**Natural killer cells efficiently target multiple myeloma clonogenic tumor cells**

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**Supplementary tables**

| Antigen | Clone | Fluorochrome | Source | Catalog number |
|---|---|---|---|---|
| CD3 | UCHT1 | PE/Cy7 | Biolegend | 351304 |
| CD4 | RPA-T4 | APC/Cy7 | Biolegend | 300518 |
| CD7 | CD7-6B7 | FITC | Biolegend | 343104 |
| CD16 | 3G8 | APC/Cy7 | BD Pharmingen | 557758 |
| CD19 | SJ25C1 | PE | Biolegend | 363004 |
| CD25 | BC96 | FITC | Biolegend | 302604 |
| CD31 | WM59 | FITC | Biolegend | 301104 |
| CD45 | HI30 | FITC | Biolegend | 304006 |
| CD56 (NCAM) | HCD56 | APC | Biolegend | 318310 |
| CD127 (IL-7Rα) | A019D5 | PE | Biolegend | 351304 |
| CD69 | FN50 | PE | Biolegend | 310906 |
| CD178 (FasL) | NOK-1 | PE | Biolegend | 306407 |
| CD253 (TRAIL) | RIK-2 | PE | Biolegend | 308206 |
| DNAM-1 (CD226) | TX25 | FITC | Biolegend | 337104 |
| NKG2A (CD159a) | #131411 | PE | R&D Systems | FAB1059P |
| NKG2D (CD314) | 1D11 | PE | Biolegend | 320806 |
| NKp30 | AF29-4D12 | PE | Miltenyi | 130-092-483 |
| NKp44 | Z231 | PE | IOtest | PNIM3710 |
| NKp46 | 9E2 | PE | Biolegend | 331908 |
| PROPIDIUM IODURE | | | Sigma Aldrich | P4864 |

**Supplementary Table S1**. **Antibodies used in flow cytometry.** FITC, fluorescein isothiocyanate; PE, phycoerythrin; PE/Cy7, tandem constituted by phycoerythrin and cyanin 7; APC, allophycocyanin; APC/Cy7, tandem constituted by allophycocyanin and cyanin 7.

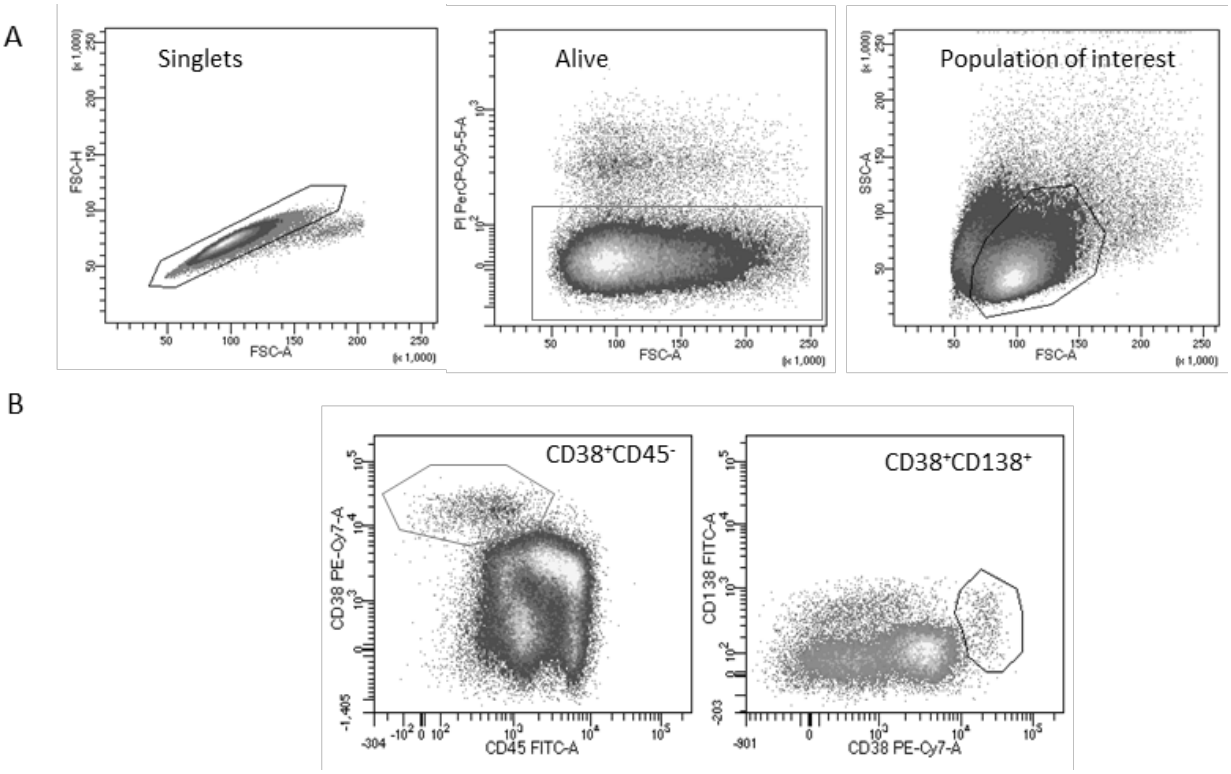
| Patient | Age, years | Sex | Percentage of side population | Type | Bone marrow infiltration | Situation when taking sample |
|---|---|---|---|---|---|---|
| 01 | 56 | M | 1.05% | IgG κ | 98% | Newly diagnosed |
| 02 | 72 | F | 3.69% | IgG κ | 53% | Biological progression |
| 03 | 81 | M | 0.8% | IgA κ | 1% | MGUS |
| 04 | 64 | F | 0.3% | IgG λ | 38% | Newly diagnosed |
| 05 | 84 | M | 2.3% | IgG λ | 2.1% | Stable disease |

**Supplementary Table S2**. **Clinical characteristics of the analyzed multiple myeloma patients.** Samples from multiple myeloma patients were used for side population studies and phenotyping.

