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Pharmacological activation of LRH-1/NR5A2 associates with IL-7R downregulation and immune cell remodeling in pediatric type 1 diabetes

Jaime M. Franco[1], Nadia Cobo-Vuilleumier[1], Francesc Mitjans[2], Maria Isabel García Sánchez[3], Maria Asunción Martínez-Brocca[4], Benoit R. Gauthier[1]

(1) Andalusian Center of Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucía, Seville, Spain.
(2) DiabetesCERO Foundation, Écija, Spain.
(3) Biobank of the Andalusian Public Health System, Node Hospital Virgen Macarena, Seville, Spain.
(4) Endocrinology and Nutrition department, Hospital Universitario Virgen Macarena, Seville, Spain.

cabimer — Andalusian Center for Molecular Biology and Regenerative Medicine
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Introduction

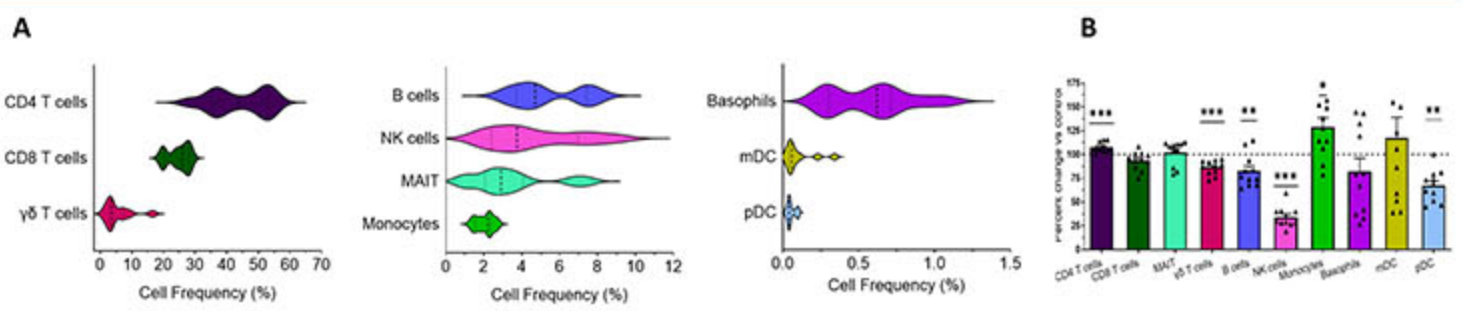
We previously demonstrated that agonistic activation of the nuclear receptor LRH-1/NR5A2 by the small molecule BL001 promotes a shift from a pro-inflammatory to an anti-inflammatory phenotype in professional antigen-presenting cells from adults with long-standing type 1 diabetes (T1D) [1]. However, similar immunological studies in pediatric populations have been limited, mainly due to constraints in blood volume collection. To overcome this limitation and to determine whether BL001 elicits comparable immunomodulatory effects in children with recent-onset T1D, we employed cytometry by time of flight (CyTOF). This high-dimensional, low-input technique enables comprehensive immune profiling using minimal sample volumes, thereby making it particularly suitable for pediatric studies.

