



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

Mélanie Chesneau, Sabine Le Bot, Cyrielle Poulaouec, Richard Danger, Florian Dubois, Maxim Durand, Lola Jacquemont, Pierrick Guerrif, Nicolas Degauque, Magali Giral, et al.

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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⁺) 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.

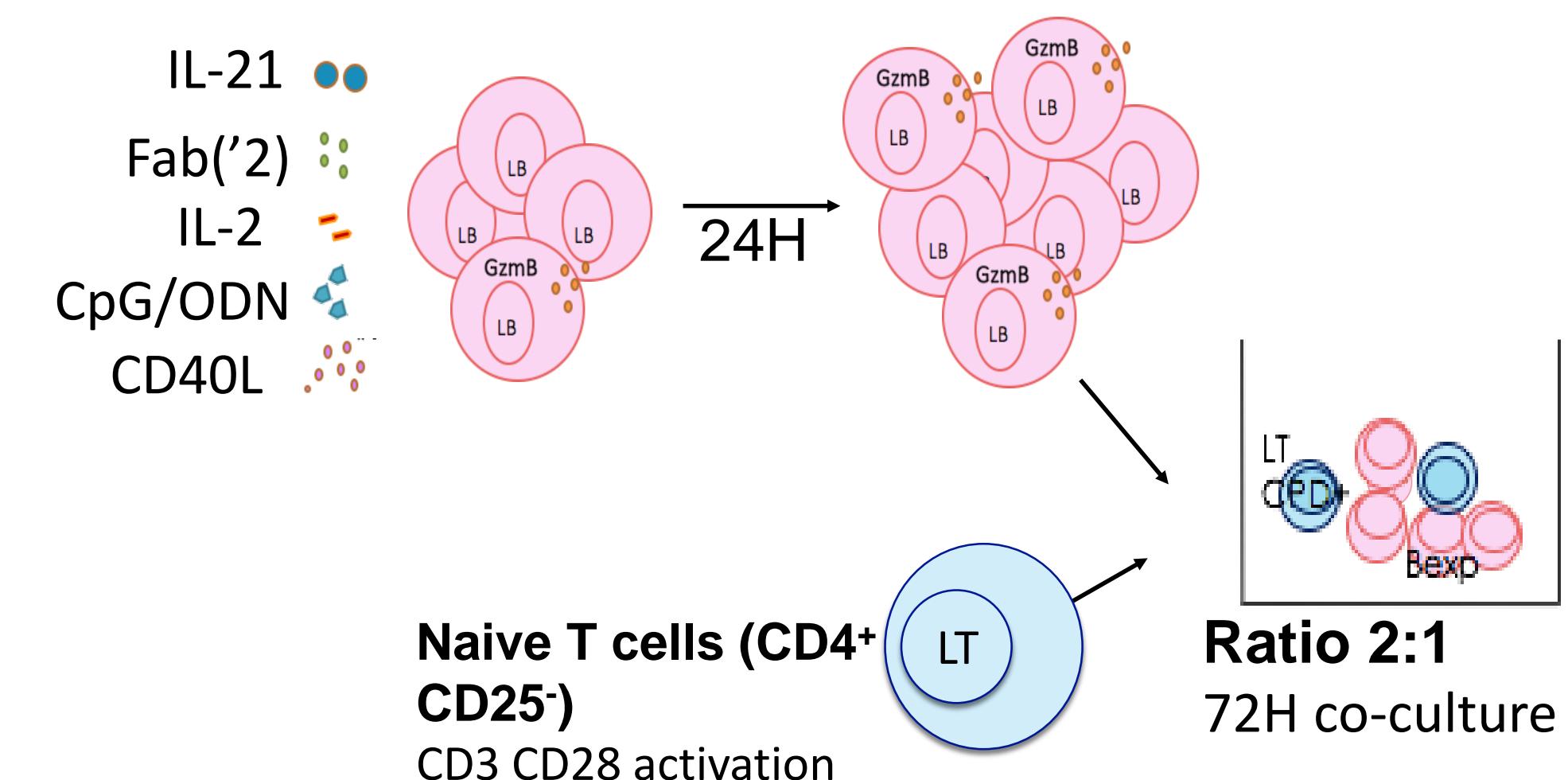
The aim of our study is to characterize their phenotype, their mode of action and we propose a method to induced them for future cell therapy.

