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## **GZMB+ B cells, a key factor of cell immunity in human?**

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## 1-INTRODUCTION

Accumulating evidences show the existence of B-cells able to exert suppressing activities (Bregs) through different mechanisms. We report on an increase of a specific B cell population with suppressive regulatory functions in the blood of transplanted patients with long-term graft outcome.

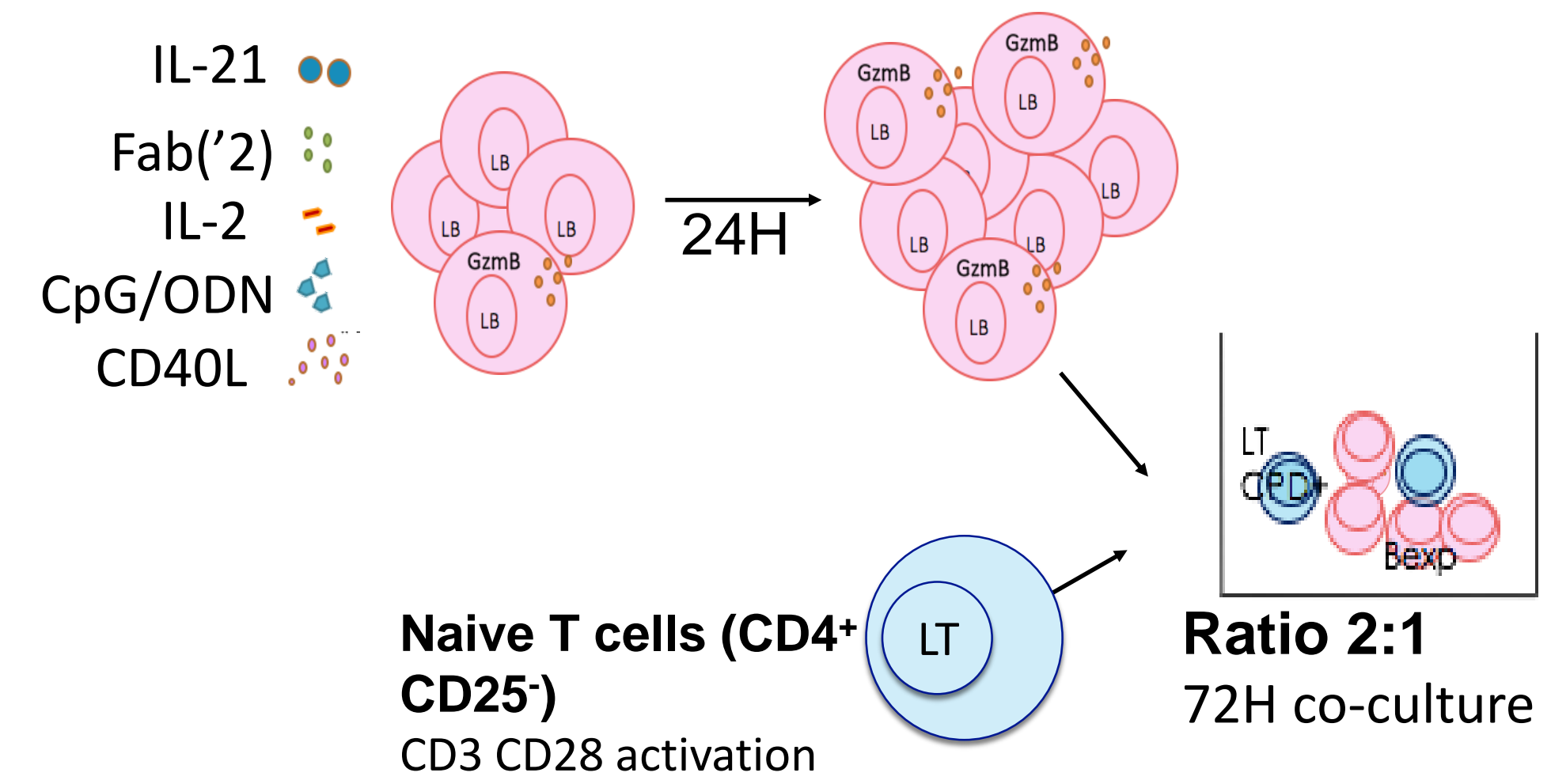
These B cells inhibit an effector T cell response through a granzyme B (GZMB<sup>+</sup>) dependent mechanism. We showed that such a population is present in healthy volunteer likely participating to a complex homeostasis cell orchestra and key regulator of immune response in chronic inflammation.

