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The nuclear factor-κ B inhibitor SN50 enhances the efficacy of B-cell maturation antigen-targeted chimeric antigen receptor T-cell therapy

Jinlan Long[1*], Shufeng Xie[2*], Wenjie Zhang[1*], Weiyu Dou[3], Yixin Wang[2], Ruiheng Wang[2], Han Liu[2#], Zhenshu Xu[1#]

1, Fujian Institute of Hematology, Fujian Provincial Key Laboratory of Hematology, Fujian Medical University Union Hospital, Fuzhou, China

2, Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and School of Life Sciences and Biotechnology, Shanghai, China

3, Emergency Department, Chinese PLA Southern Theater Command General Hospital, Guangzhou, China

*JLL, SFX, and WJZ contributed equally as co-first authors.

#ZSX and HL contributed equally as co-senior authors.

Correspondence:

Zhenshu Xu: xuzs@fjmu.edu.cn

Han Liu: liuhan68@sjtu.edu.cn

Jinlan Long: longjinlan2023@163.com

Disclosures

No conflicts of interest to disclose.

Contributions

ZSX and HL designed the study and contributed equally as co-senior authors. JLL, SFX, and WJZ contributed equally as co-first authors; they drafted the manuscript and prepared the figures. JLL and YXW performed the experiments. WYD and RHW participated in statistical analyses and data interpretation. All authors participated in the process of drafting and revising the manuscript. All the authors have read and approved the final manuscript.

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Not applicable in this section.

Data-sharing statement

For original data, please contact the authors for correspondence.

To the Editor,

Multiple myeloma (MM) is the second most common hematologic malignancy in high-income countries. Although the prognosis of MM has been significantly improved with the use of proteasome inhibitors, immunomodulators, monoclonal antibodies, and stem cell transplantation, disease progression or relapse is still an inevitable reality(1). The introduction of chimeric antigen receptor (CAR) T-cell therapy marks a significant breakthrough in the field of cancer treatment. B-cell maturation antigen (BCMA) is a member of the tumor necrosis factor receptor superfamily. It is specifically expressed at high levels in both normal and malignant plasma cells, making it an ideal target antigen for novel immunotherapies in MM(2). BCMA CAR T-cells have been proven to be highly effective in treating relapsed or refractory multiple myeloma. However, some patients still experience relapse(3), highlighting the urgent need for measures to enhance the efficacy of BCMA CAR T-cell therapy. This study investigates the cytotoxic efficacy of BCMA CAR T-cell therapies, comparing two monoepitopic BCMA CAR T-cells (353T and 917T) and a biepitopic BCMA CAR T-cell (353/917T). Our results demonstrate that the biepitopic BCMA CAR T-cell exhibits superior cytotoxic effects against MM cell lines compared to its monoepitopic counterparts. We observed that the differential activation levels of the nuclear factor-kappa B (NF-κB) pathway contribute to the variations in BCMA CAR T-cell efficacy, with 353T showing the highest activation, followed by 917T, and 353/917T the least. The overactivation of the NF-κB pathway promotes the survival and resistance of MM cells. We further explored the combination effect of BCMA CAR T-cells with the NF-κB pathway inhibitor SN50, finding that this combination enhances the cytotoxic effects of BCMA CAR T-cells in vitro and reduces tumor growth in a non-obese diabetic/severe combined immunodeficiency disease mouse model. These findings suggest that SN50 can enhance the efficacy of BCMA CAR T-cell therapy.

Cilta-cel is a CAR T-cell therapy product that includes two tandem nanobodies

targeting BCMA. Its unique biepitopic BCMA CAR structure has demonstrated exceptional therapeutic efficacy in clinical practice(4-6). In this study, we constructed two monoepitopic BCMA CARs (named 353 and 917) and one biepitopic BCMA CAR (named 353/917) based on the structure of Cilta-cel (Fig. 1A). All constructs were efficiently transduced into primary human activated T-cells, resulting in detectable CAR expression, as confirmed by flow cytometry (Fig. 1B). Our aim was to compare the killing efficacy of these two types of CAR T-cells and investigate the reasons behind any observed differences. This would enable us to develop targeted combination therapy strategies to further enhance the clinical efficacy of BCMA CAR T-cell in treating MM.

First, we selected the MM.1S, ARP-1, and ARD cell lines as target cells for in vitro cytotoxicity validation. Co-cultures of 353T, 917T, and 353/917T with target cells were conducted at an effector-to-target (E:T) ratio of 1:5 for 16 hours. Compared to control T-cells, all three BCMA CAR T-cells exhibited specific cytotoxic effects against MM cells. Among them, 353/917T showed the strongest killing effect on MM cell lines, followed by 917T, and 353T demonstrated the weakest effect ($P<0.05$, $n=3$) (Fig. 1C).

