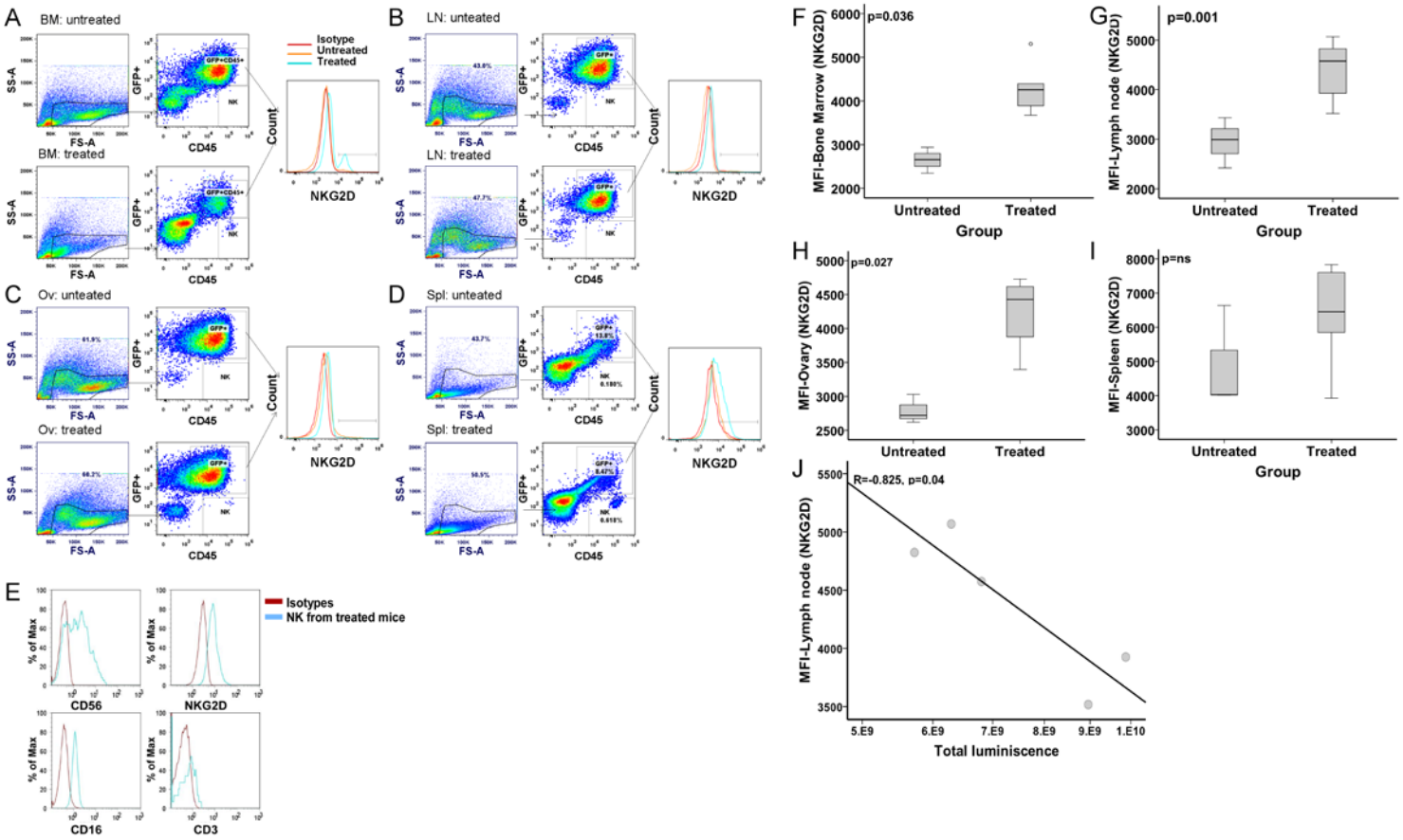
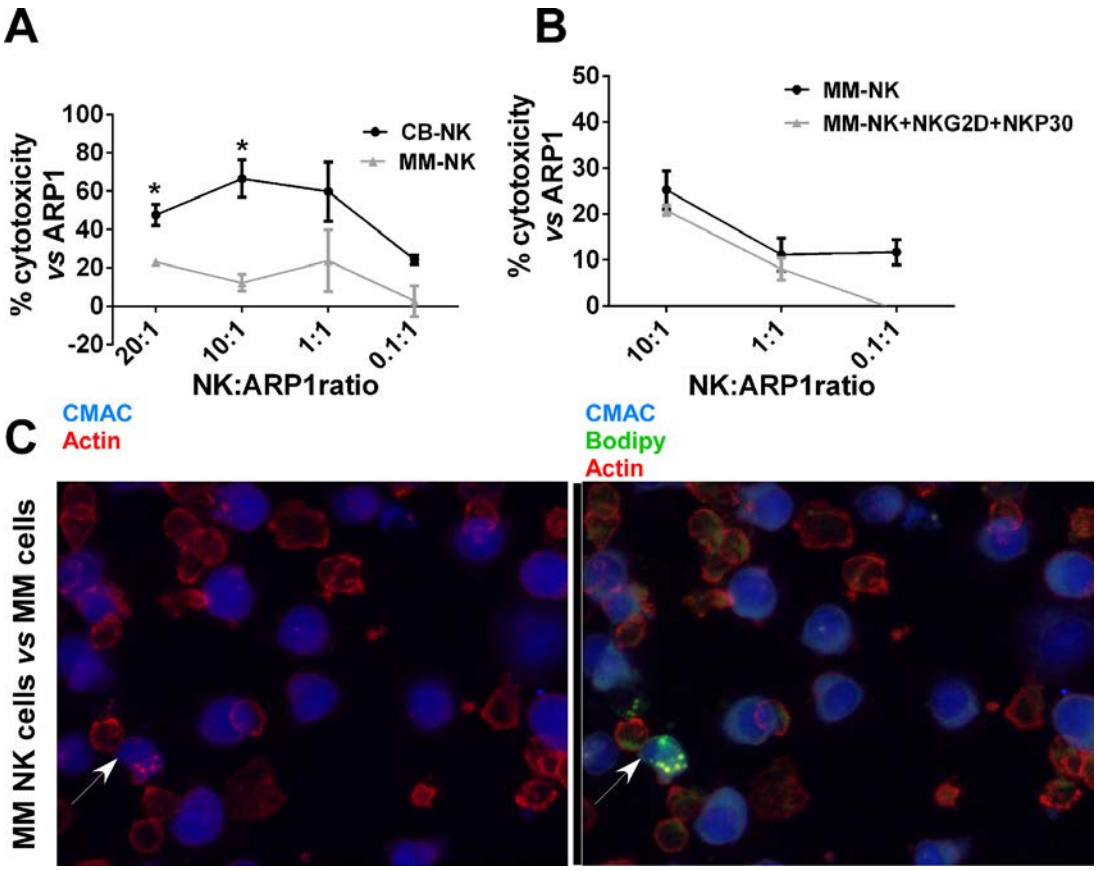
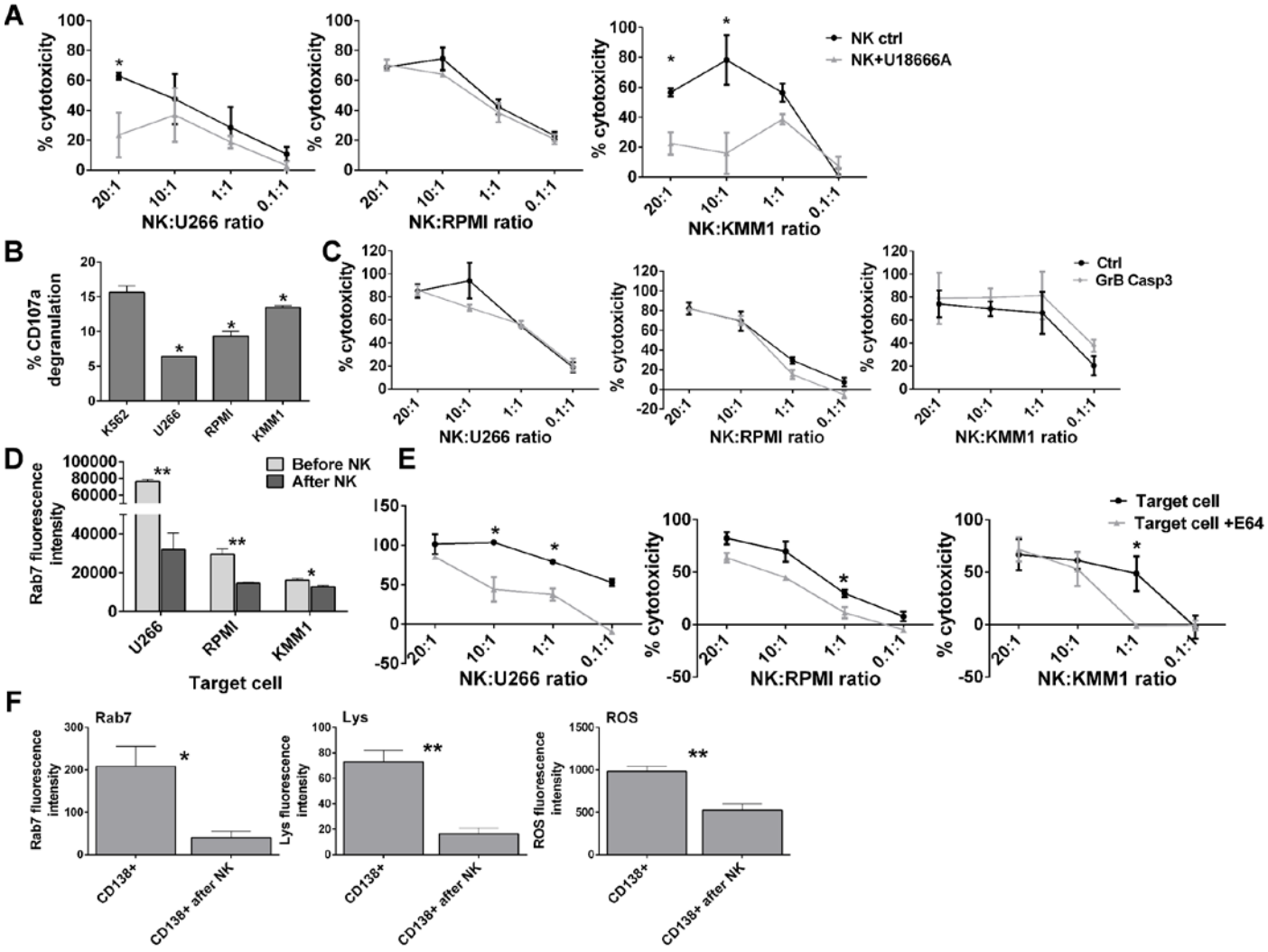


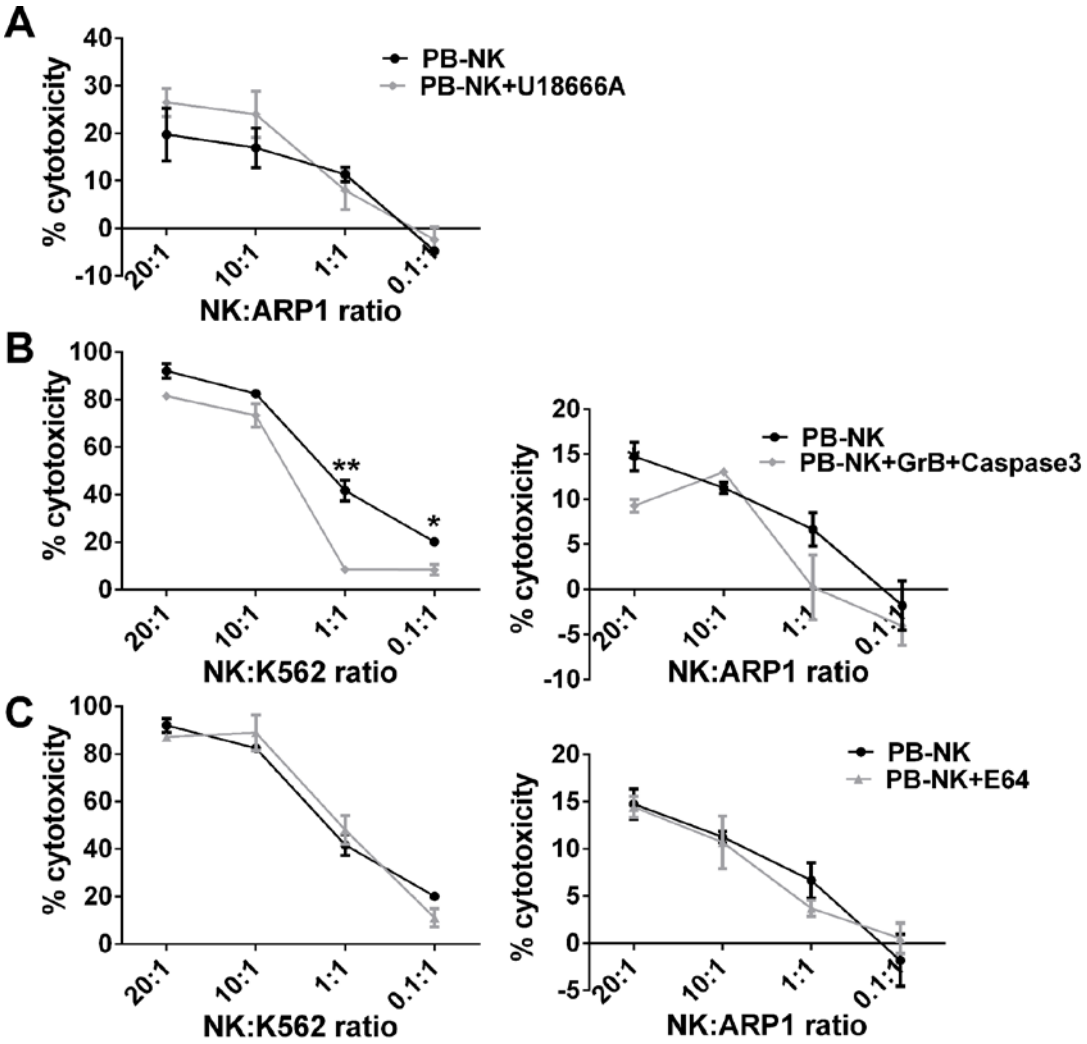
Supplementary Figure 1: NKG2D expression in multiple myeloma (MM) cells after cord blood derived natural killer cell (CB-NK) treatment correlates with good prognosis in an *in vivo* murine MM model: **A** to **D**: Flow cytometry plots showing ARP1 cells in mice in the different tissues and the comparison of median fluoresecence intensity (MFI) for NKG2D in ARP1 cells in bone marrow (BM) (**A**), lymph node areas (LN) (**B**), ovaries (Ov) (**C**), and spleen (Spl) (**D**) in untreated *vs* CB-NK treated mice. **E**: representative plot of the phenotype of CB-NK detected in CB-NK treated mice. **F** to **I**: Comparison analysis in all the mice of MFI values for NKG2D in ARP1 