL3 ENSG00000160856	-1,3884	0,0024	<1x10^4
CERS6 ENSG00000172292	-1,3906	0,0044	<1x10^4
ZNF165 ENSG00000197279	-1,3907	0,0049	<1x10^4
OTUD1 ENSG00000165312	-1,3913	0,0033	<1x10^4
ATP8B2 ENSG00000143515	-1,4038	0,0091	1,00E-04
FCER2 ENSG00000104921	-1,4069	0,0063	<1x10^4
CCL3 ENSG00000277632	-1,4095	2,00E-04	<1x10^4
GRIN2B ENSG00000273079	-1,4114	0,0059	<1x10^4
SPATA31D3 ENSG00000186788	-1,4157	0,0033	<1x10^4
FOS ENSG00000170345	-1,4199	0,0091	1,00E-04
CCL18 ENSG00000275385	-1,4226	0,0075	1,00E-04
LY9 ENSG00000122224	-1,4227	0,0055	<1x10^4
GOLPH3L ENSG00000143457	-1,4283	0,0092	1,00E-04
AIF1 ENSG00000204472	-1,4283	0,0098	1,00E-04
KCNN3 ENSG00000143603	-1,4311	0,0059	<1x10^4
SLAMF6 ENSG00000162739	-1,4508	7,00E-04	<1x10^4
NAXE ENSG00000163382	-1,4514	0,0065	<1x10^4
GOLGA8H ENSG00000261794	-1,4549	0,0078	1,00E-04
SEMA4A ENSG00000196189	-1,4562	0,0065	<1x10^4
UCHL1 ENSG00000154277	-1,4565	<1x10^4	<1x10^4
JUN ENSG00000177606	-1,4596	0,0091	1,00E-04
SCN9A ENSG00000169432	-1,4612	8,00E-04	<1x10^4
TCEA3 ENSG00000204219	-1,4676	0,0056	<1x10^4
NUCB2 ENSG00000070081	-1,4683	0,0077	1,00E-04
HIST2H2BE ENSG00000184678	-1,4699	0,001	<1x10^4
IRF2BP2 ENSG00000168264	-1,4724	0,005	<1x10^4
SELL ENSG00000188404	-1,4735	0,0049	<1x10^4
PDIA4 ENSG00000155660	-1,4766	0,0033	<1x10^4
RNASE6 ENSG00000169413	-1,4768	0,0033	<1x10^4
P2RY13 ENSG00000181631	-1,4777	0,0033	<1x10^4
DAPK1 ENSG00000196730	-1,4787	0,0025	<1x10^4
SLC46A3 ENSG00000139508	-1,4799	0,0063	<1x10^4