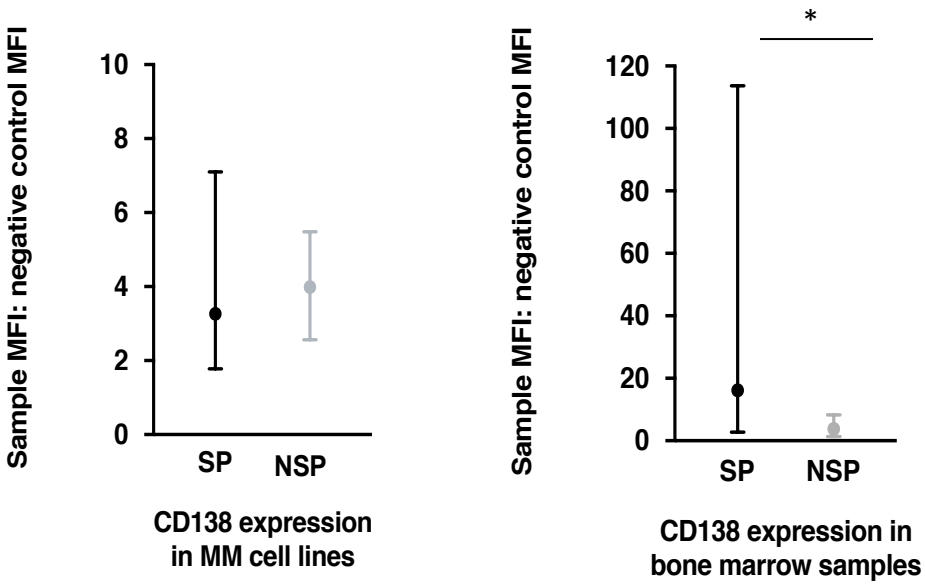
| Cell line | SP | SP + RES | Bone marrow samples | SP | SP + RES |
|---|---|---|---|---|---|
| JJN-3 | 1.3% | 0.9% | 1 | 1.9% | 0.2% |
| L-363 | 2.1% | 0.2% | 2 | 1.48% | 0.00% |
| MM.1S | 0.2% | 0.2% | 3 | 2.3% | 0.2% |
| NCI-H929 | 0.834% | 0.007% | 4 | 11.4% | 1.3% |
| OPM-2 | 0.6% | 0.1% | 5 | 0.5% | 0.4% |
| RPMI-8226 | 4.5% | 0.6% | 6 | 0.2% | 0.2% |
| SK-MM-2 | 0.136% | 0.007% | 7 | 1.9% | 1.2% |
| U-266 | 2.2% | 0.1% | 8 | 0.9% | 0.6% |

**Supplementary Table S3. Multiple myeloma side population (SP) distribution.** Data are given as the percentages of SP in multiple myeloma cell lines and bone marrow samples. Percentages after incubation with reserpine (RES) are also shown for each analyzed sample. Primary patient samples were anonymized.

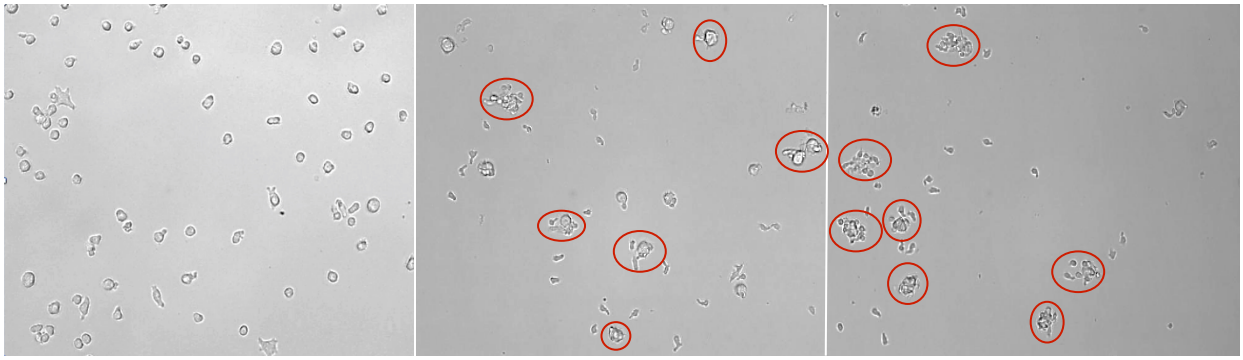
**Supplementary figures**




**Supplementary Figure S1. Flow cytometry strategy for identification of the multiple myeloma side population. (A)** Representative dot plots. Doublets and dead cells were excluded before gating the cell population of interest. **(B)** In multiple myeloma bone marrow samples, pathological plasma cells were gated based on the expression of CD138 and CD38 and lower expression of CD45.




**Supplementary Figure S2. CD138 expression in SP and NSP cells.** C138 expression on SP and NSP cells was evaluated by flow cytometry. Eight MM cell lines and five fresh primary bone marrow samples were analyzed. Data are presented as median and IQR. *$p < 0.05$ compared to NSP cells.



**Supplementary Figure S3. Natural killer (NK) cell cytotoxicity against multiple myeloma (MM) bulk and side population cells.** Representative image of time-lapse microscopy of NK cell synapses with MM. NK cells from MM patient vs. MM cells (left), NKAE from the same patient vs. MM cells (center), and NKAE cells vs. SP cells (right). NK cell-MM cell aggregates are indicated by red circles.