2-MATERIAL AND METHODS

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

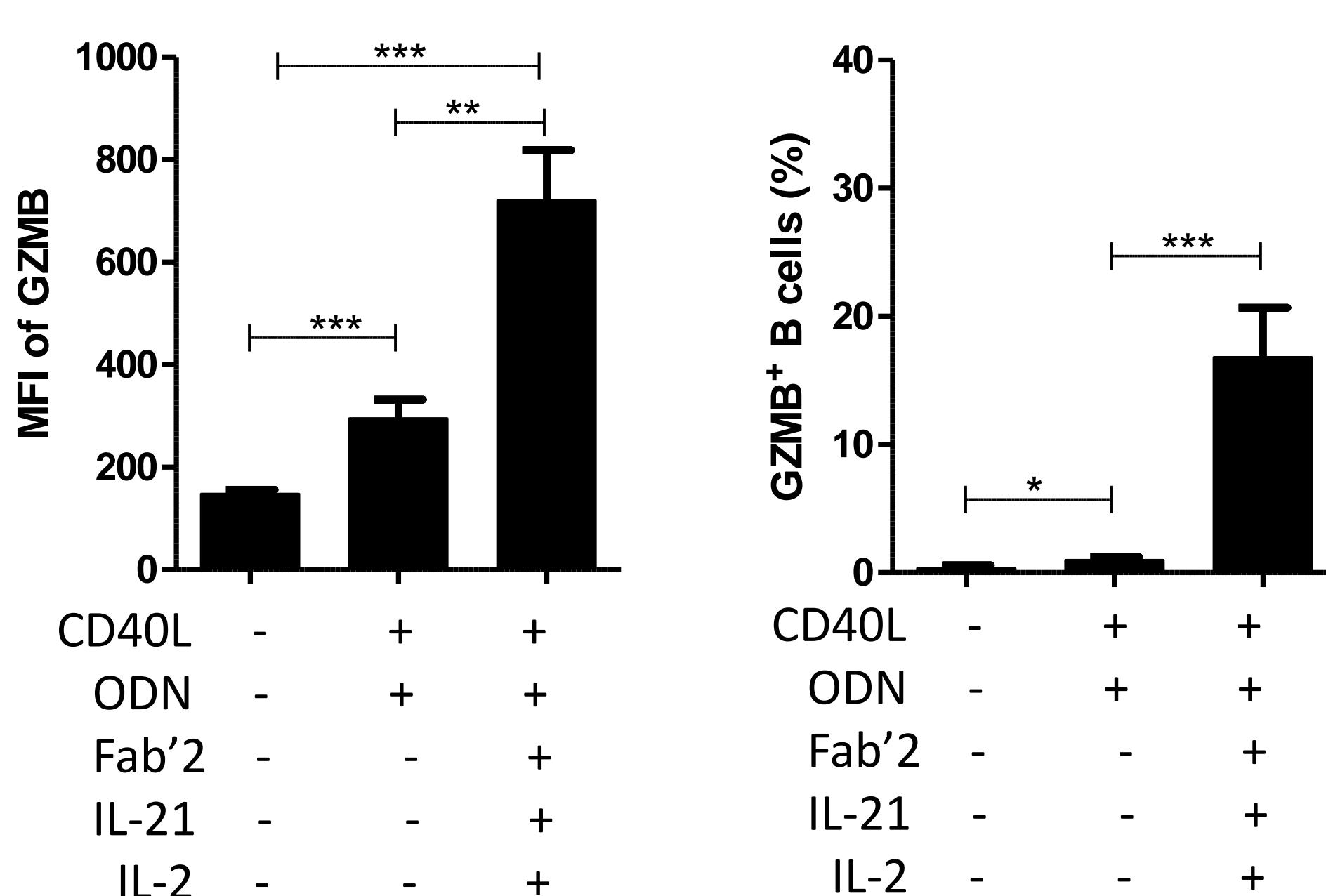
-GZMB⁺ B cells induction

