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► To cite this version:

Eros Marín, Laurence Bouchet-Delbos, Maria-Cristina Cuturi, Aurelie Moreau. Human autologous tolerogenic dendritic cells impair T-cell proliferation through contact-independent mechanisms. 22nd NAT congress "Immunotherapies in transplantation and Cancer", Jun 2017, Nantes, France. inserm-02160928

HAL Id: inserm-02160928

<https://inserm.hal.science/inserm-02160928>

Submitted on 20 Jun 2019

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Human autologous tolerogenic dendritic cells impair T-cell proliferation through contact-independent mechanisms

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Background

Autologous tolerogenic dendritic cells (ATDC) have been demonstrated to be able to increase heart, skin and pancreatic islet allograft survivals in murine models and to be safe in non-human primates. Due to their efficacy and their safety, ATDC therapy has been moved to clinic in a first phase I/II clinical trial in kidney transplantation in the context of the ONE study project. Human ATDC are generated from elutriated monocytes cultured 6 days in AIMV medium supplemented with low dose of GM-CSF. After differentiation ATDC display a tolerogenic dendritic cell profile (i.e. they display an immature phenotype, they express immunomodulatory cytokines such as IL-10 and TGF- β , they are resistant to maturation and they have suppressive activity toward T-cells). This project aims to determine the suppressive mechanisms of human ATDC toward T-cells.