Next, we explored whether the differences in killing efficacy between 353/917T, 353T, and 917T are due to variations in the internal effects induced within MM cells following their interaction with these three types of CAR T-cells. The activation of BCMA downstream pathways can promote the proliferation and survival of MM cells, and it can also contribute to the formation of an immunosuppressive microenvironment (7-9). One of the main pathways downstream of BCMA is the NF-κB pathway. Overactivation of the NF-κB pathway can lead to abnormal survival and enhanced anti-apoptotic mechanisms in MM cells, thereby promoting the growth and survival of MM cells(10). The activation of the NF-κB pathway in MM cells during interactions between BCMA-directed CAR T-cells and tumor cells has been reported(11). Therefore, we co-cultured 353T, 917T, and 353/917T with MM cell lines at an E:T ratio of 1:50 for 16 hours, sorted the MM cells by flow cytometry after co-culture (Fig. S1A), extracted the proteins from the MM cell lines, and performed

Western Blot experiments. It was found that the interaction between the three types of BCMA CAR T-cells and MM cells could all activate the NF-κB pathway in MM cells, with 353T showing the most significant activation, followed by 917T, and 353/917T being the least. NF-κB activation was associated with an increased expression of the anti-apoptotic protein BCL-2, which partially resisted the cytotoxic effects of BCMA CAR T-cells (Fig. 1D). Notably, cytokines such as TNF-α secreted by CAR T-cells are also known to activate the NF-κB pathway in MM cells(12). To further validate this finding, we treated MM cells with the supernatants collected from CAR T-cells/MM cells co-culture systems, which contain cytokines such as TNF-α and IFN-γ. In this setting, the supernatants did not induce NF-κB activation in MM cells (Fig. S1B), suggesting that NF-κB activation observed in our study primarily due to direct interaction between BCMA CAR T-cells and MM cells. However, we cannot exclude the possibility that specific cytokine conditions or higher cytokine concentrations in other contexts might influence NF-κB activation. These results highlight that NF-κB pathway activation supports the resistance of MM cells to BCMA CAR T-cell therapy and partially explains the differential killing effects observed among 353T, 917T, and 353/917T. This also indicates that the combination of BCMA CAR T-cells with NF-κB pathway inhibitors may be a potential therapeutic strategy to improve clinical outcomes for MM patients.

The NF-κB pathway inhibitor SN50 is a small molecule compound that serves as a cell-permeable NF-κB translocation inhibitor(13). First, we need to determine the concentration at which SN50 can inhibit the activation of the NF-κB pathway in MM cells. A proliferation inducing ligand (APRIL) binding to BCMA can promote B-cell proliferation and survival(14). We treated MM cells with APRIL recombinant protein to activate the NF-κB pathway as a positive control while simultaneously treating with different concentrations of SN50. Western Blot results indicated that SN50 effectively inhibited NF-κB pathway activation at 2 μM in MM.1S and ARP-1 cells, and at 3 μM in ARD cells (Fig. 2A). Given the critical role of the NF-κB pathway in CAR T-cell function, we next evaluated whether SN50 affects CAR T-cell function. we treated CAR T-cells with SN50 and demonstrated that SN50 at 2.5 μM, 5 μM, and

10 μM had no significant impact on the apoptosis ($P>0.05$, n=3) (Fig. S2A). At 2 μM, SN50 did not affect the differentiation phenotype or exhaustion of CAR T-cells ($P>0.05$, n=3) (Fig. S2B and S2C), but it significantly increased CD69 expression and cytokine secretion (including IL-2, TNF-α, IFN-γ, Granzyme B) in 353T cells ($P<0.05$, n=3). However, SN50 at 2 μM had no significant effect on CD69 expression or cytokine secretion in 917T or 353/917T cells ($P>0.05$, n=3) (Fig. S2D-H). These results demonstrate that SN50 at 2 μM does not impair CAR T-cell function. Next, we combined SN50 with these three types of BCMA CAR T-cells. The results showed that blocking the activation of the NF-κB pathway enhanced the cytotoxic effects of BCMA CAR T-cells on MM cells ($P<0.05$, n=3) (Fig. 2B). To further validate the specificity of NF-κB inhibition in enhancing the efficacy of CAR T-cells, we replicated the experiments using another NF-κB pathway inhibitor, IKKγ NBD inhibitory peptide TFA (IKK-NBD). Similar to SN50, IKK-NBD treatment enhanced the cytotoxic effects of BCMA CAR T-cells on MM cells ($P<0.05$, n=3) (Fig. S3A-C).

Finally, we evaluated the antitumor activity of combining SN50 with BCMA CAR T-cells in a non-obese diabetic/severe combined immunodeficiency disease mouse model. This study was conducted in accordance with the principles of the Declaration of Helsinki and relevant ethical guidelines for research involving human participants and animal studies. The research protocol was reviewed and approved by the Ethics Committee of Fujian Medical University Union Hospital on March 31, 2021 (approval file number: 2021KJT079). ARP-1 cells were subcutaneously implanted on day 0. BCMA CAR T-cells were injected on days 3 and 5, and SN50 was administered on days 3, 5, 7, 9, 11, 13, and 15 at a dose of 20 mg/kg (Fig. 2C). Compared to the control group, the SN50 group showed lower tumor weight ($P<0.05$, n=3) (Fig. 2D and 2E) and smaller tumor volume ($P<0.05$, n=3) (Fig. 2F), demonstrating that SN50 can enhance the efficacy of BCMA CAR T-cells in vivo.

In summary, our results indicate that the combination of the NF-κB pathway inhibitor SN50 with BCMA CAR T-cells can enhance the efficacy of MM treatment. This provides a scientific basis for further optimization of treatment strategies for MM patients and offers important references and insights for clinical practice and research.