CA1 ENSG00000133742	-1,4811	0,0048	$<1x10^{4}$
MEF2D ENSG00000116604	-1,4863	0,0079	1,00E-04
PLP2 ENSG00000102007	-1,4925	0,0093	1,00E-04
WARS ENSG00000140105	-1,4951	6,00E-04	$<1x10^{4}$
FCRL5 ENSG00000143297	-1,4984	0,0062	$<1x10^{4}$
SGK1 ENSG00000118515	-1,5035	0,0049	$<1x10^{4}$
GSTA4 ENSG00000170899	-1,5075	0,0065	$<1x10^{4}$
TYROBP ENSG00000011600	-1,5081	0,0041	$<1x10^{4}$
HIST1H2AL ENSG00000276903	-1,5094	0,006	$<1x10^{4}$
HLA-DRA ENSG00000204287	-1,5121	0,0033	$<1x10^{4}$
NCSTN ENSG00000162736	-1,5156	0,0049	$<1x10^{4}$
S100A11 ENSG00000163191	-1,5233	0,0073	1,00E-04
VNN1 ENSG00000112299	-1,5248	0,0059	$<1x10^{4}$
CDA ENSG00000158825	-1,5289	0,005	$<1x10^{4}$
HSBP1L1 ENSG00000226742	-1,5296	0,0036	$<1x10^{4}$
PADI4 ENSG00000159339	-1,5348	0,0079	1,00E-04
RFLNB ENSG00000183688	-1,5375	0,0011	$<1x10^{4}$
HOOK1 ENSG00000134709	-1,5377	0,0011	$<1x10^{4}$
CCND2 ENSG00000118971	-1,5381	$<1x10^{4}$	$<1x10^{4}$
GAREM1 ENSG00000141441	-1,5389	0,0045	$<1x10^{4}$
AHSP ENSG00000169877	-1,5438	0,0036	$<1x10^{4}$
CCND1 ENSG00000110092	-1,5448	0,0013	$<1x10^{4}$
CD52 ENSG00000169442	-1,5456	0,0028	$<1x10^{4}$
FCER1G ENSG00000158869	-1,5466	0,0011	$<1x10^{4}$
ALDH1L2 ENSG00000136010	-1,5591	0,0024	$<1x10^{4}$
AC136428.1 ENSG00000259680	-1,5608	$<1x10^{4}$	$<1x10^{4}$
HLA-DMA ENSG00000204257	-1,5635	0,0039	$<1x10^{4}$
PTGS2 ENSG00000073756	-1,5654	5,00E-04	$<1x10^{4}$
FCAR ENSG00000186431	-1,5684	0,0035	$<1x10^{4}$
BPI ENSG00000101425	-1,5805	0,0025	$<1x10^{4}$
ALAS2 ENSG00000158578	-1,5815	0,0017	$<1x10^{4}$
ELANE ENSG00000197561	-1,5844	0,0011	$<1x10^{4}$
ANXA1 ENSG00000135046	-1,5848	7,00E-04	$<1x10^{4}$
ADA2 ENSG00000093072	-1,5853	0,0013	$<1x10^{4}$
IGF1R ENSG00000140443	-1,5889	0,0018	$<1x10^{4}$
SLC7A5 ENSG00000103257	-1,5946	0,0012	$<1x10^{4}$
OR51A4 ENSG00000205497	-1,5968	0,0021	$<1x10^{4}$
ALOX5AP ENSG00000132965	-1,6004	0,0019	$<1x10^{4}$
ZFY ENSG00000067646	-1,6025	2,00E-04	$<1x10^{4}$
ERAP2 ENSG00000164308	-1,6109	$<1x10^{4}$	$<1x10^{4}$
AGA ENSG00000038002	-1,6127	0,0018	$<1x10^{4}$
TCN1 ENSG00000134827	-1,6213	0,0033	$<1x10^{4}$
SGPP2 ENSG00000163082	-1,6238	0,0038	$<1x10^{4}$
HIST2H2BF ENSG00000203814	-1,6316	5,00E-04	$<1x10^{4}$
LCN2 ENSG00000148346	-1,6355	0,0011	$<1x10^{4}$
PLAGL1 ENSG00000118495	-1,6373	0,0018	$<1x10^{4}$