-Analysis of regulatory function



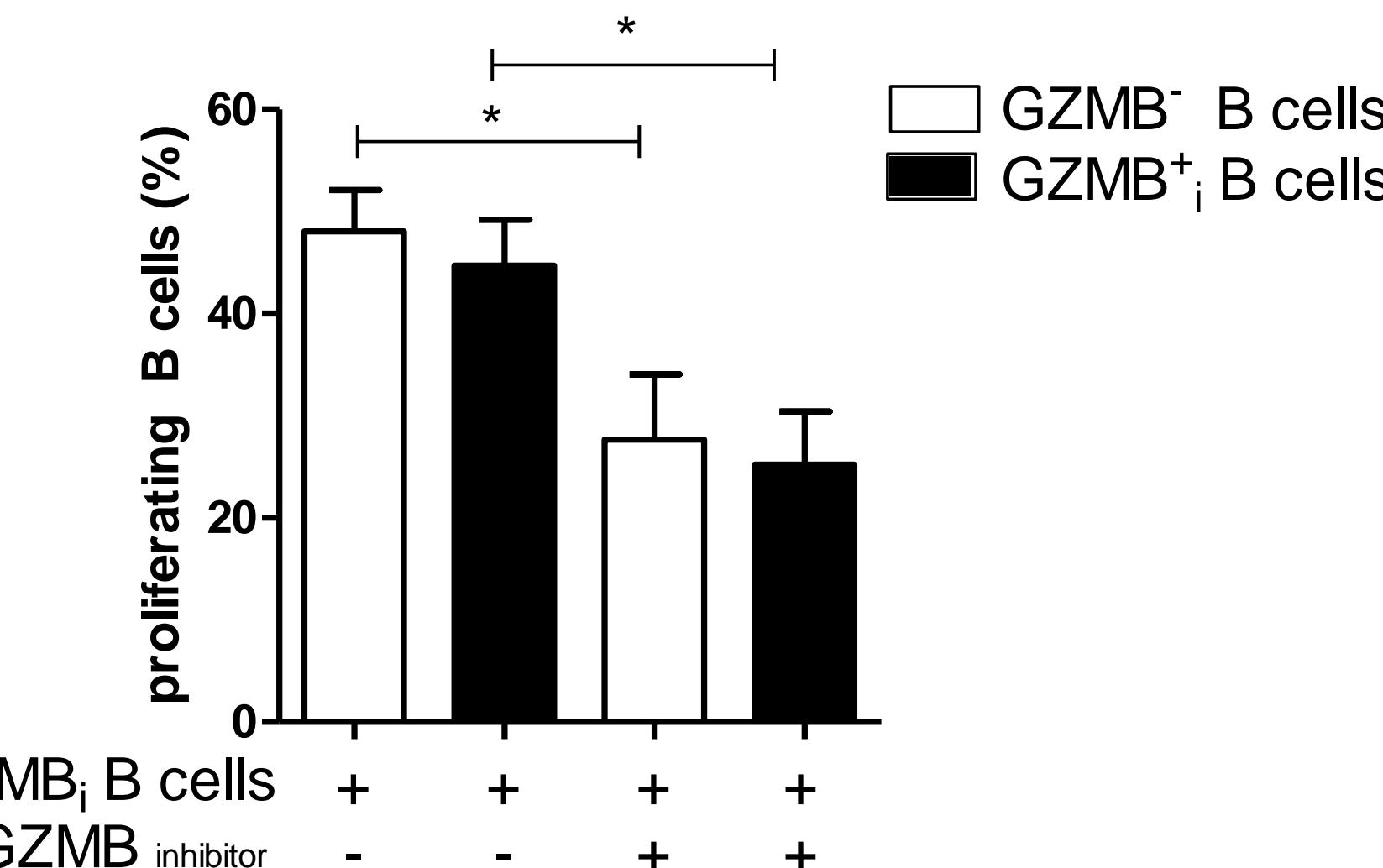
3- RESULTS

1- In vitro GZMB⁺ B cells induction