ATDC impair CD4⁺ T-cell proliferation through contact independent mechanisms

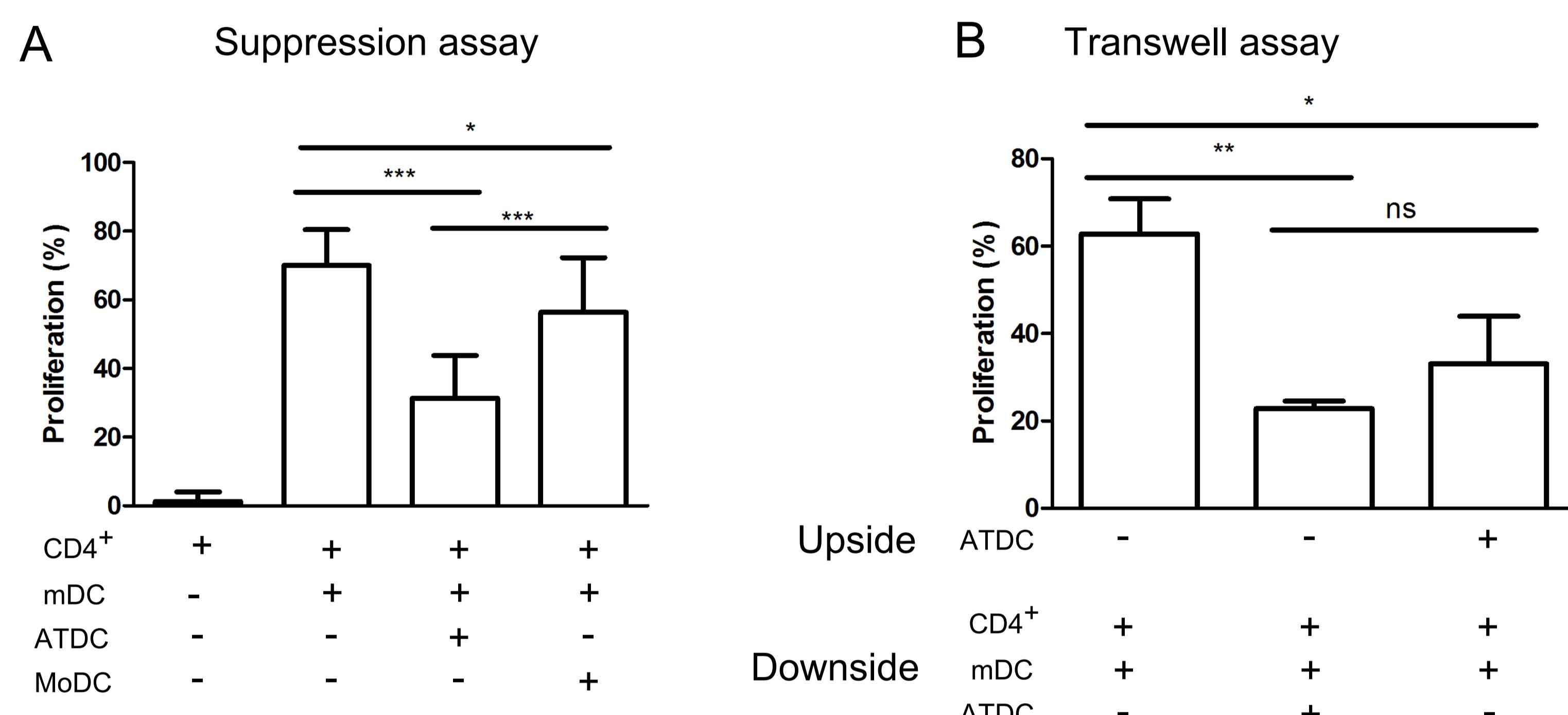


Figure 1. (A) CD4⁺ T-cell proliferation in suppression assay and (B) transwell assay

ATDC impair CD4⁺ T-cell proliferation through G0/G1 phase blockade without inducing apoptosis nor anergy