MS4A3 ENSG00000149516	-1,6445	8,00E-04	$<1x10^{4}$
ZNF608 ENSG00000168916	-1,6507	0,0011	$<1x10^{4}$
PTP4A3 ENSG00000184489	-1,6546	$<1x10^{4}$	$<1x10^{4}$
IL6R ENSG00000160712	-1,6551	2,00E-04	$<1x10^{4}$
CYBB ENSG00000165168	-1,6687	$<1x10^{4}$	$<1x10^{4}$
HBA2 ENSG00000188536	-1,6713	4,00E-04	$<1x10^{4}$
RNASE3 ENSG00000169397	-1,6762	7,00E-04	$<1x10^{4}$
C1orf21 ENSG00000116667	-1,6764	$<1x10^{4}$	$<1x10^{4}$
TIMP1 ENSG00000102265	-1,6807	$<1x10^{4}$	$<1x10^{4}$
SERPINB10 ENSG00000242550	-1,6976	5,00E-04	$<1x10^{4}$
MPO ENSG00000005381	-1,7059	1,00E-04	$<1x10^{4}$
RNASE2 ENSG00000169385	-1,7062	2,00E-04	$<1x10^{4}$
MAL ENSG00000172005	-1,7142	$<1x10^{4}$	$<1x10^{4}$
DUSP10 ENSG00000143507	-1,7194	$<1x10^{4}$	$<1x10^{4}$
AC008770.2 ENSG00000257355	-1,7321	$<1x10^{4}$	$<1x10^{4}$
CTSG ENSG00000100448	-1,7513	$<1x10^{4}$	$<1x10^{4}$
MYADM ENSG00000179820	-1,7529	$<1x10^{4}$	$<1x10^{4}$
CST3 ENSG00000101439	-1,7774	$<1x10^{4}$	$<1x10^{4}$
EIF1AY ENSG00000198692	-1,7776	$<1x10^{4}$	$<1x10^{4}$
MMP9 ENSG00000100985	-1,7797	5,00E-04	$<1x10^{4}$
LYZ ENSG00000090382	-1,7816	$<1x10^{4}$	$<1x10^{4}$
ANXA3 ENSG00000138772	-1,7838	1,00E-04	$<1x10^{4}$
RASD1 ENSG00000108551	-1,8009	$<1x10^{4}$	$<1x10^{4}$
HBB ENSG00000244734	-1,8046	$<1x10^{4}$	$<1x10^{4}$
PLTP ENSG00000100979	-1,8055	$<1x10^{4}$	$<1x10^{4}$
PARP15 ENSG00000173200	-1,8187	$<1x10^{4}$	$<1x10^{4}$
C16orf54 ENSG00000185905	-1,8306	$<1x10^{4}$	$<1x10^{4}$
DOCK11 ENSG00000147251	-1,8377	$<1x10^{4}$	$<1x10^{4}$
ORM1 ENSG00000229314	-1,8525	$<1x10^{4}$	$<1x10^{4}$
CAMP ENSG00000164047	-1,8581	$<1x10^{4}$	$<1x10^{4}$
S100A8 ENSG00000143546	-1,8736	$<1x10^{4}$	$<1x10^{4}$
MNDA ENSG00000163563	-1,8818	$<1x10^{4}$	$<1x10^{4}$
PLBD1 ENSG00000121316	-1,8968	$<1x10^{4}$	$<1x10^{4}$
SPN ENSG00000197471	-1,9212	$<1x10^{4}$	$<1x10^{4}$
KDM5D ENSG00000012817	-1,9594	$<1x10^{4}$	$<1x10^{4}$
TSPAN6 ENSG00000000003	-2,0533	$<1x10^{4}$	$<1x10^{4}$
P2RX1 ENSG00000108405	-2,0849	$<1x10^{4}$	$<1x10^{4}$
UTY ENSG00000183878	-2,0884	$<1x10^{4}$	$<1x10^{4}$
OLFM4 ENSG00000102837	-2,1122	$<1x10^{4}$	$<1x10^{4}$
CEACAM8 ENSG00000124469	-2,1799	$<1x10^{4}$	$<1x10^{4}$
VPREB3 ENSG00000128218	-2,2277	$<1x10^{4}$	$<1x10^{4}$
ZNF681 ENSG00000196172	-2,2424	$<1x10^{4}$	$<1x10^{4}$
DEFA4 ENSG00000164821	-2,3089	$<1x10^{4}$	$<1x10^{4}$
S100A9 ENSG00000163220	-2,3698	$<1x10^{4}$	$<1x10^{4}$
CD27 ENSG00000139193	-2,3818	$<1x10^{4}$	$<1x10^{4}$
LTF ENSG00000012223	-2,3818	$<1x10^{4}$	$<1x10^{4}$

DDX3Y ENSG00000067048	-2,4111	$<1x10^4$	$<1x10^4$
S100A12 ENSG00000163221	-2,5974	$<1x10^4$	$<1x10^4$
CDR1 ENSG00000184258	-2,6349	$<1x10^4$	$<1x10^4$
MMP8 ENSG00000118113	-2,6568	$<1x10^4$	$<1x10^4$
CRISP3 ENSG00000096006	-2,82	$<1x10^4$	$<1x10^4$

Supplementary Table 2: 65 long non-coding genes differentially expressed in P-SMM versus NP-SMM CD138+ samples. In the table, the 7 most variable genes with a least 2 absolute fold change expression variation are highlighted in light blue.

