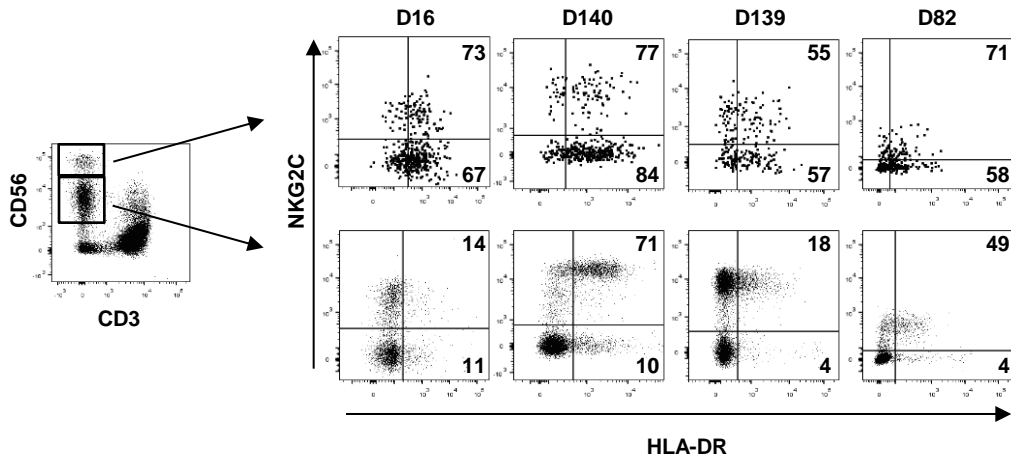
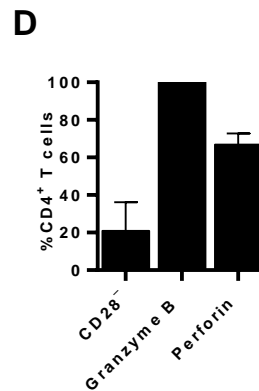
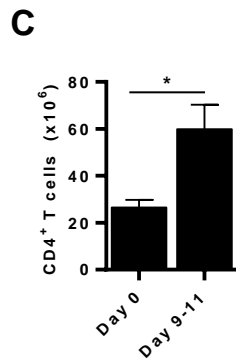
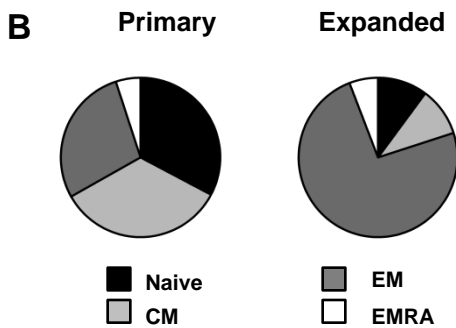
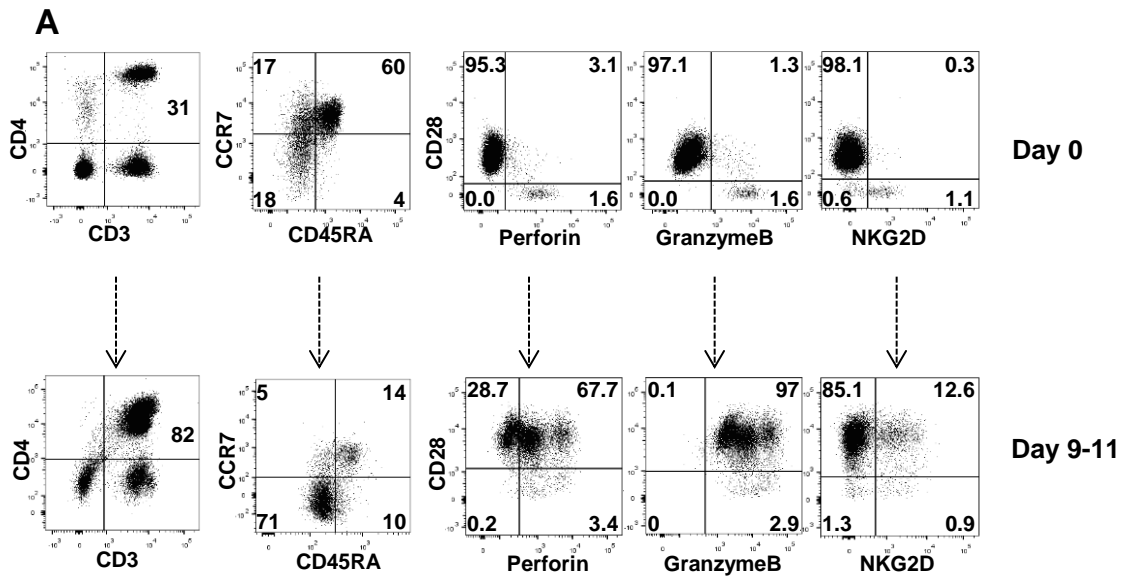


Supplementary figure 1: Differential expression of genes involved in antigen presentation by MHC class II in adaptive NKG2C+ NK cells. Publicly available gene expression data was obtained from NIH GEO Accession GSE66564 (24) and GSE66124 (25). Already normalized data was log₂ transformed, linear model was designed using R limma package and a moderated t-test between the two population groups was applied for paired-wise comparison using eBayes function. A volcano plot of the modelled data was generated using the ggplot2 package.