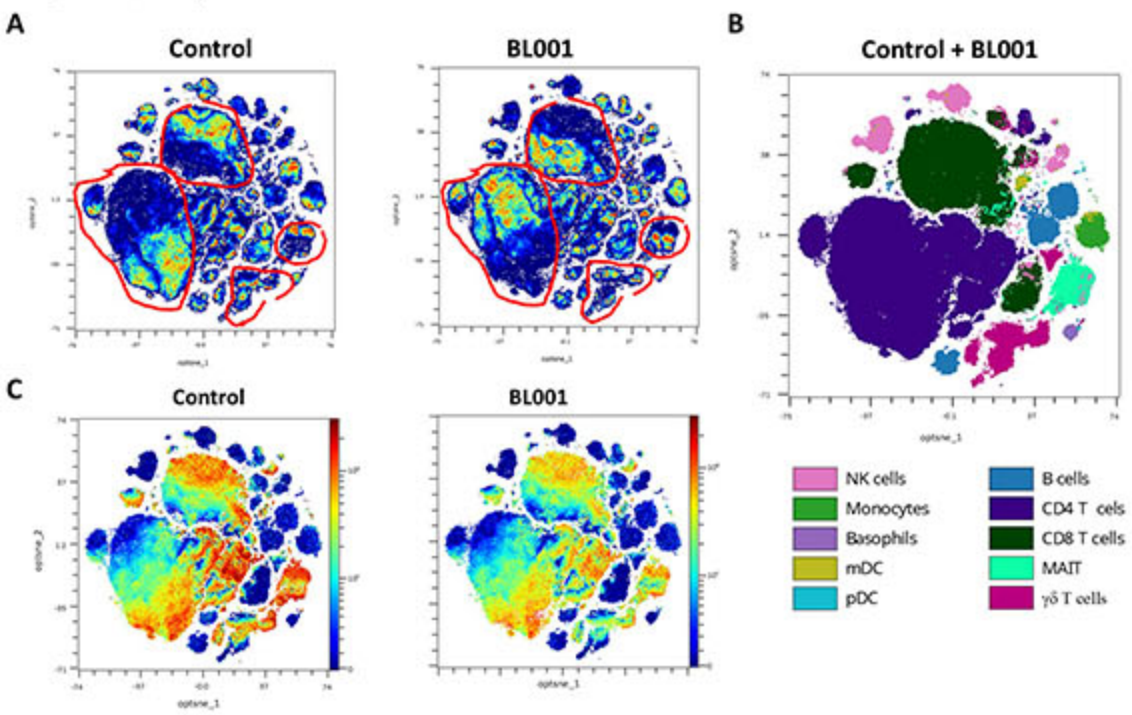
Methods

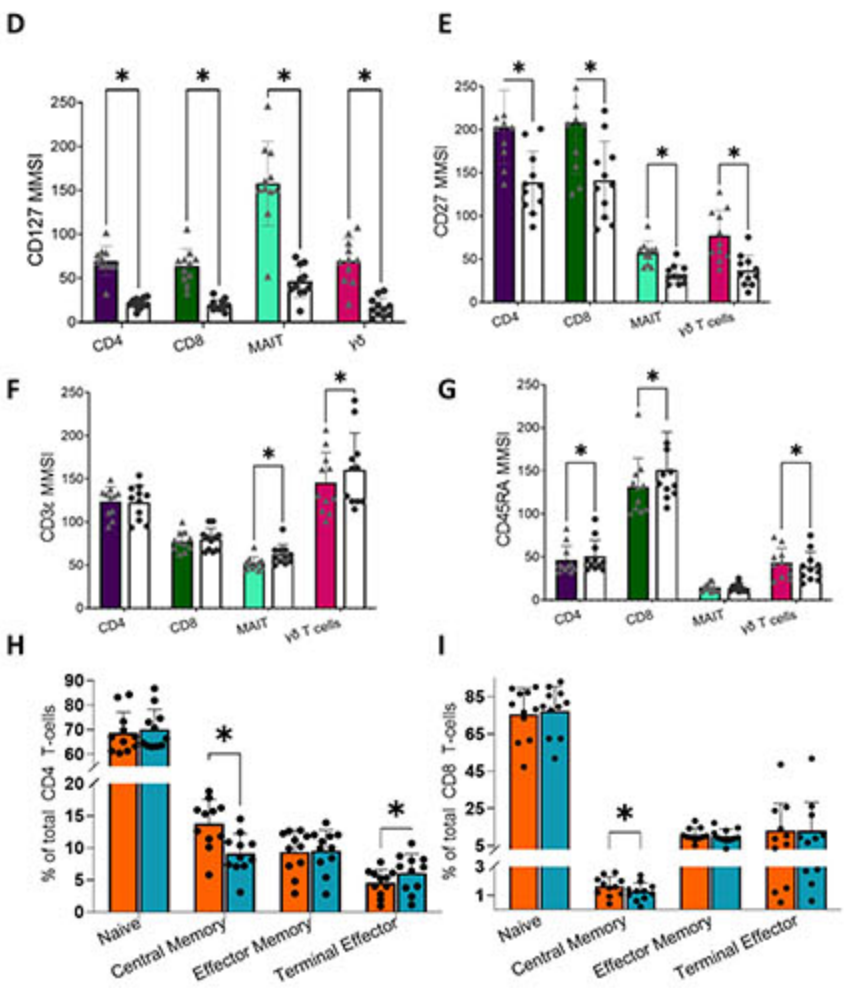
Children aged 9–12 years with T1D diagnosed within the previous <2 years were recruited in collaboration with the DiabetesCero Foundation. Peripheral blood (8 mL) was obtained via the Biobank of the Andalusian Public Health System at Hospital Universitario Virgen Macarena (HUVM). PBMCs were isolated and cultured for 72 hours under either control (DMSO) or LRH-1–activating (BL001, 10 µM) conditions. Subsequently, immune profiling was performed by CyTOF using the Maxpar Direct Immune Profiling Assay (MDIPA). For data interpretation, we applied optimized t-distributed stochastic neighbor embedding (opt-SNE) algorithm through the Omiq platform, enabling detailed visualization of immune dynamics.