**The aim of our study is to characterize their phenotype, their mode of action and we propose a method to induced them for future cell therapy.**

## 2-MATERIAL AND METHODS

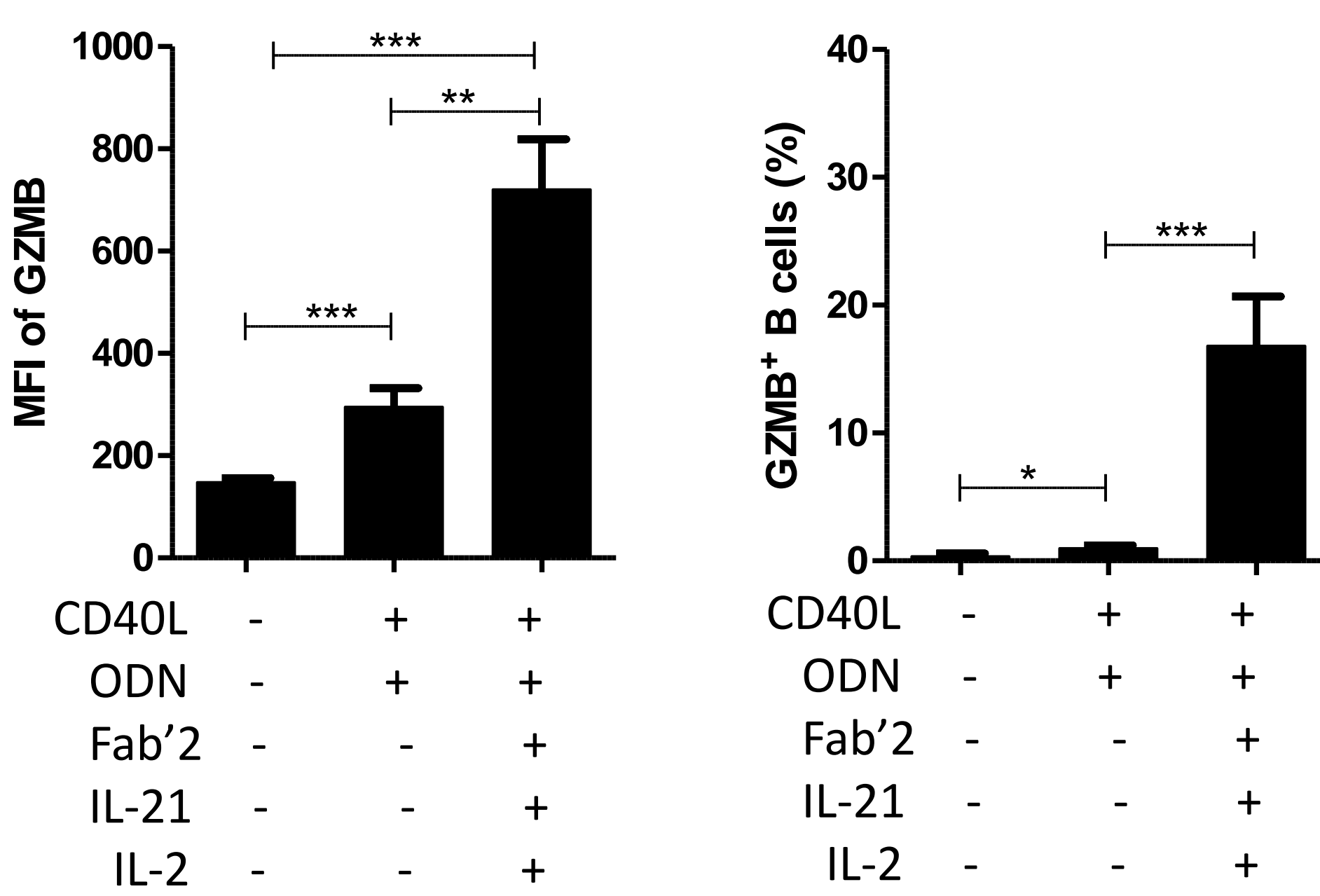
PBMCs from Heathy volunteers => B cells isolation (negative selection)