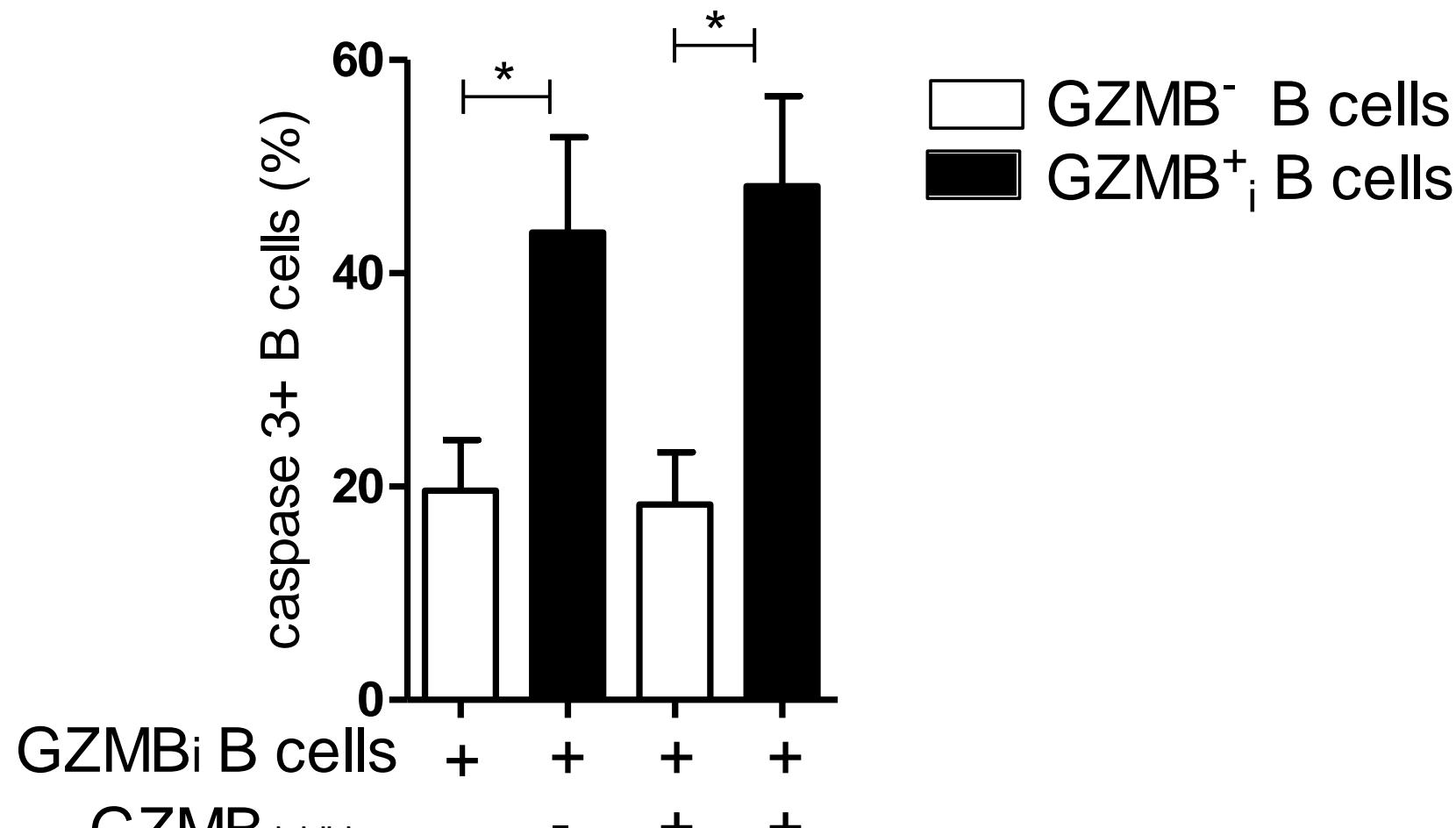


Around 17 % of GZMB⁺ B cells were induced (GZMB⁺_i B cells) after 3 days culture with CD40L, ODN, Fab'2, IL-21 and IL-2.