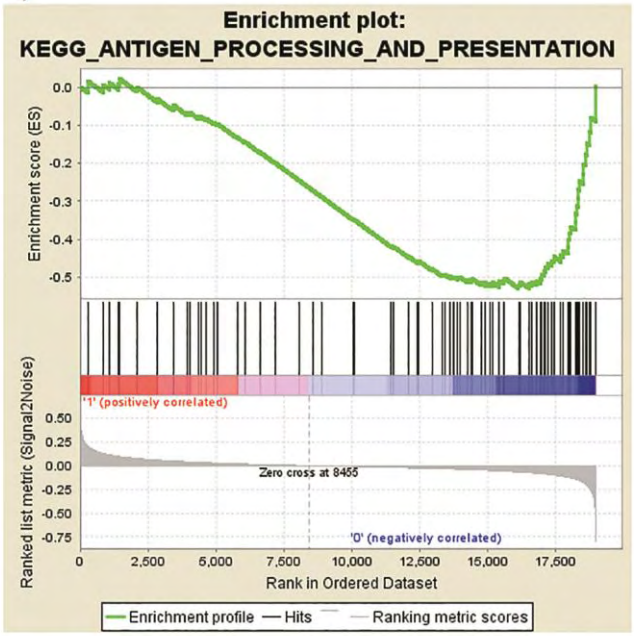
Gene symbol -ENSG	Fold Change (class SMM-P vs SMM-NP)	Pfp (<1%)	Approximate P.value
AC012414.5 ENSG00000260409	2,822466836	$<1x10^4$	$<1x10^4$
XIST ENSG00000229807	2,811357886	$<1x10^4$	$<1x10^4$
AC092611.2 ENSG00000251603	2,225189141	$<1x10^4$	$<1x10^4$
AL138899.1 ENSG00000176320	2,138122728	$<1x10^4$	$<1x10^4$
AL390208.1 ENSG00000271730	2,133105802	$<1x10^4$	$<1x10^4$
AL391834.1 ENSG00000272842	2,030869212	$<1x10^4$	$<1x10^4$
DUXAP8 ENSG00000206195	1,944390434	$<1x10^4$	$<1x10^4$
LINC02024 ENSG00000241213	1,94024059	0,001	$<1x10^4$
NPTN-IT1 ENSG00000281183	1,911680367	$<1x10^4$	$<1x10^4$
LINC01480 ENSG00000270164	1,908396947	$<1x10^4$	$<1x10^4$
AF127936.2 ENSG00000232884	1,897173212	$<1x10^4$	$<1x10^4$
NAV2-IT1 ENSG00000255270	1,706484642	0,001	$<1x10^4$
AP000756.1 ENSG00000255183	1,693766938	0,0077	$<1x10^4$
AC006058.1 ENSG00000261786	1,691474966	6,00E-04	$<1x10^4$
AC124290.1 ENSG00000253524	1,66002656	0,0035	$<1x10^4$
AC092691.1 ENSG00000239268	1,653165813	0,0079	$<1x10^4$
RSF1-IT2 ENSG00000254985	1,638269987	0,0042	$<1x10^4$
AC007326.5 ENSG00000284294	1,636929121	0,0029	$<1x10^4$
AL158206.1 ENSG00000260912	1,634788295	0,0039	$<1x10^4$
DISC1FP1 ENSG00000261645	1,623903865	0,0081	$<1x10^4$
AC012485.3 ENSG00000283635	1,570105197	0,0062	$<1x10^4$
FAM74A1 ENSG00000215112	1,550147264	0,0027	$<1x10^4$
AC090970.1 ENSG00000259398	1,541307028	0,0087	$<1x10^4$
LARGE-IT1 ENSG00000232081	1,531159087	0,0089	$<1x10^4$
AC010931.2 ENSG00000248540	1,521606817	0,0097	$<1x10^4$
AL139351.1 ENSG00000276923	1,500150015	0,0058	$<1x10^4$
AC020978.8 ENSG00000263276	1,449485433	0,0104	$<1x10^4$
PWAR6 ENSG00000257151	1,444251878	0,0082	$<1x10^4$
LINC01484 ENSG00000253686	1,43000143	0,0106	$<1x10^4$
AC007684.1 ENSG00000273035	1,357404642	0,0099	$<1x10^4$
AC025031.3 ENSG00000274591	1,35501355	0,0087	$<1x10^4$
AL353753.1 ENSG00000276759	1,3374348	0,0093	$<1x10^4$