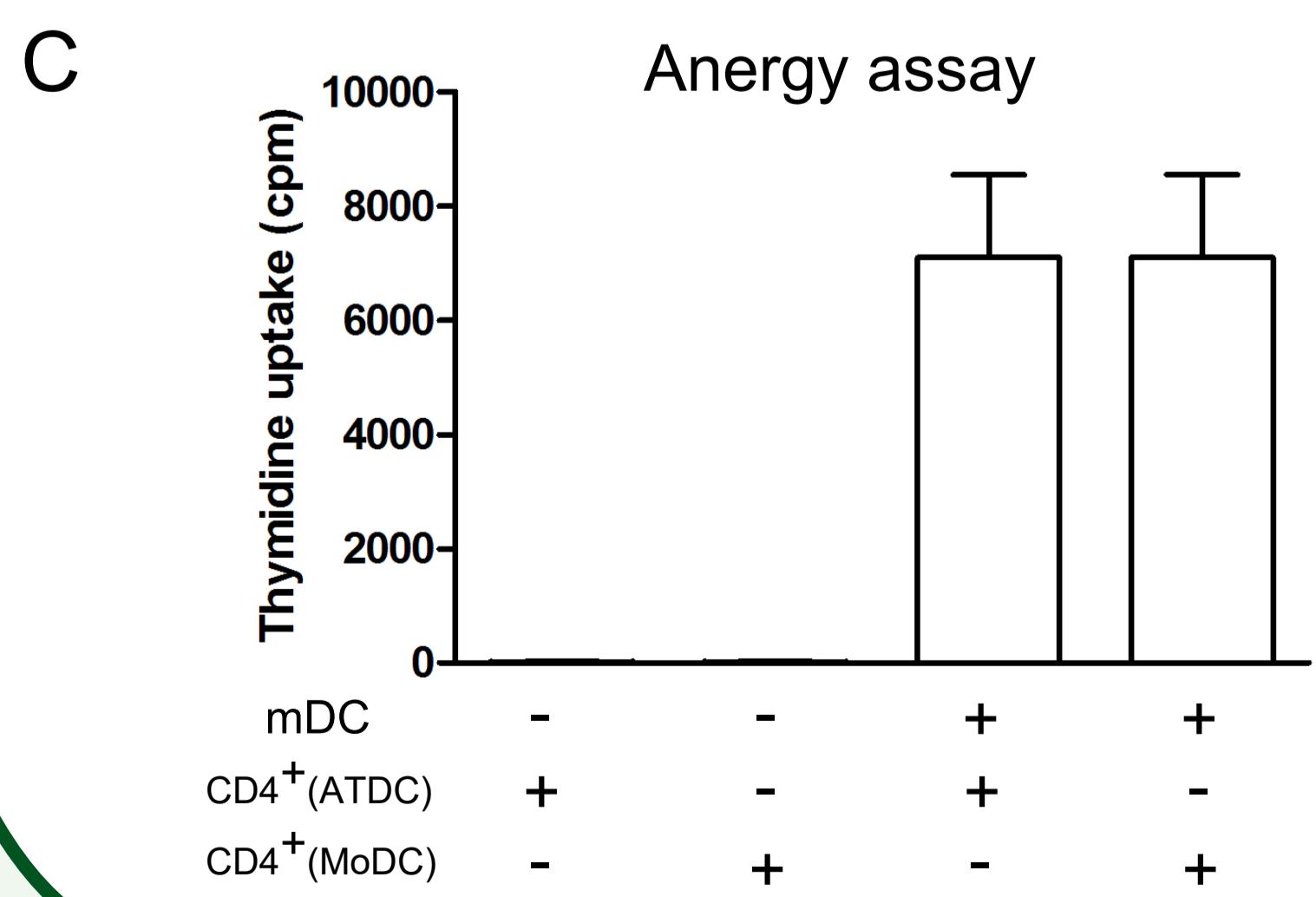
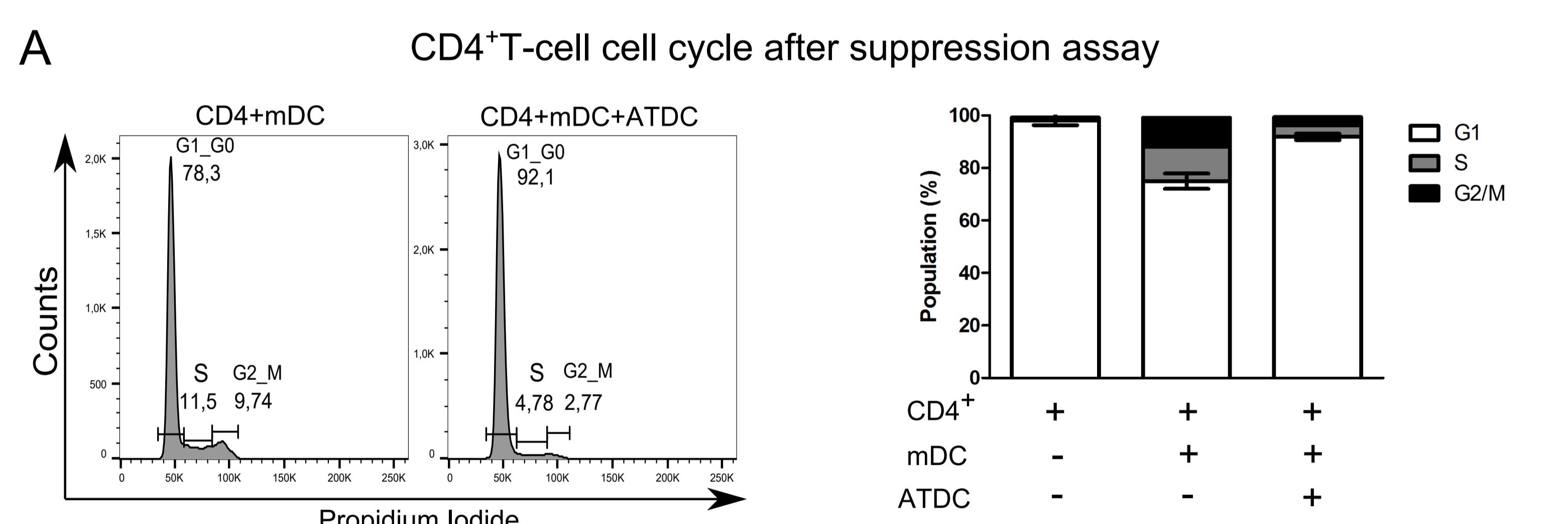


Figure 2. (A) CD4⁺ T-cell cell cycle and (B) apoptosis in suppression assay. (C) Anergy assay. First, CD4⁺ T-cells were cultured with allogeneic ATDC or MoDC. After 6 day, CD4⁺ T-cells were recovered and cultured with allogeneic mDC.