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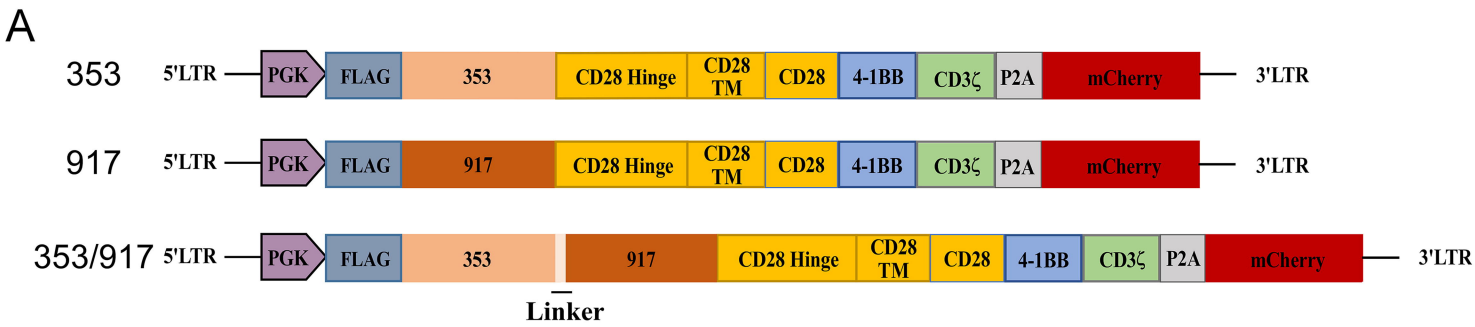
Figure 1. Comparison between monoepitopic and biepitopic B-cell maturation antigen-targeted chimeric antigen receptor T-cells. (A) Schematic diagram of chimeric antigen receptor (CAR) structure: 353, 917, 353/917. (B) Transduction efficiency of B-cell maturation antigen-targeted CARs in human T-cells. (C) 353T, 917T, and 353/917T cells were evaluated for their cytotoxic activity against multiple myeloma (MM) cell lines MM.1S, ARP-1, and ARD. The killing efficiency was assessed using flow cytometry. Target cells were co-cultured with T-cells or CAR T-cells at an effector-to-target ratio of 1:5 for 16 hours. Cell viability was determined by staining with annexin V and 7-AAD, and the percentage of dead target cells was quantified. Results are presented as mean ± SD from three independent experiments. Statistical significance was determined by t-test, with p-values indicated as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$, ns represent no significant. (D) MM cell lines were co-cultured with T, 353T, 917T, and 353/917T cells at an effector-to-target ratio of 1:50 for 16 hours. Following co-culture, MM cells were harvested and lysed for protein extraction. The activation of the nuclear factor-kappa B pathway was assessed by Western blot analysis.

Figure 2. Enhancement of B-cell maturation antigen-targeted chimeric antigen receptor T-cells cytotoxicity by the nuclear factor-κ B pathway inhibitor SN50. (A) Multiple myeloma (MM) cell lines (MM.1S, ARP-1 and ARD) were treated with a proliferation inducing ligand recombinant protein (400 ng/mL) to activate the nuclear factor-kappa B (NF-κB) pathway, serving as a positive control. Simultaneously, MM cells were incubated with the NF-κB pathway inhibitor SN50 at various concentrations (0, 1.0, 2.0, and 3.0 μM) for 16 hours. After treatment, protein extracts were prepared from the cells and subjected to Western blot analysis. (B) MM cell lines were co-cultured with T-cells or B-cell maturation antigen-targeted chimeric antigen receptor T-cells (353T, 917T, and 353/917T), in the presence of the NF-κB pathway inhibitor SN50. MM.1S and ARP-1 cells were treated with SN50 at a concentration of 2.0 μM, while ARD cells were treated with SN50 at a concentration of 3.0 μM. The effector-to-target ratio was 1:10, and co-cultures were maintained for

