INB-619 - A Novel Gamma-Delta (γδ) T cell Engager to Target B cells in Autoimmune Diseases

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Introduction

T cell engagers (TCEs) redirect T cells to bind target cells by linking T cells with target-associated antigens (TAAs) expressed on cells responsible for disease pathology. Most TCEs to-date target alpha-beta (αβ) T cells, binding both an antigen such as CD20 on the cell of interest and CD3 on the T cell. This approach is complex, requiring CD3 de-tuning due to the risks of T cell exhaustion and severe, potentially life-threatening complications such as cytokine release syndrome (CRS) which limits dose. Gamma-delta (γδ) T cells offer a promising alternative due to their innate, MHC-independent cell killing and low production of CRS-associated cytokines. INB-619, a novel CD19 pan-γδ TCE, drives robust activation and expansion of both Vδ1+ and Vδ2+ γδ T cells and induces complete depletion of B cells. These unique properties potentially solve the challenge of current B cell depleting TCE's, like *Blinatumomab* (CD19 - BLI) and *Mosunetuzumab* (CD20 - MOS) where dysfunctional immune cells, tissue-resident B cells and potential toxicities may limit the depth of B cell depletion. These findings position INB-619 as a promising therapeutic candidate for autoimmune indications.

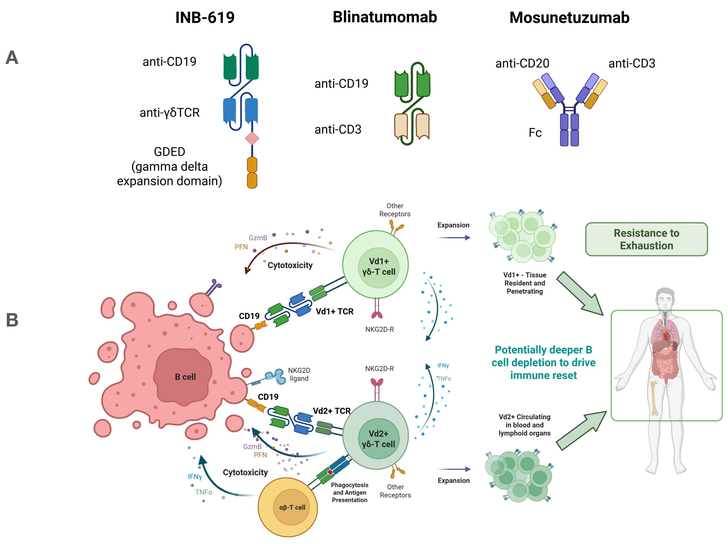

Fig. 1. INB-619 is a pan-γδ T-cell engager targeting CD19⁺ B cells.

(A) Schematic representation of INB-619, Blinatumomab (BLI) and Mosunetuzumab (MOS). (B) INB-619 targets CD19⁺ B cells and induces robust activation and expansion of pan-γδ T cells, including both the Vδ1+ and Vδ2+ subsets.

INB-619 induces γδ T cytotoxicity against CD19+ target cells

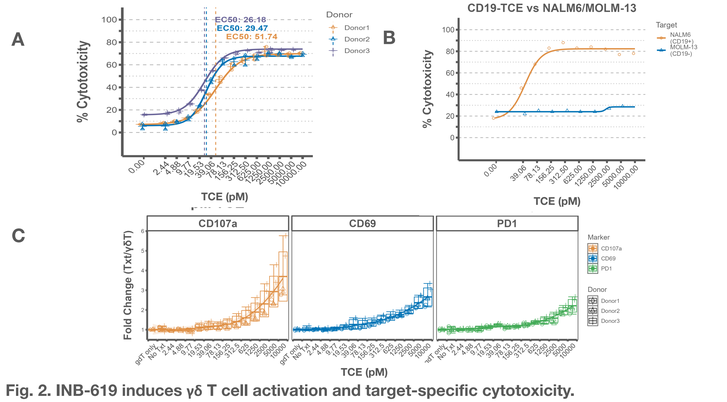

Fig. 2. INB-619 induces γδ T cell activation and target-specific cytotoxicity.

(A) INB-619 elicits dose-dependent γδ T cell–mediated killing of NALM-6 (CD19⁺) target cells. (B) Cytotoxicity is restricted to CD19⁺ target cells. (C) Expression of activation and degranulation markers (CD107a, CD69, PD-1) was quantified by flow cytometry.