cells from plots corresponding to **A**, **B**, **C** and **D**. **J**: Correlation analysis for MFI for NKG2D in LN areas with the total luminescence coming from ARP1 cells in mice treated with CB-NK. Correlation coefficient (R) and p values are shown.



Supplementary Figure 2: NK from MM patients (MM-NK) are less cytotoxic than CB-NK and NKG2D and NKP30 don't have a relevant role in the MM-NK cytotoxicity *vs* MM cells. A: Cytotoxicity assay of both CB-NK and MM-NK as effectors *vs* ARP1 MM cells. **B**: MM-NK cytotoxicity reduction *vs* ARP1 MM cells after blocking NKG2D and NKP30 (MM-NK+NKG2D +NKP30) in NK-MM. **C**: Confocal fluorescence images of MM-NK (in green with bodipy) *vs* ARP1 MM cells (in blue with CMAC). Actin is shown in red. Arrows indicate some transfer of contents between MM-NK and ARP1 MM cells. * indicates $p \leq 0.05$.



Supplementary Figure 3: CB-NK induce cell death in MM cells by a mechanism which involves lipid transfer, is Granzyme-B and Caspase-3 independent cell death and involves lysosomal cell death. A: CB-NK cytotoxicity reduction in MM cell lines (U266, RPMI and KMM1) after incubating CB-NK with U18666A (NK+U18666A) for 2 hours. **B**: Mean±SEM values of CB-NK degranulation (CD107a expression) after 4 hours of incubation with K562 or MM cells (n=3). P values represent comparison of K562 *vs* MM cells. **C**: CB-NK cytotoxicity reduction after inhibiting GrB in CB-NK and Caspase-3 (GrB Casp3) in target MM cells. **D**: Mean±SEM values of Rab7 levels in MM cells before and after co-culture with CB-NK for 40 minutes. **E**: CB-NK cytotoxicity reduction after inhibiting cysteine cathepsins (with E64) in target cells (Target cell+E64). **F**: Mean±SEM values of Rab7, lysosomes (Lys: Lyso-tracker), and ROS levels in primary CD138+MM cells before and after co-culture with CB-NK for 40 minutes. Values in **D** and **F** were determined by confocal fluorescence microscopy after labeling MM cells in blue (CMAC) and CB-NK in green (Bodipy). * indicates $p \leq 0.05$.



Supplementary Figure 4: Cytotoxicity of peripheral blood NK (PB-NK) in healthy individuals is different from CB-NK cytotoxicity. A: PB-NK cytotoxicity reduction *vs* ARP1 MM cells after incubating PB-NK with U18666A for 2 hours (PB-NK+U18666A). **B**: PB-NK cytotoxicity reduction after inhibiting GrB in PB-NK and Caspase-3 in target K562 and ARP1 cells (PB-NK+GrB+Caspase3). **C**: PB-NK cytotoxicity reduction after inhibiting cysteine cathepsins in target K562 and ARP1 cells (PB-NK+E64) with E64 previous to the assay.