16 hours. The cytotoxic activity was assessed using flow cytometry by staining the cells with annexin V and 7-AAD, and the percentage of dead target cells was quantified. (C) Schematic representation of the in vivo study design in NOD-SCID mice. NOD-SCID female mice were injected subcutaneously with 1×10^6 ARP-1 cells into the right upper limb axilla on Day 0. On Days 3 and 5, the mice received intravenous injections of 2×10^6 T-cells or BCMA CAR T-cells via the tail vein. Additionally, mice were administered intraperitoneal injections of SN50 (20 mg/kg) or DPBS on Days 3, 5, 7, 9, 11, 13, and 15. (D) Subcutaneous tumors were excised from the right upper limb axilla on Day 16. (E) Tumor weights from each treatment group. (F) Tumor volumes from each treatment group. Tumor volumes were calculated using the following formula: length × width^2 × 0.5. Results are presented as mean ± SD from three independent experiments. Statistical significance was determined by t-test, with p-values indicated as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$, ns represent no significant.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PGK
FLAG
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CD3ζ
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917
5'LTR
PGK
FLAG
917
CD28 Hinge
CD28 TM
CD28
4-1BB
CD3ζ
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353/917
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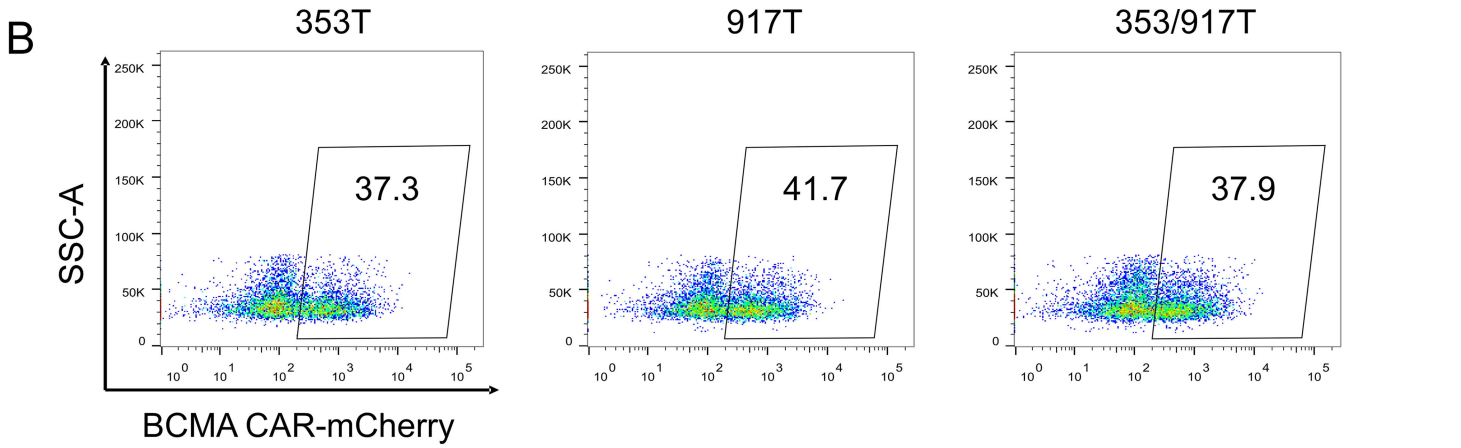
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353T
917T
353/917T
SSC-A
BCMA CAR-mCherry
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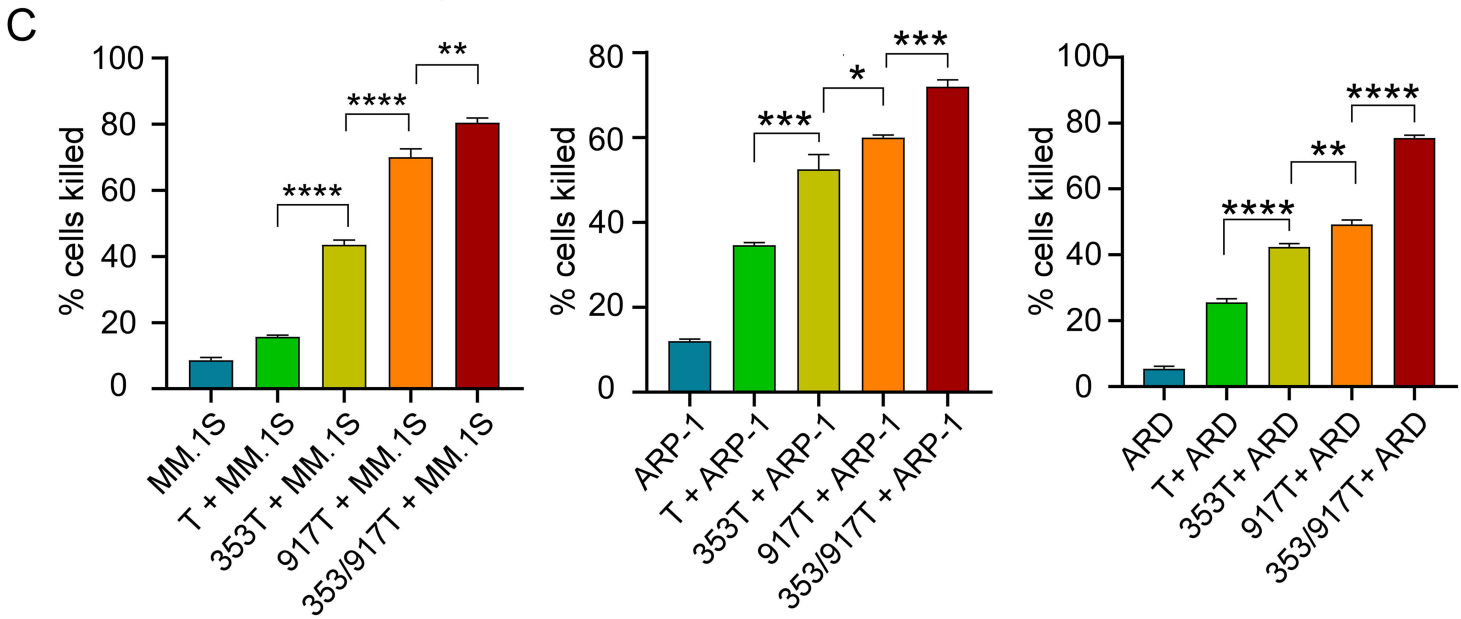
41.7
37.9