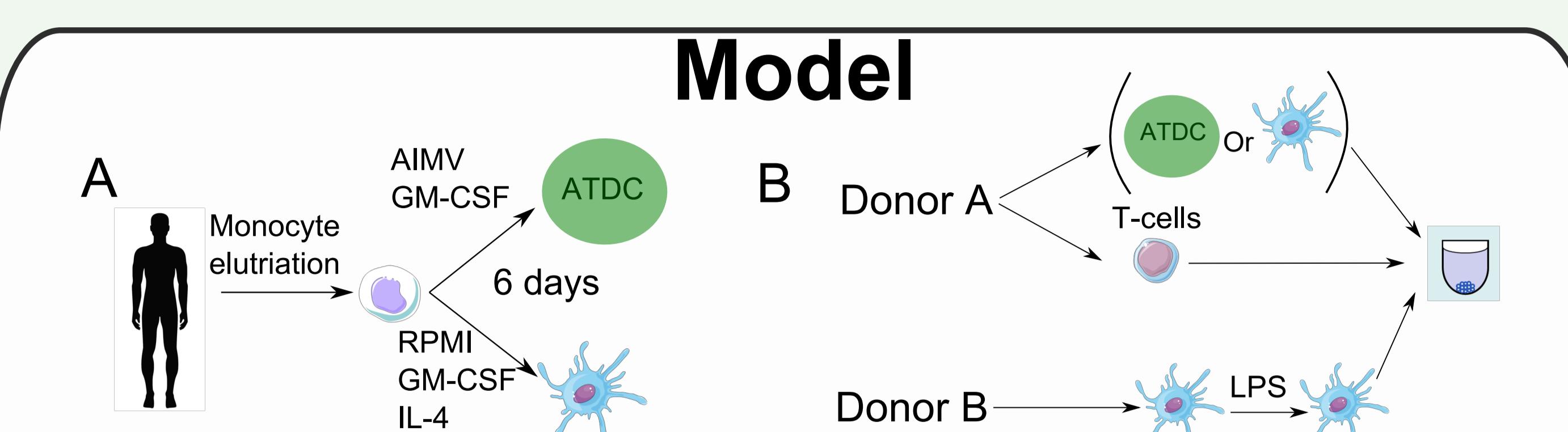


Figure 1. (A) Schematic representation of ATDC and MoDC differentiation. In this study we used MoDC as control cells. (B) Model of suppression assay used in this study. CD4⁺ T-cells are cultured with allogeneic mature dendritic cells (mDC) with or without ATDC or MoDC (autologous to CD4⁺ T-cells)

