**Supplemental Information**

**Supplemental Figures**

Supplemental Figure 1. A proposed ribbon model of HCW9201 heteromeric cytokine fusion created in PyMOL

Supplemental Figure 2. IL-15 signaling pathway molecules pAKT and pERK show no change in phosphorylation from baseline

Supplemental Figure 3. Activation schema, HFPC dose response curves, and CD16, CD107a, and TNF summary data.

Supplemental Figure 4 RNA sequencing data comparing 12/15/18, HCW9201, and HCW9207.

Supplemental Figure 5. Methylation status of individual CpG sites within the IFN- CNS-1 region from two human donors following short-term (overnight) or long term (14 days) activation and differentiation.

Supplemental Figure 6. 12/15/18 or HCW9201 activation resulted in increased cellular metabolism that was inhibited by Rapamycin (Rapa).

Supplemental Figure 7. ADCC on Daudi and Raji cell lines was increased with both 12/15/18 and HCW9201 activation equivalently compared to low dose IL-15.

Supplemental Figure 8. Bioluminescence of K562 bearing NSG mice treated with control and activated NK cells, and NK cell/NKG2A flow cytometry data for in vivo persistence assay.

**Supplemental Tables (Excel)**

Supplemental Table 1. Antibodies used for FACs

Supplemental Table 2. Antibodies used for CyTOF

Supplemental Table 3. HCW9201 GMP protein Characteristics

Supplemental Table 4. Activation Induced Transcriptomic Changes Naïve, LD IL-15 *vs.* 12/15/18, HCW9201, and HCW9207 (Excel spreadsheet).

Supplemental Table 5. ML transcriptomic differences LD IL-15 *vs.* 12/15/18 and HCW9201 and HCW9207(Excel spreadsheet).