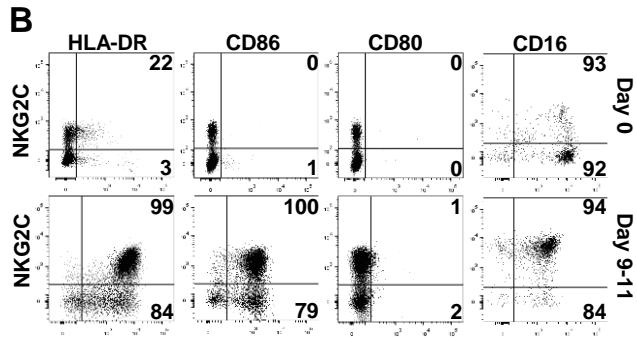
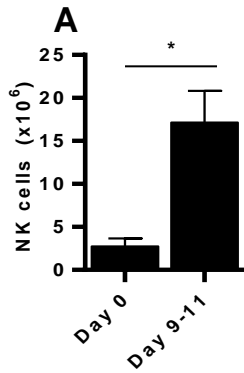
A) Re-analysis of the available microarray data published in Schlums et al. Immunity. 2015. Volcano plot showing fold-change of gene expression in NKG2C+ CD57^{bright} compared to NKG2A+ CD57⁻ CD56^{dim} NK cells. Blue horizontal line indicates a p-value of 0.05 and selected genes are labeled. **B)** Table extracted from the gene expression microarray analysis data published by Lee et al. Immunity. 2015. comparing sorted NKG2C+ versus NKG2C⁻ NK cells from a donor displaying expansions of adaptive NK cells.



Supplementary figure 2: NKG2C and HLA-DR co-expression in CD56^{bright} and CD56^{dim} NK cells. Representative dot plots of NKG2C and HLA-DR expression in circulating CD56^{bright} and CD56^{dim} NK cells from seropositive individuals with adaptive NKG2C+ NK cell expansions. Inset numbers indicate the percentage of HLA-DR+ cells in NKG2C+ and NKG2C- subpopulations.



Supplementary Figure 3. Cytotoxic CD4⁺ T cells expand upon PBMC co-culture with HCMV. CD4⁺ T cells were expanded by co-culturing PBMC from seropositive donors with HCMV particles (MOI = 0.3) for 9-11 days with 25 U/ml IL-2. **A)** Dot plots showing CD45RA, CCR7 and CD28 expression versus perforin, granzyme B and NKG2D in CD4⁺ T cells prior and after stimulation with HCMV. Data correspond to a representative expansion. **B)** Pie charts showing the distribution of T cell subpopulations based on CCR7 and CD45RA expression prior and after expansion (mean, n=4). **C)** Average CD4⁺ T cell numbers prior and after expansion (mean+SEM, n=6). **D)** Frequency of CD28⁻, perforin⁺ and granzyme B⁺ CD4⁺ T cells after expansion (mean+SEM, n=4).



Supplementary Figure 4. NKG2C⁺ HLA-DR⁺ NK cell expansion with the HLA-E⁺ 721.221-AEH cell line. PBMC were cultured with irradiated 721.221-AEH lymphoblastoid cells for 9-11 days. **A)** Average NK cell numbers obtained upon expansion (mean+SEM, n=4). **B)** Dot plots displaying HLA-DR, CD86, CD80, CD16 and NKG2C in NK cells at days 0 and 9-11 (*p < 0.05).

| Donor | HLA-DRB1-1 | HLA-DRB1-2 | HLA-DQB1-1 | HLA-DQB1-2 | HLA-DPB1-1 | HLA-DPB1-2 | %TNF α + IFN γ + NK | %TNF α + IFN γ + DC |
|-------------|------------|------------|------------|------------|------------|------------|--------------------------------------|--------------------------------------|
| D16 | 11:04 | | 03:01 | | 02:01 | 04:02 | 0.23 | 0.6 |
| D28 | 07:01 | | 02:02 | 03:03 | 04:01 | 13:01 | 0.061 | 0.45 |
| D67 | 07:01 | 13:02 | 02:02 | 06:04 | 01:01 | 02:01 | 0.43 | 1.22 |
| D117 | 07:01 | 11:01 | 02:02 | 03:01 | 04:01 | | 0.32 | 2.42 |
| D104 | 03:01 | 07:01 | 02:01 | 02:02 | 04:01 | 04:02 | 0.744 | |
| D82 | 03:01 | 08:02 | 02:01 | 04:02 | 04:01 | 02:01 | 0.35 | 1.48 |

Supplementary Table I. HLA class II genotype in individuals displaying expansions of HLA-DR+NKG2C+ adaptive NK cells. Last two columns indicate the percentage of CD4+ T cells producing TNF α and IFN γ in antigen-presentation assays using NK cells or DC as APCs.