C
% cells killed
MM.1S
T + MM.1S
353T + MM.1S
917T + MM.1S
353/917T + MM.1S
ARP-1
T + ARP-1
353T + ARP-1
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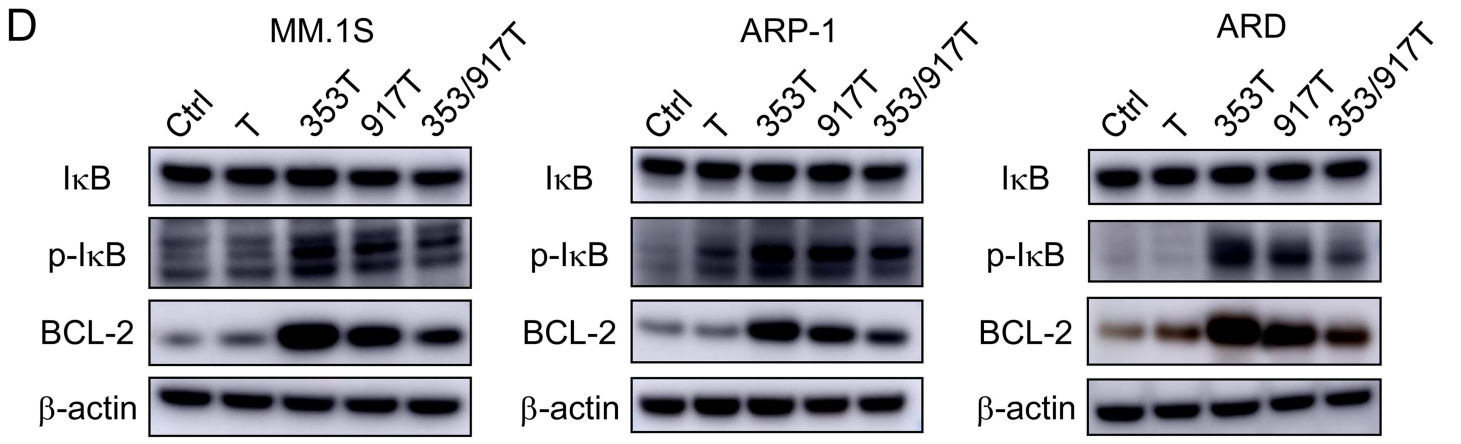
917T+ ARD
353/917T+ ARD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ARD
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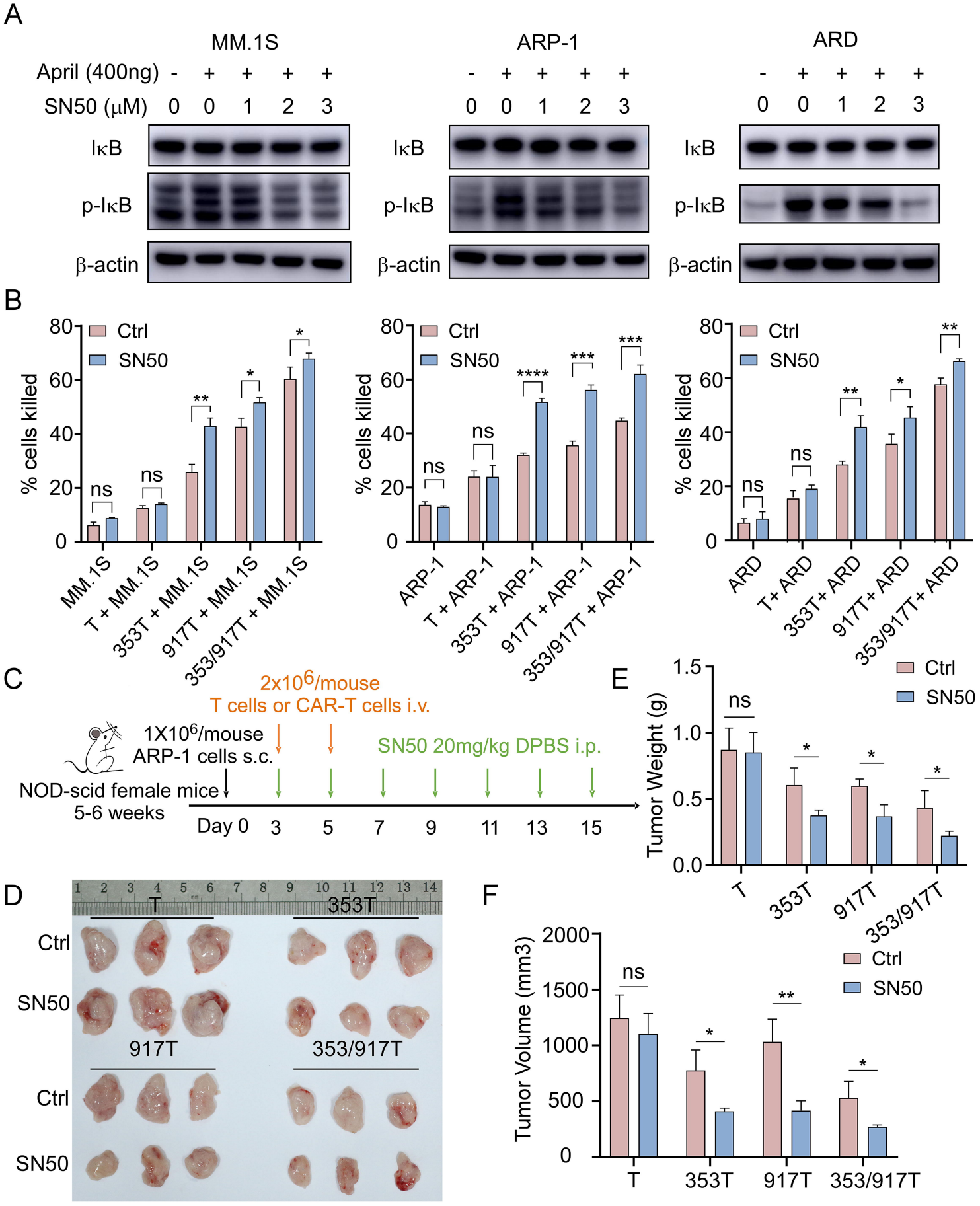
917T
353/917T
IκB
p-IκB
BCL-2
β-actin