3- Homeostasis of GZMB⁺ B cells

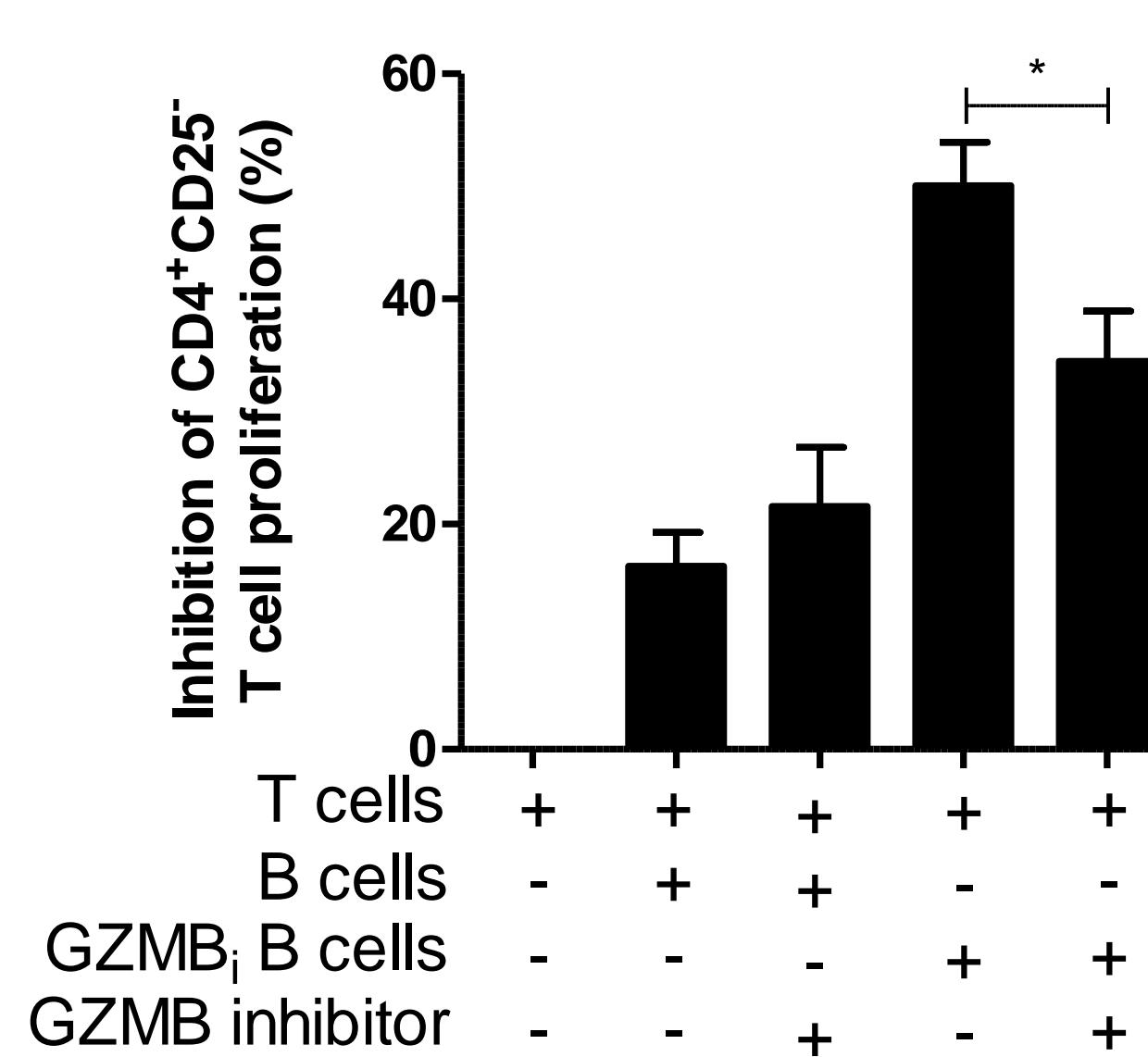


Addition of GZMB inhibitor in 3 days culture prevents B cell proliferation suggesting that GZMB secreted by GZMB⁺ B cells concurs to their own proliferation.