INB-619 induces B cell depletion in healthy and SLE PBMCs

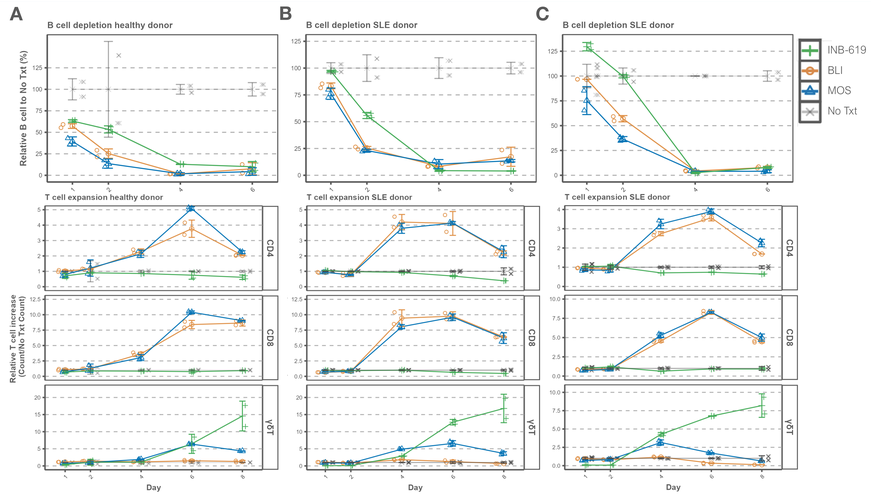

Fig. 3. B cell depletion, αβ and γδ T cell levels in healthy and SLE donor PBMCs treated with INB-619, BLI and MOS.

Comparative, time-course analysis from a healthy donor (A) and two SLE donors (B, C) were treated with BLI, MOS, or INB-619 and analyzed over an 8-day time course. B cell depletion and T cell expansion are shown through day 6, by which time B cells were fully depleted by INB-619, BLI and MOS. Expansion is shown as relative expansion of the CD4⁺ αβ T cells, CD8⁺ αβ T cells, and γδ T cells, which was quantified and normalized to untreated controls (No Txt).

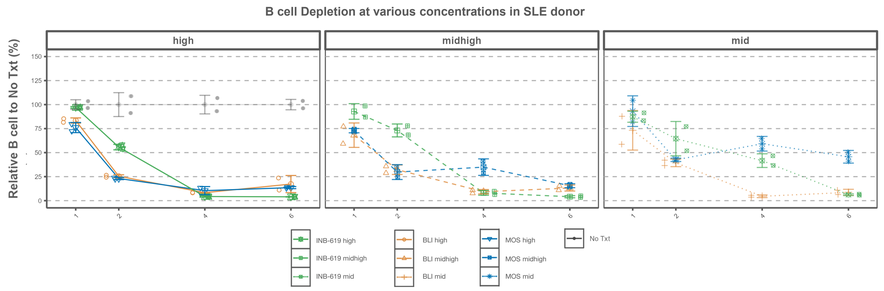

Fig. 4. Comparative, time-course analysis of B-cell depletion at varying concentrations of INB-619, BLI and MOS in SLE donor PBMCs.

Comparative, time-course analysis of B-cell depletion at varying concentrations of BLI, MOS, or INB-619 in PBMCs from healthy donors and SLE patients.

INB-619 induces robust expansion of γδ T cells

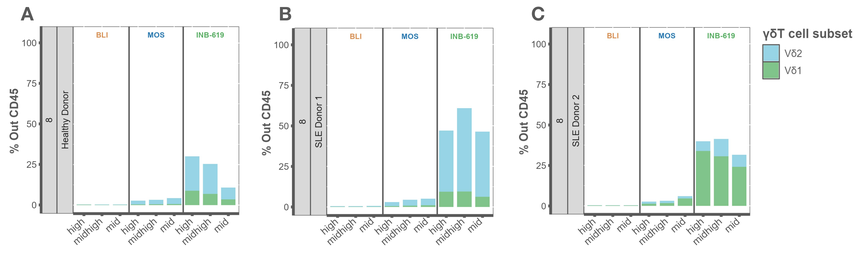

Fig 5. INB-619 induces dose-dependent expansion of Vδ1⁺ and Vδ2⁺ γδ T cells.