Results

BL001 exposure led to a marked remodeling of immune cell composition, as compared with DMSO-treated controls. Baseline abundances of immune subpopulations after 72 h under control conditions are displayed in violin plots (**A**), whereas fold changes induced by BL001 treatment are summarized in (**B**). Overall, BL001 induced: i) a modest but significant increase in CD4+ T cells (53.3% ± 9.9 → 55.9% ± 9.1, Wilcoxon test; p=0.0010), ii) a reduction in γδ T cells (6.1% ± 5.4 → 5.0% ± 4.1, p=0.0010), and iii) a pronounced ~70% decrease in NK cells (4.7% ± 2.4 → 1.6% ± 1.1, p=0.0010). (Wilcoxon test; * p<0.05, ** p<0.01, ***p=0.001, n=11).







BL001 induces coordinated remodeling of T-cell phenotype characterized by CD127 downregulation and shifts in memory differentiation across T-cell subsets. opt-SNE projections revealed distinct shifts in cell distribution following BL001 treatment (highlighted regions in A). A color-coded reference map of major immune subpopulations is provided in (B). Among all evaluated markers, the most prominent BL001-associated change was the downregulation of the IL-7 receptor (IL-7R/CD127). This effect is illustrated by Z-axis intensity overlays on opt-SNE maps (C), and quantified as reduced metal mean signal intensity (MMSI) across CD4+, CD8+, MAIT, and γδ T-cell subsets (D). Furthermore, BL001 induced moderate decreases in CD27 (E) and CD28 co-stimulatory receptors (CD28 not shown), while CD45RA (F) and CD3 (G) expression exhibited mild but significant increases in CD4+ and CD8+ T cells. Notably, BL001 also caused a significant reduction specifically in central memory T-cell populations in both CD4+ and CD8+ compartments, suggesting a coordinated effect on memory differentiation. (Asterisks denote significant differences using the procedure of Benjamini, Krieger, and Yekutieli, with an FDR (Q) set at 1%. n=11).

Conclusions

Together, these findings demonstrate that LRH-1/NR5A2 activation by BL001 in PBMCs from children with recent-onset T1D induces broad and coordinated immune remodeling, characterized by:

- Substantial reductions in NK cells (~70%) and γδ T cells (~20%)
- A strong, widespread downregulation of IL-7R (CD127) across multiple T-cell subsets
- Mild but consistent decreases in CD27 and CD28 expression
- Preservation or upregulation of CD3e and CD45RA, supporting the specificity of BL001-driven modulation
- Altered balance of central memory T-cell subsets

Overall, this immune signature suggests that LRH-1 activation dampens IL-7–mediated survival pathways and reduces co-stimulatory capacity, thereby promoting immune de-escalation. Such modulation may help limit T-cell inflammatory potential in children with recent-onset T1D, thereby supporting β-cell mass preservation or recovery.

References

(1) Cobo-Vuilleumier, N. et al. Clin Transl Med 14, e70134 (2024). https://doi.org/10.1002/ctm2.70134

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