A
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ARD
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SN50 (μM) 0 0 1 2 3
IκB
p-IκB
β-actin
B
Ctrl
SN50
% cells killed
ns
MM.1S
T + MM.1S
353T + MM.1S
917T + MM.1S
353/917T + MM.1S
ARP-1
T + ARP-1
353T + ARP-1
917T + ARP-1
353/917T + ARP-1
ARD
T+ ARD
353T+ ARD
917T+ ARD
353/917T+ ARD
C
2x10^6/mouse
T cells or CAR-T cells i.v.
1X10^6/mouse
ARP-1 cells s.c.
SN50 20mg/kg DPBS i.p.
NOD-scid female mice
5-6 weeks
Day 0 3 5 7 9 11 13 15
D
T
353T
Ctrl
SN50
917T
353/917T
E
Tumor Weight (g)
F
Tumor Volume (mm3)

Figure S1. Sorting patterns of B-cell maturation antigen-targeted chimeric antigen receptor T-cells and MM cell lines co-culture and nuclear factor-κ B pathway activation after treatment with co-culture supernatants. (A) Multiple myeloma (MM) cells were labeled with CellTrace Violet dye before co-culturing and co-cultured with T-cells or B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cells (353T, 917T, 353/917T) at an effector-to-target ratio of 1:50 for 16 hours. MM cells were sorted using a flow cytometer based on the BV421 channel, and the purity of the sorted MM cells was verified by flow cytometry analysis. (B) MM cell lines were co-cultured with T-cells or BCMA CAR T-cells (353T, 917T, 353/917T) at an effector-to-target ratio of 1:50 for 16 hours. Supernatants were collected from these co-cultures and used to treat fresh MM cell lines for 16 hours. After treatment, proteins were extracted from MM cells and subjected to Western Blot analysis to assess the activation of the nuclear factor-kappa B pathway.

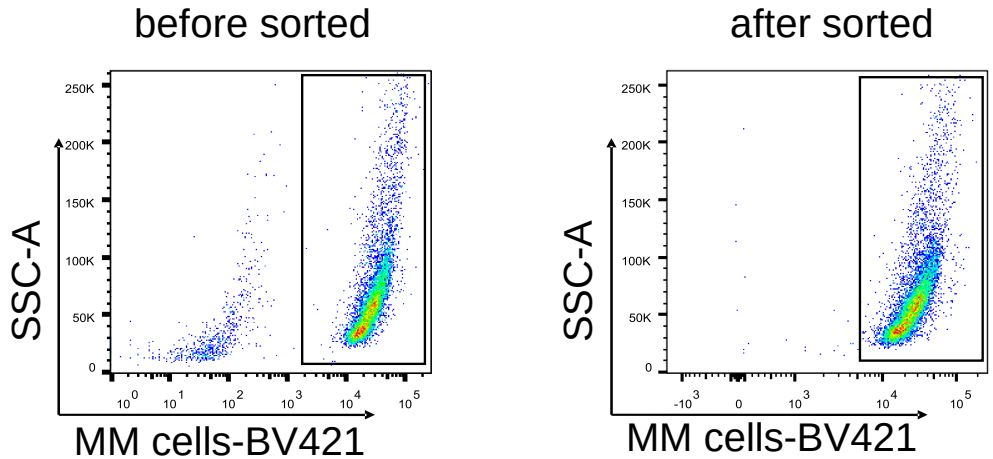
Figure S2. **Effects of SN50 on apoptosis, memory phenotype，exhaustion, activation and cytokine secretion in T-cells and B-cell maturation antigen-targeted chimeric antigen receptor T-cells.** (A) Apoptosis in T-cells and B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T-cells (353T, 917T, 353/917T) treated with DPBS or SN50 at concentrations of 0, 2.5, 5.0, and 10 μM for 16 hours. (B) Memory phenotype changes in T-cells and BCMA CAR T-cells (353T, 917T, 353/917T) after 72 hours of co-culture with MM.1S cells at an effector-to-target (E:T) ratio of 1:1 in the presence of 2.0 μM SN50 or DPBS, including naïve T-cells, central memory T-cells, effector memory T-cells, and terminally differentiated effector memory T-cells. (C) LAG-3 expression on T-cells and BCMA CAR T-cells (353T, 917T, 353/917T) after 48 hours of co-culture with MM.1S cells at an E:T ratio of 1:1 in the presence of 2.0 μM SN50 or DPBS. (D) CD69 expression on T-cells and BCMA CAR T-cells (353T, 917T, 353/917T) after 16 hours of co-culture with MM.1S cells at an E:T ratio of 1:1 in the presence of 2 μM SN50 or DPBS. (E-H) Cytokine secretion by BCMA CAR T-cells (353T, 917T,

353/917T) after 16 hours of co-culture with MM.1S cells at an E:T ratio of 1:10 in the presence of 2.0 μM SN50 or DPBS. The supernatants were collected for detection of cytokines by LEGENDplex™ Human CD8/NK Panel. Data are presented as mean ± SD from three independent experiments. Statistical significance was determined by t-test, with p-values indicated as follows: **p < 0.01, ****p < 0.0001, ns represent no significant.

Figure S3. Enhancement of B-cell maturation antigen-targeted chimeric antigen receptor T-cells cytotoxicity by the nuclear factor-κ B pathway inhibitor IKKγ NBD inhibitory peptide TFA. (A-C) Multiple myeloma cell lines MM.1S (A), ARP-1 (B), and ARD (C) were co-cultured with T-cells or B-cell maturation antigen-targeted chimeric antigen receptor T-cells (353T, 917T, and 353/917T) at an effector-to-target ratio of 1:10 for 16 hours in the presence of 50 nM IKKγ NBD inhibitory peptide TFA. The cytotoxic activity was assessed using flow cytometry by staining the cells with annexin V and 7-AAD, and the percentage of dead target cells was quantified. Data are presented as mean ± SD from three independent experiments. Statistical significance was determined by t-test, with p-values indicated as follows: *p < 0.05, **p < 0.01, ns represent no significant.

