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A novel preclinical tool to unlock the potential of IL-18 in cancer immunotherapy: genO-hIL-18/hIL-18R mice

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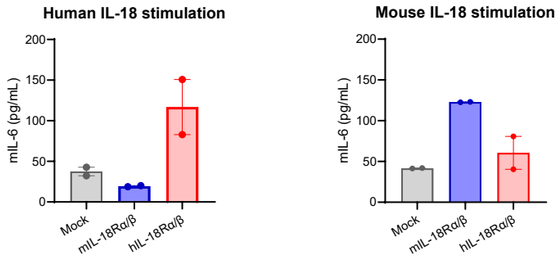
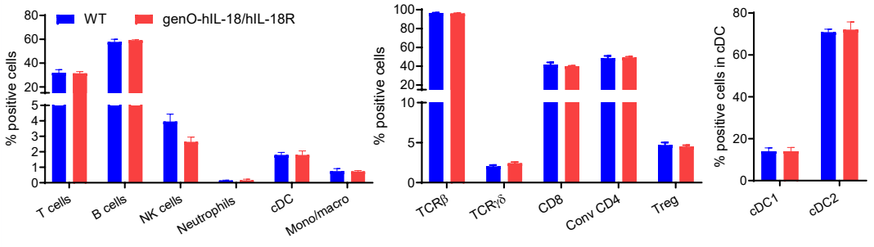
Background: Interleukin-18 (IL-18) has emerged as a promising immunomodulatory cytokine in immuno-oncology due to its ability to enhance both innate and adaptive immune responses. It promotes IFN-γ production by T and NK cells, thereby amplifying anti-tumor immunity, especially when combined with checkpoint inhibitors or engineered pro-drugs to resist natural inhibition by IL-18BP. Recent studies suggest that IL-18-based therapies may overcome resistance mechanism in "cold" tumors, making them responsive to immunotherapies[1]. Humanized mouse models expressing human IL-18R are essential to accurately assess efficacy and guide development of human-directed IL-18-based therapies. Therefore, we describe here a new IL-18/IL-18R double humanized mouse model to assess the efficacy of therapeutics targeting the IL-18/IL-18R axis.

1. Mouse IL-18 partially induces signaling through human IL-18Rα/β, requiring humanization of both IL-18 and IL-18Rα/β to maintain functional IL-18/IL-18R axis



B16F10 cells stably expressing mouse or human IL-18Rα/β were stimulated with recombinant mouse or human IL-18 (10 ng/mL) for 24 hours. Mouse IL-6 secretion in the supernatant was then assessed by ELISA.

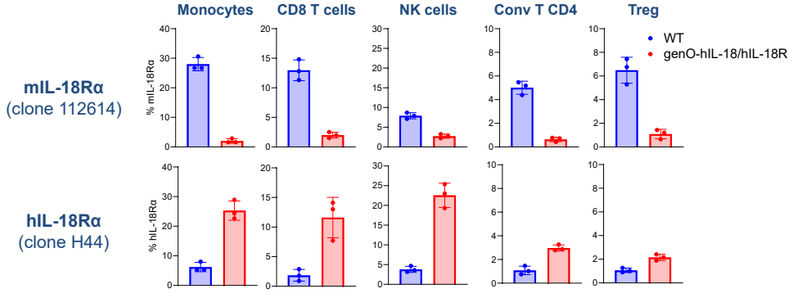
2. Humanization of both IL-18 and IL-18R does not alter immune cell distribution



Freshly isolated splenocytes, gated on live CD3⁺ CD19⁻ (T cells) and CD3⁻ CD19⁺ (B cells), in CD3⁻CD19⁻cells: NKp46⁺ (NK cells), CD317⁺ (pDC), Ly-6G⁺ (Neutrophils), Ly-6G⁻ CD11c⁺ MHCII⁺ (cDC) and Ly-6G⁻ Ly-6C⁺ CD11b⁺ (Monocytes/macrophages). T cell subsets gated on CD3⁺ TCRb⁺ TCRγδ⁻: CD4⁻ CD8⁺ (CD8), CD4⁺CD25⁻ FoxP3⁻(convCD4) and CD4⁺CD25⁺FoxP3⁺ (Treg). In cDC: CD8⁺ CD11b⁻ (cDC1) and CD8⁻ CD11b⁺ (cDC2).

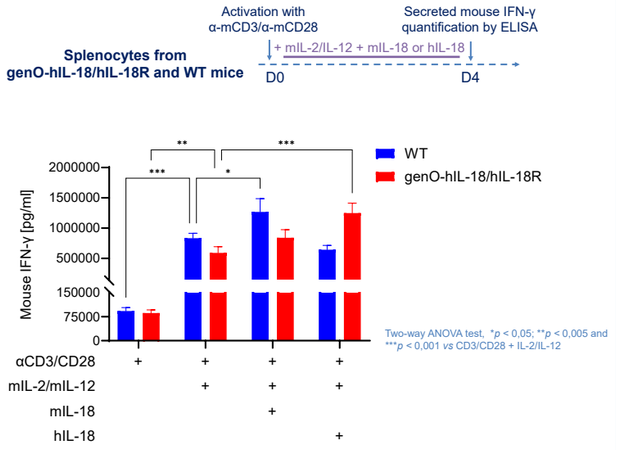
⇒ **Similar results of immune profiling in blood and bone marrow – *data not shown***