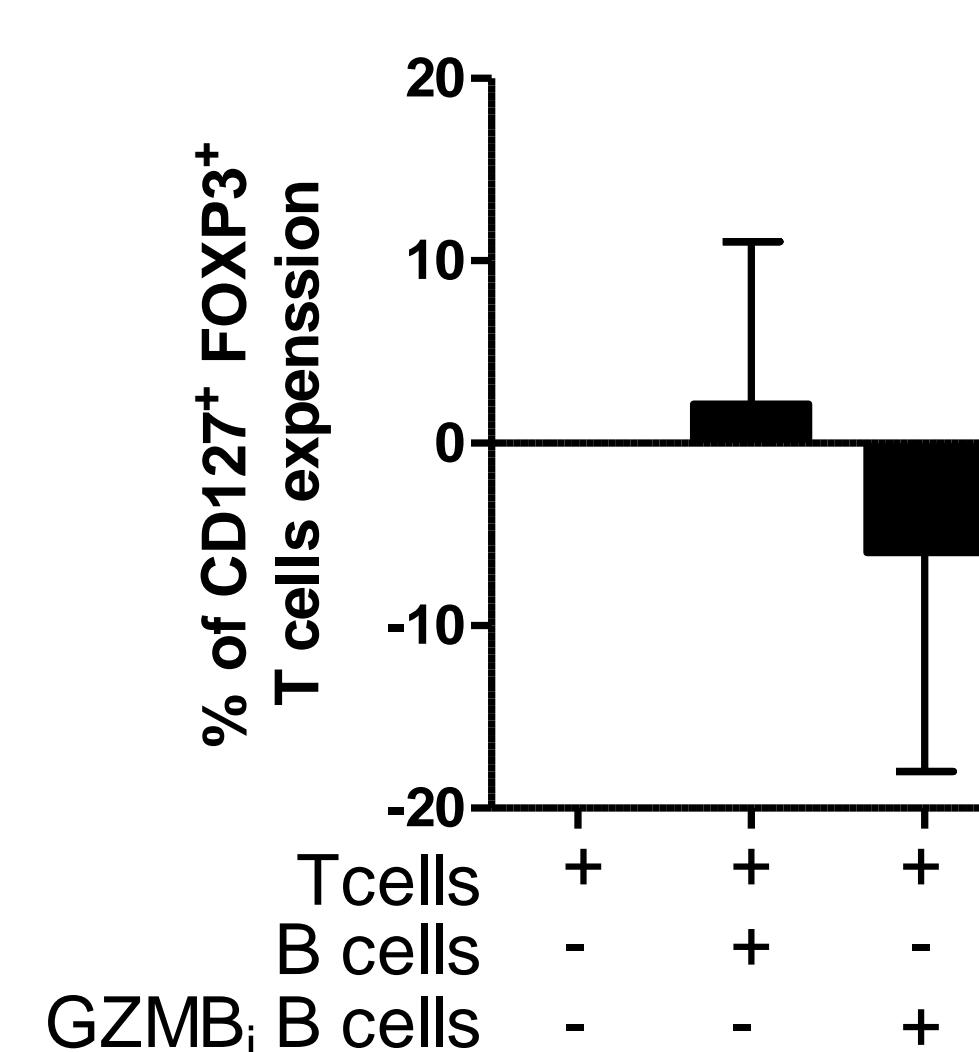
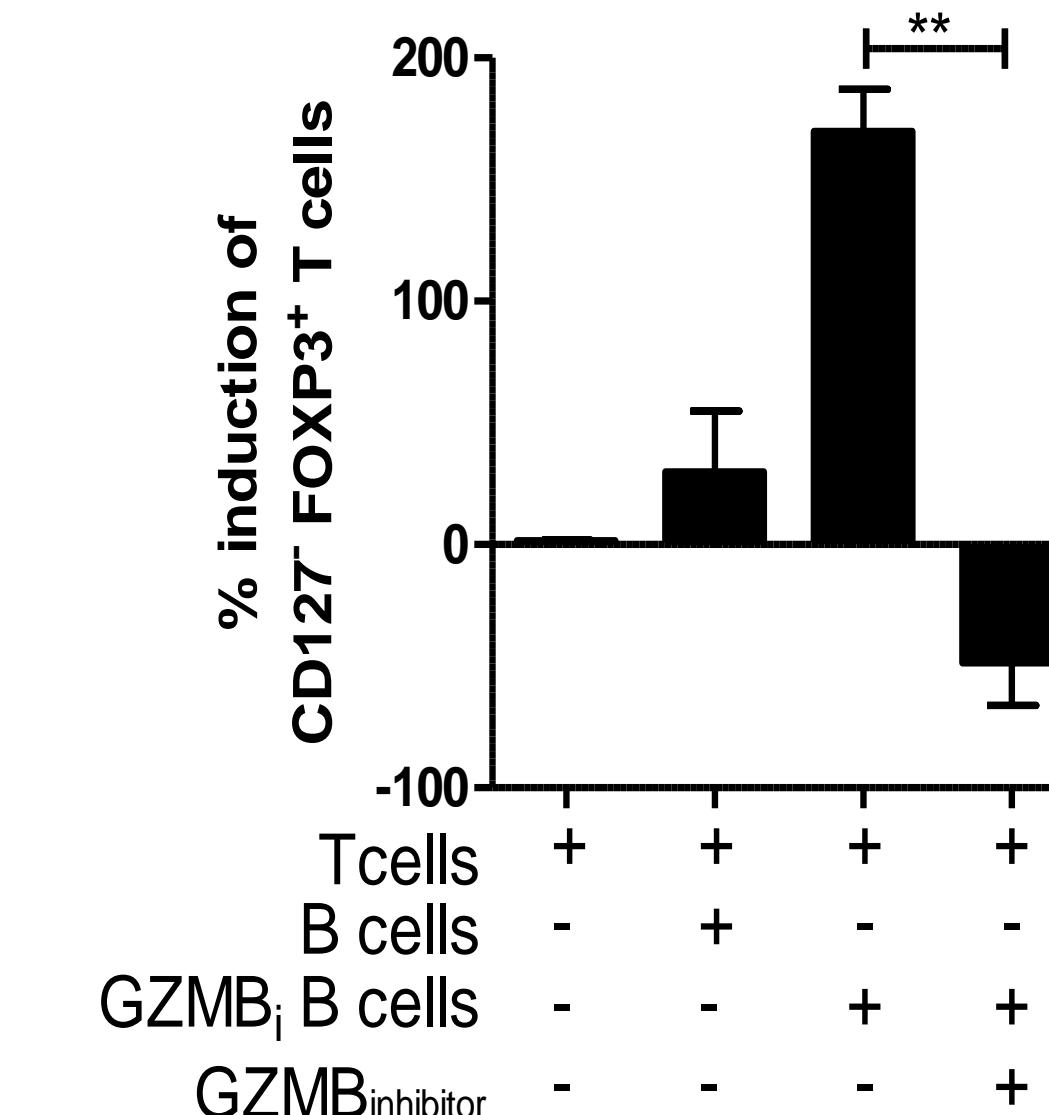


GZMB⁺_i B cells are significantly more sensitive to apoptosis compared to GZMB⁻ B cells.

2- Regulatory function of induced GZMB⁺ B cells



GZMB⁺_i B cells inhibits effector T cells proliferation higher than non induced GZMB⁺ B cells in GZMB and contact dependent manner, without inducing T cells apoptosis.



After coculture with effector T cells, GZMB⁺_i 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 inducting Treg cells but also maintaining cell homeostasis. These data evidence that GZMB⁺ 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⁺ B cell biology and function as well as new clues for novel future therapies in inflammatory diseases and cancers.