- GZMB<sup>+</sup> B cells induction
- Analysis of regulatory function

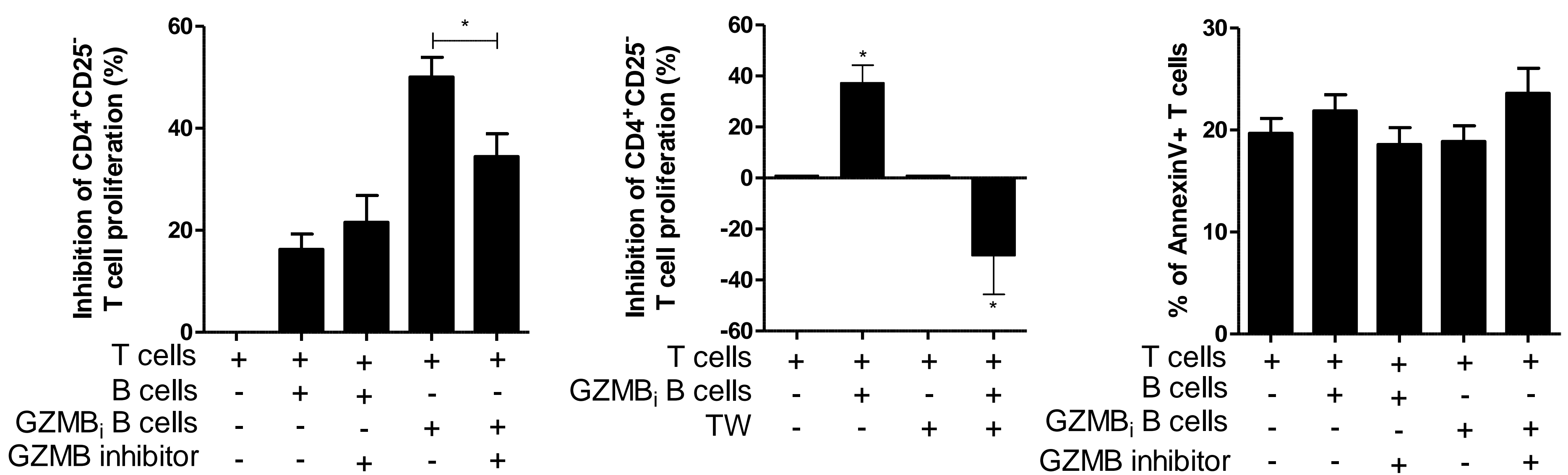


## 3- RESULTS

### 1- In vitro GZMB<sup>+</sup> B