Figure S1

A


before sorted
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SSC-A
MM cells-BV421
250K
200K
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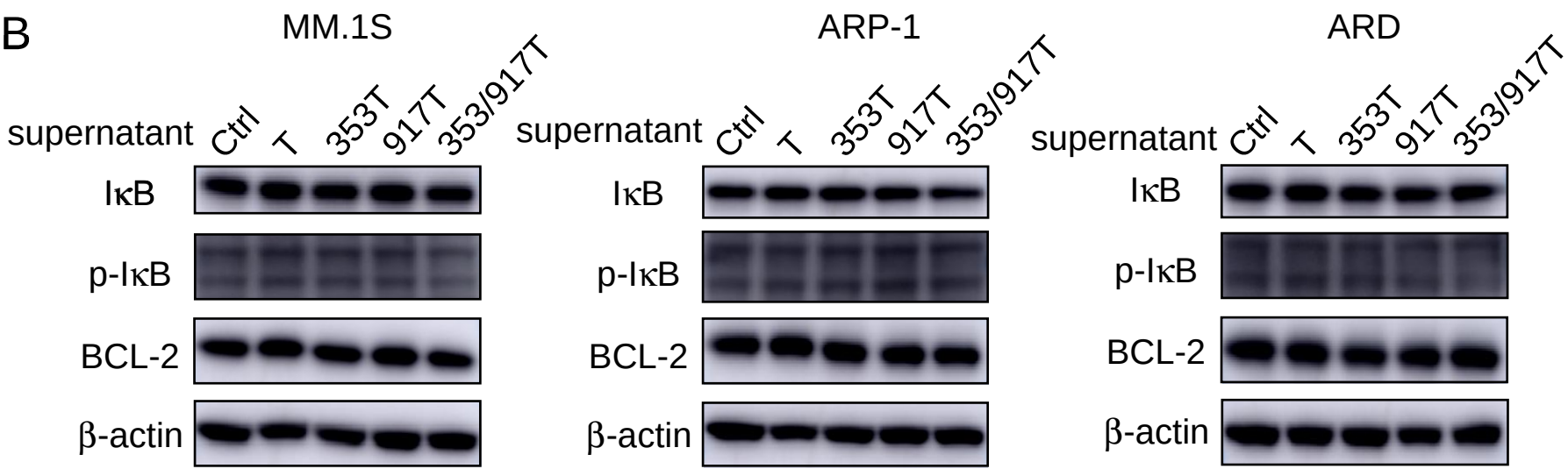
B


MM.1S
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IκB
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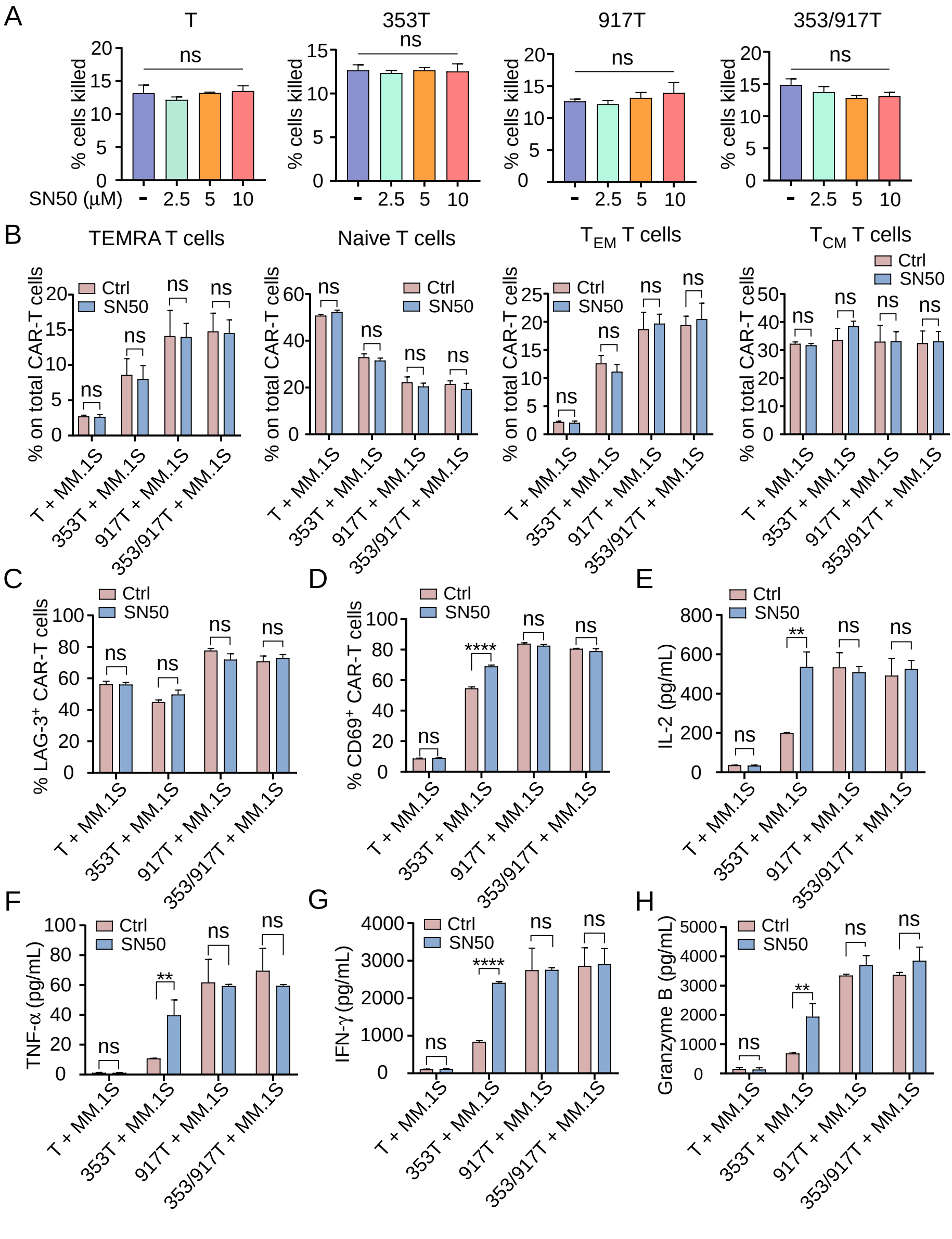
β-actin