AC106882.1 ENSG00000248571	1,323977228	0,0096	$<1x10^{4}$
AC099793.1 ENSG00000259815	1,313887794	0,0102	$<1x10^{4}$
AL022067.1 ENSG00000269919	1,254862593	0,0097	$<1x10^{4}$
AC107983.2 ENSG00000273018	1,156203029	0,0062	$<1x10^{4}$
LINC01055 ENSG00000235366	1,155134573	0,0104	$<1x10^{4}$
AL078639.1 ENSG00000281508	-4,1746	$<1x10^{4}$	$<1x10^{4}$
AC245128.3 ENSG00000268734	-1,8731	$<1x10^{4}$	$<1x10^{4}$
Z93241.1 ENSG00000270022	-1,8142	$<1x10^{4}$	$<1x10^{4}$
AC092279.1 ENSG00000268362	-1,7979	5,00E-04	$<1x10^{4}$
AC136475.8 ENSG00000270105	-1,7237	8,00E-04	$<1x10^{4}$
LINC00582 ENSG00000229228	-1,6621	0,0021	$<1x10^{4}$
AC012313.7 ENSG00000269106	-1,6412	0,0012	$<1x10^{4}$
AC087463.3 ENSG00000261598	-1,5986	7,00E-04	$<1x10^{4}$
AC103591.3 ENSG00000273338	-1,5945	4,00E-04	$<1x10^{4}$
AP001330.5 ENSG00000271882	-1,5859	0,0017	$<1x10^{4}$
AC092120.2 ENSG00000261692	-1,5822	0,002	$<1x10^{4}$
HYMAI ENSG00000283122	-1,5637	0,0094	$<1x10^{4}$
AC007032.1 ENSG00000273320	-1,5502	0,0022	$<1x10^{4}$
AC007556.1 ENSG00000235321	-1,5454	7,00E-04	$<1x10^{4}$
AC009812.4 ENSG00000260317	-1,4977	0,0016	$<1x10^{4}$
AC008074.3 ENSG00000260101	-1,4782	0,0022	$<1x10^{4}$
AC008440.2 ENSG00000232220	-1,4702	0,0013	$<1x10^{4}$
CYTOR ENSG00000222041	-1,4344	0,0051	$<1x10^{4}$
AC016831.5 ENSG00000271204	-1,4223	0,01	$<1x10^{4}$
TTTY15 ENSG00000233864	-1,414	0,0014	$<1x10^{4}$
AC245041.2 ENSG00000276850	-1,4135	0,0052	$<1x10^{4}$
AC104248.1 ENSG00000253796	-1,412	0,0021	$<1x10^{4}$
AC017002.1 ENSG00000224959	-1,3805	0,0018	$<1x10^{4}$
AL449106.1 ENSG00000273062	-1,3769	0,0076	$<1x10^{4}$
AC026369.3 ENSG00000256948	-1,3674	6,00E-04	$<1x10^{4}$
LINC02085 ENSG00000214407	-1,3353	0,0098	$<1x10^{4}$
AP000240.1 ENSG00000273017	-1,3253	0,0038	$<1x10^{4}$
AC010889.1 ENSG00000260197	-1,2938	0,0051	$<1x10^{4}$