cells induction



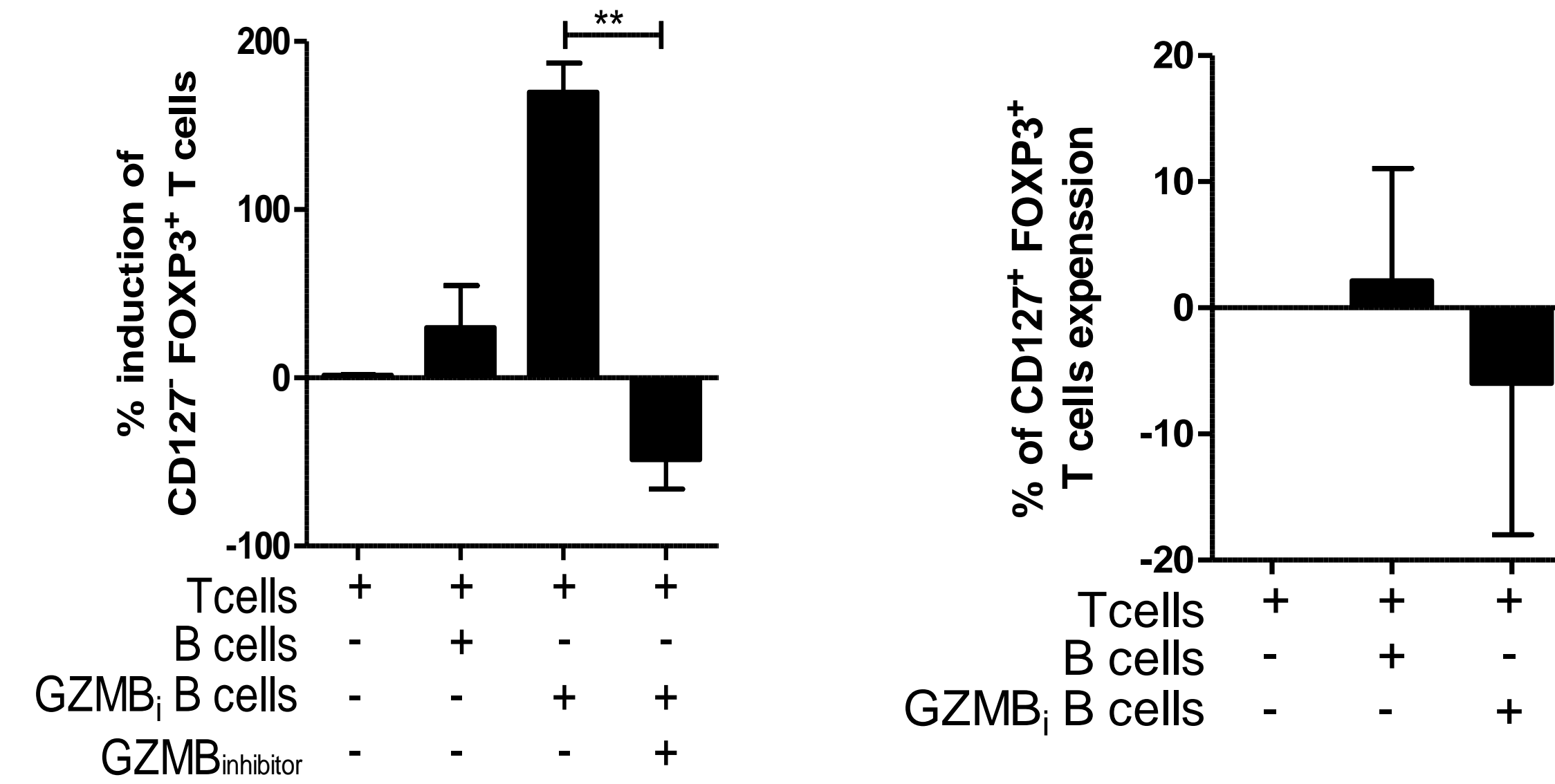
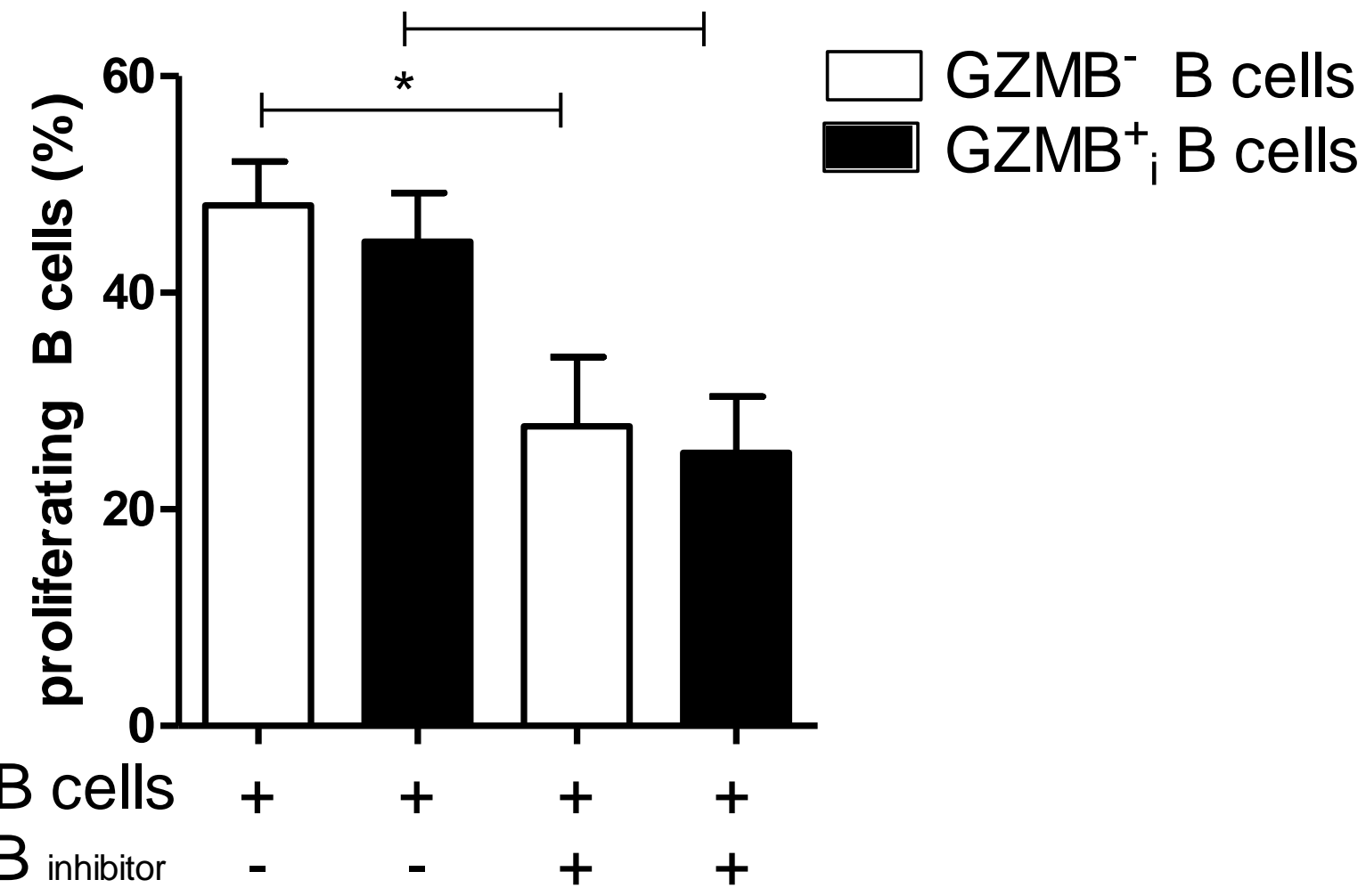
### 2- Regulatory function of induced GZMB<sup>+</sup> B cells