Figure S2


A
T
353T
917T
353/917T
% cells killed
ns
SN50 (μM)
- 2.5 5 10
B
TEMRA T cells
Naive T cells
T_EM T cells
T_CM T cells
% on total CAR-T cells
Ctrl
SN50
T + MM.1S
353T + MM.1S
917T + MM.1S
353/917T + MM.1S
C
% LAG-3+ CAR-T cells
D
% CD69+ CAR-T cells
****
E
IL-2 (pg/mL)
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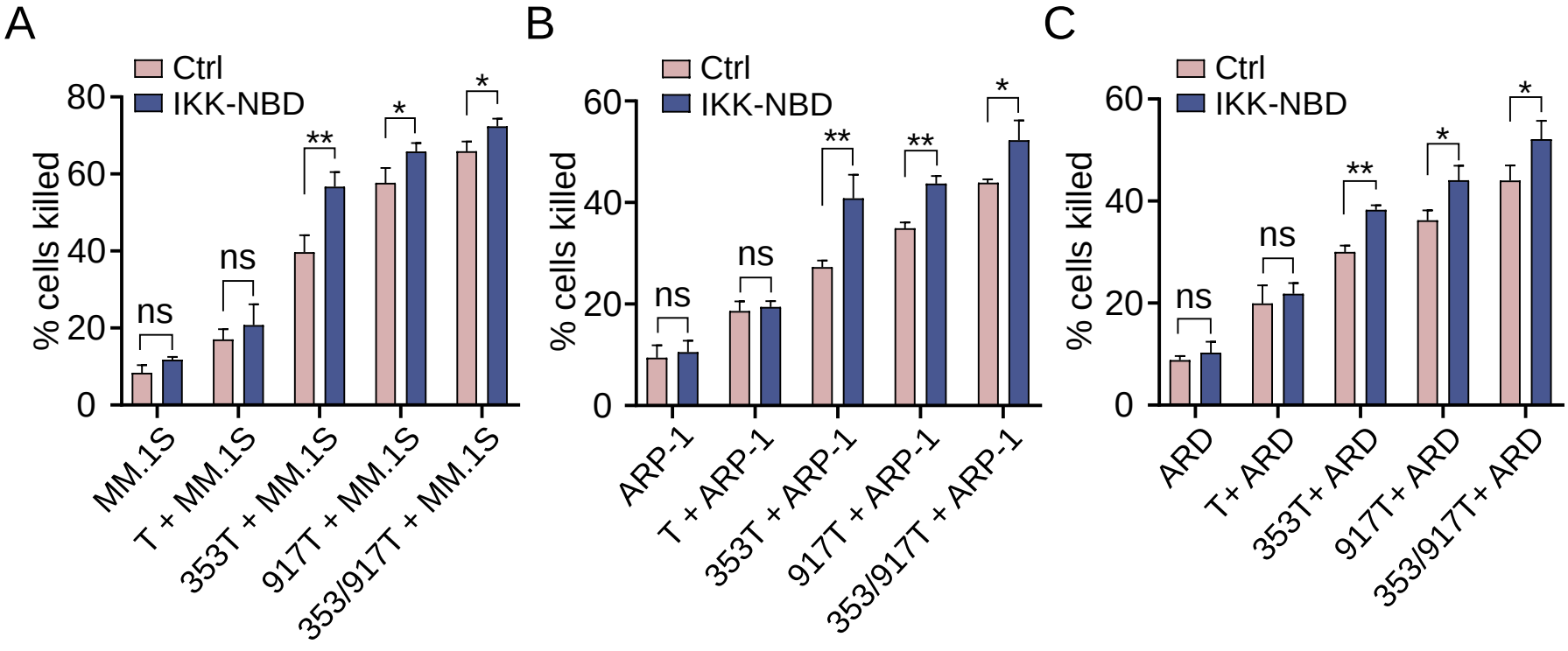
TNF-α (pg/mL)
G
IFN-γ (pg/mL)
H
Granzyme B (pg/mL)

Figure S3


A
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IKK-NBD
% cells killed
0
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80
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MM.1S
T + MM.1S
353T + MM.1S
917T + MM.1S
353/917T + MM.1S
B
Ctrl
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% cells killed
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ARP-1
T + ARP-1
353T + ARP-1
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353/917T + ARP-1
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