3. Human IL-18Rα expression on immune cells from genO-hIL-18/hIL-18R mice



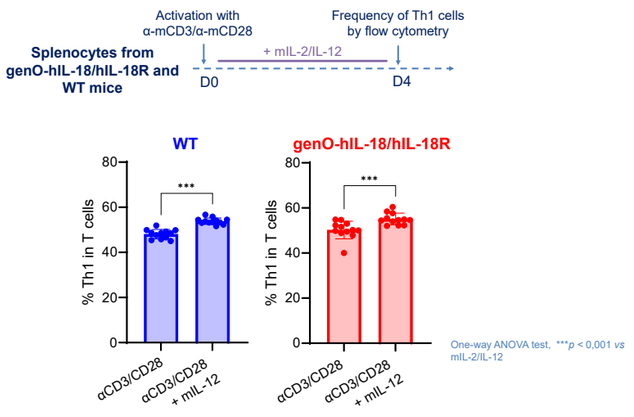
Freshly isolated splenocytes, gated on single live CD3⁻CD19⁻ NKp46⁻ CD317⁻ Ly-6G⁻ Ly-6C⁺ Ly-6C⁺ CD11b⁺ (Monocytes/macrophages), CD3⁻CD19⁻ NKp46⁺ (NK cells), CD3⁺TCRβ⁺ TCRγδ⁻CD4⁻CD8⁺(CD8 T cells), CD3⁺TCRβ⁺ TCRγδ⁻CD4⁺CD25⁻FoxP3⁻(convCD4), CD3⁺ TCRβ⁺ TCRγδ⁻CD4⁺CD25⁺FoxP3⁺ (Treg).

4. Human IL-18 induces IFN-γ secretion in splenocytes from genO-hIL-18/hIL-18R mice



⇒ **Human IL-18R is functional**

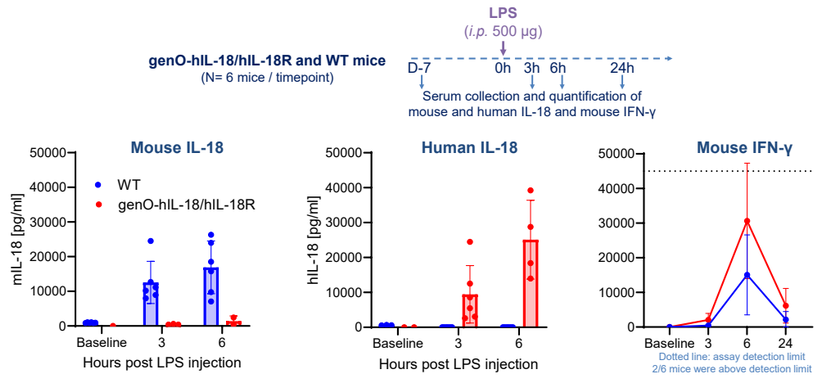
5. Th1 differentiation is unaltered in genO-hIL-18/hIL-18R mice



⇒ **genO-hIL-18/hIL-18 T cells polarize toward Th1 upon CD3/CD28 activation**

⇒ **IL-12 increases Th1 frequency similarly in WT and genO-hIL-18/hIL-18R T cells**

6. *In vivo* LPS-induced IL-18 and IFN-γ release

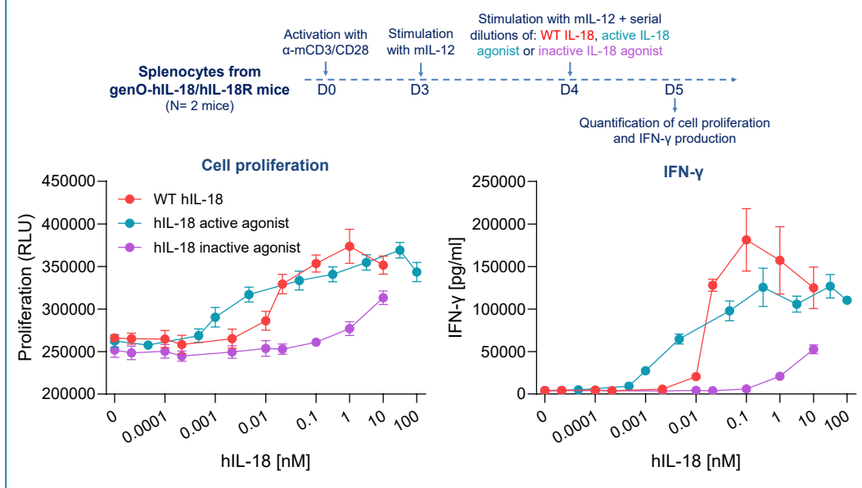


⇒ **LPS-induced human IL-18 secretion in genO-hIL-18/hIL-18R mice mirrors mouse IL-18 secretion in WT mice**

⇒ **IFN-γ is secreted in a similar kinetic in genO-hIL-18/hIL-18R and WT mice**

⇒ **mIL-18BP expression is increased by LPS similarly in genO-hIL-18/hIL-18R and WT mice *(data not shown)***

7. *Ex vivo* efficacy of IL-18 agonists



⇒ **Splenocytes from genO-hIL-18/hIL-18R mice treated with engineered hIL-18 exhibit enhanced cell proliferation and increased IFN-γ secretion compared to inactive hIL-18**

Conclusion: Altogether, these results support the suitability of the genO-hIL-18/hIL-18R mouse model for assessment of new therapies targeting this axis.

Reference: 1. Kessel C, Rossig C, Abken H. Weal and woe of interleukin-18 in the T cell therapy of cancer. *Journal for ImmunoTherapy of Cancer*. 2025;13:e010545. https://doi.org/10.1136/jitc-2024-010545

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