Around 17 % of GZMB<sup>+</sup> B cells were induced (GZMB<sup>+</sup><sub>i</sub> B cells) after 3 days culture with CD40L, ODN, Fab'2, IL-21 and IL-2.

GZMB<sup>+</sup><sub>i</sub> B cells inhibits effector T cells proliferation higher than non induced GZMB<sup>+</sup> B cells in GZMB and contact dependent manner, without inducing T cells apoptosis.

### 3- Homeostasis of GZMB<sup>+</sup> B cells



Addition of GZMB inhibitor in 3 days culture prevents B cell proliferation suggesting that GZMB secreted by GZMB<sup>+</sup><sub>i</sub> B cells concurs to their own proliferation.

After coculture with effector T cells, GZMB<sup>+</sup><sub>i</sub> B cells induces T cells with regulatory function in a GZMB dependent manner.

## 4-CONCLUSION

We identified Breg cells with a dual regulatory role, both blocking conventional T cell proliferation and inducing Treg cells but also maintaining cell homeostasis. These data evidence that GZMB<sup>+</sup> B cells are tightly regulated through a feed back loop control of proliferation and death suggesting a fine control of these cells able to maintain a physiological T cell response in healthy volunteers.

We identified an efficient induction protocol for Bregs with stable suppressive activity.

These data provide new insights into the GZMB<sup>+</sup> B cell biology and function as well as new clues for novel future therapies in inflammatory diseases and cancers.