ATDC impair Th1 and Th17 proliferation while promote Treg

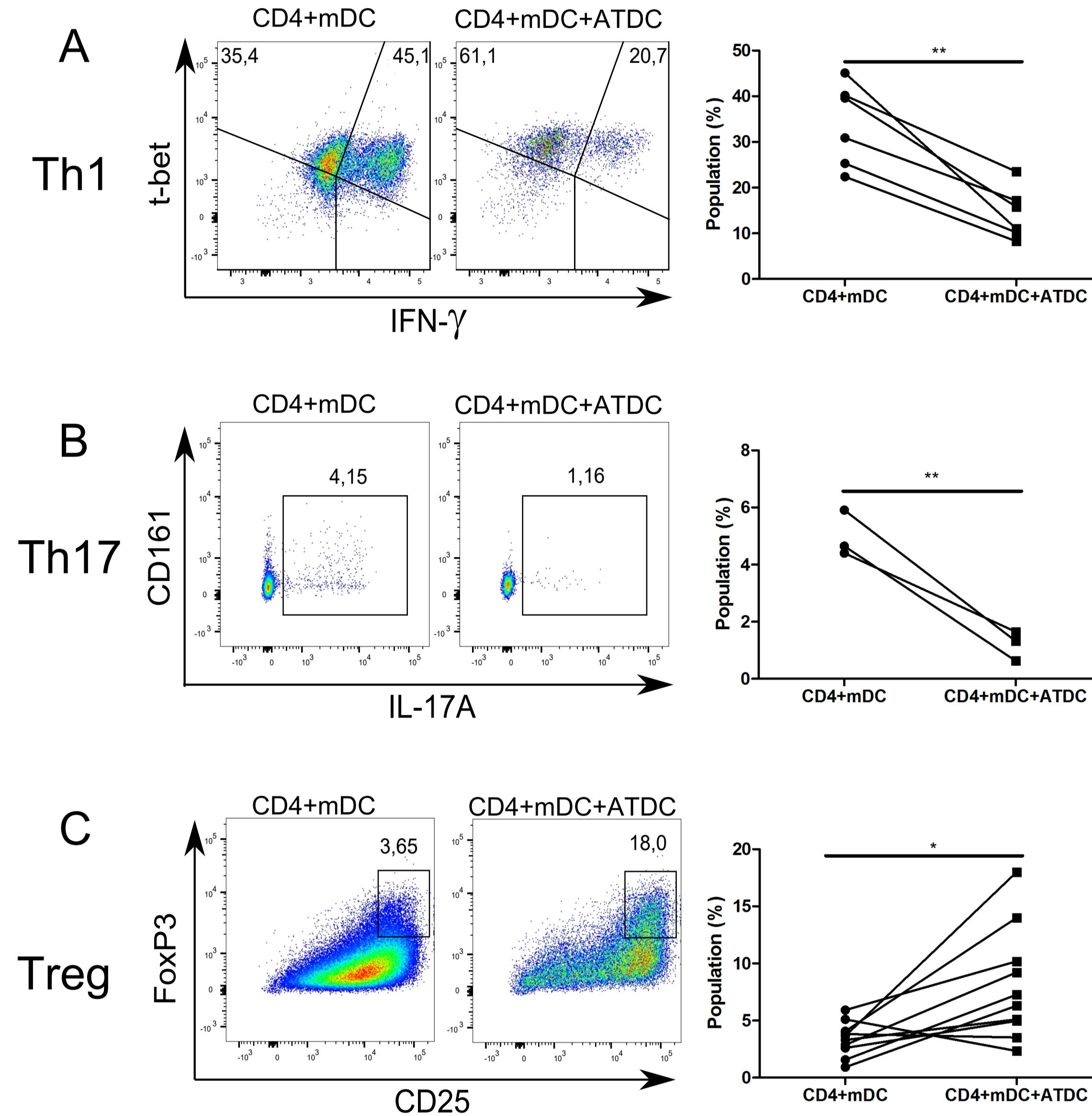


Figure 3. (A) Percentage of proliferating CD4⁺ t-bet⁺IFN- γ ⁺ Th1 cells, (B) CD4⁺ IL17A⁺ Th17 cells, and (C) CD4⁺ CD25^{hi} FoxP3^{hi} Treg cells after suppression assay

ATDC induce the generation of "de novo" Treg partially through the production of TGF- β