PBMCs from a healthy donor (A) and two SLE donors (B and C) were treated with BLI, MOS, or INB-619 for 8-days. Expansion of γδ T cells, including both Vδ1⁺ and Vδ2⁺ subsets, was quantified by flow cytometry.

T cell phenotypes induced by INB-619, BLI, and MOS

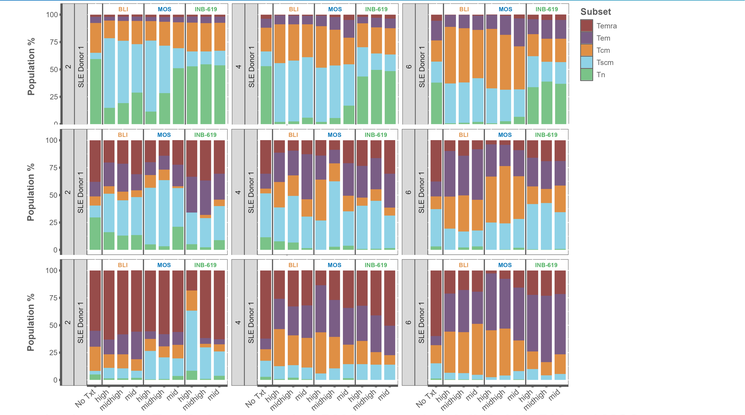

Fig. 6. Dynamic changes of T cell phenotypes in PBMCs treated with INB-619, BLI and MOS.

SLE donor PBMCs were treated with INB-619, BLI, or MOS at varying concentrations. Frequencies of effector/memory phenotypes in αβ T cells and Vδ1+ and Vδ2+ γδ T cells were quantified by flow cytometry on days 2, 4, and 6.

Comparative cytokine release by INB-619, BLI, and MOS

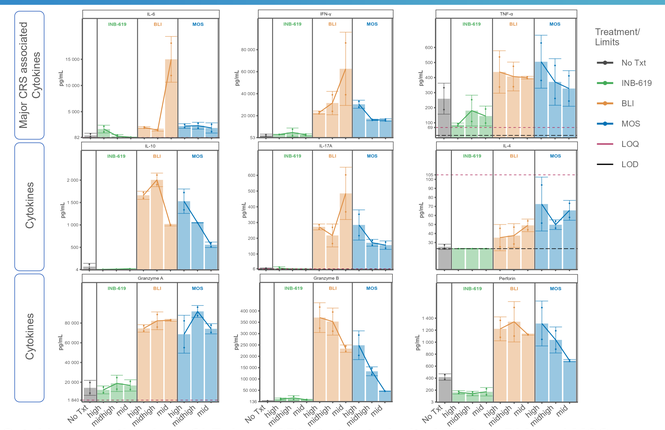

Fig. 7. Cytokine secretion from SLE donor PBMCs treated with INB-619, BLI, and MOS.

Cytokines were measured in culture supernatant from SLE donor PBMCs treated with varying concentrations of INB-619, Blinatumomab (BLI), or Mosunetuzumab (MOS) on day 4, following complete B cell elimination.

Conclusions

- INB-619 is a novel pan-γδ T cell engager that specifically functions to expand and activate γδ T cells to drive powerful dose-dependent target elimination.
- Robust expansion of both Vδ1+ and Vδ2+ γδ T cells drives the complete depletion of B cells from SLE donor PBMCs without CD4 or CD8 expansion, demonstrating precision activation that offers a powerful approach to treat B cell-mediated autoimmune diseases across multiple target organs and systems.
- INB-619 demonstrated complete depletion of B cells comparable to commercially available, clinical CD3-based bi-specific engagers with a more favorable cytokine release profile. Importantly, INB-619 exhibits minimal release of CRS associated cytokines including IL-6, IL-10, IL-4, and TNFa. Cytokine secretion at equivalent picomolar (pM) concentrations required for total B cell depletion was multiple times lower for INB-619
- INB-619 expanded γδ T cells and exhibited a robust depletion of its target with minimal release of CRS associated cytokines. This demonstrates a precise and potentially safer approach to TCE mediated cell targeting in autoimmune diseases with a larger therapeutic window, which could allow for higher dosing to achieve total B cell depletion and immune reset.