SUPPLEMENTARY FIGURE

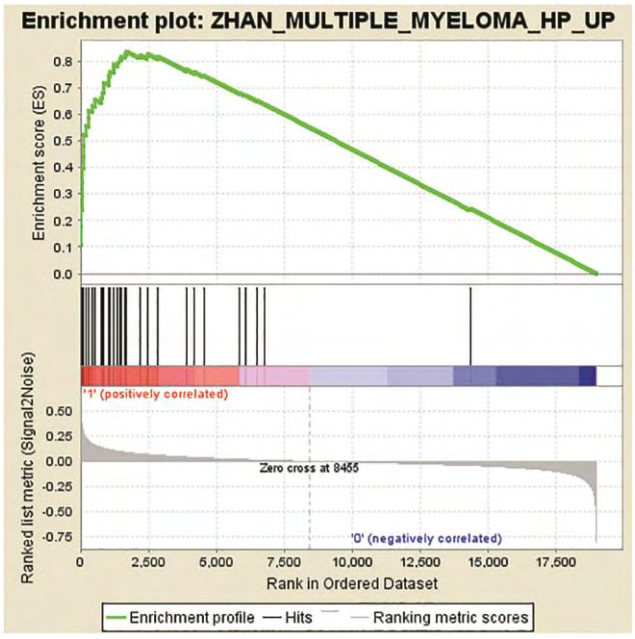
Supplementary Figure 1. Enrichment plots derived from Gene Set Enrichment Analysis (GSEA) in P-SMM (group 1) versus NP-SMM (group 0) samples **A)** Antigen processing and presentation gene set enrichment plot in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database **B)** Enrichment plots of genes sets associated with proliferation and hyperdiploidy in MM according to Zahn et al.[1] NES: normalized enrichment score; Nom *p*-value: Nominal *p* –Value.

A)

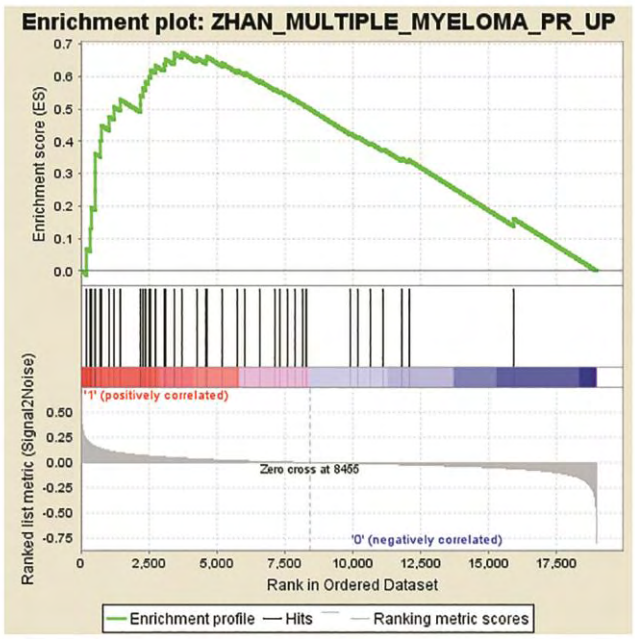


NES	NOM p-value
-1.44	0.000

B)