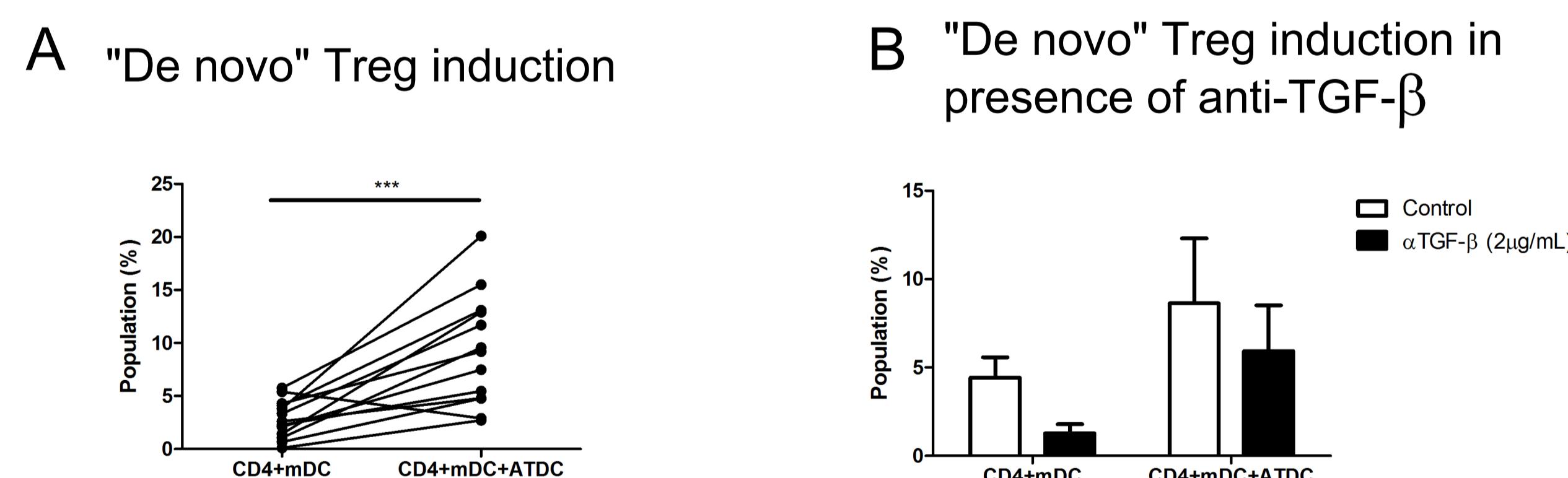
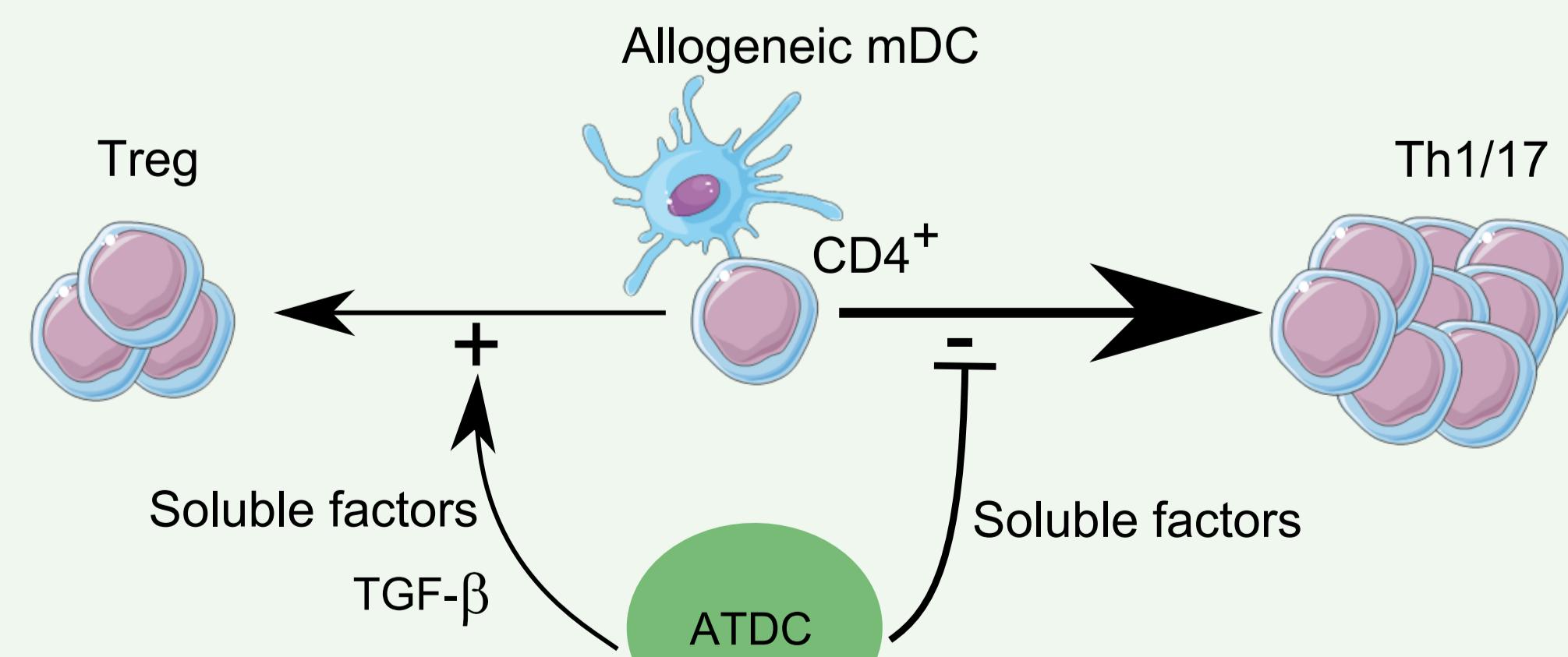


Figure 4. (A and B) Suppression assay starting with CD4⁺CD25⁻ T-cells instead of total CD4⁺ T-cells. (A) Percentage of proliferating CD4⁺ CD25^{hi} FoxP3^{hi} Treg cells and (B) after adding TGF- β blocking antibody.

Conclusion



These results altogether showed that low dose GM-CSF-induced ATDC are able to suppress CD4⁺ T-cell proliferation and to induce "de novo" Treg in part through the expression of TGF- β . Moreover we evinced that ATDC impair T-cell proliferation by contact-independent mechanisms without association with apoptosis nor anergy but with the blockade of cell cycle in G0/G1 phase. In-depth investigations will be performed to determine the molecular mechanisms underlying ATDC.