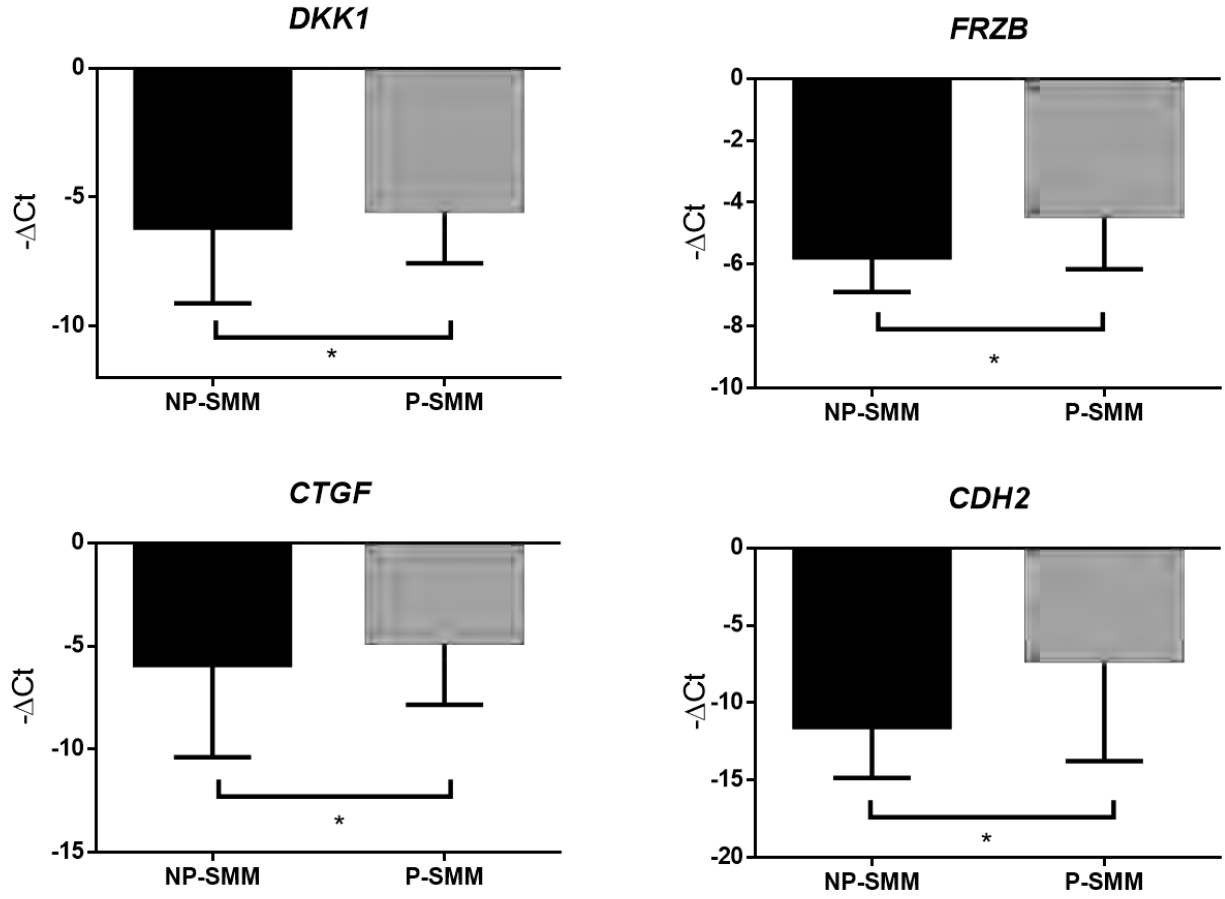


NES	Nom p-value
1.53	0.000

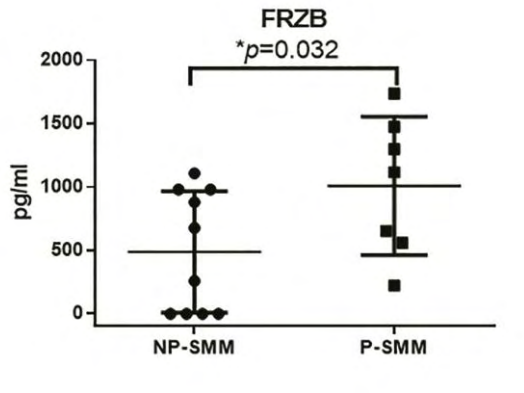


NES	Nom p-value
1.76	0.000

Supplementary Figure 2. The expression of *DKK1, FRZB, CTGF* and *CDH2* mRNA were evaluated by Real-time PCR in BM CD138+ cells of the same patients' cohort of the gene expression analyses. Graphs represent median with range of -ΔCt (cycle threshold). Fold change was calculated of P-SMM patients versus NP-SMM assuming median ΔCt of NP-SMM group as control condition (fold change. *DKK1*=1,58; *FRZB*=1,61; *CTGF*=2,14; *CDH2*=19,56). *GAPDH* was used as housekeeping gene and $2^{-\Delta\Delta Ct}$ method was used to calculate the fold change. (*= fold change >1,5)



Supplementary Figure 3. BM plasma samples of the same patient cohort, when available (7 P-SMM and 10 NP-SMM), were tested by ELISA for FRZB protein. Graphs represent the median value and the interquartile range, reported as pg/µg. The statistical analysis was performed by Mahn-Whitney test.



REFERENCE

1. Zhan F, Huang Y, Colla S, Stewart JP, Hanamura I, Gupta S*, et al.* The molecular classification of multiple myeloma. *Blood* 2006 Sep 15; **108**(6)**:** 2020-2028.