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LETTER TO THE EDITOR

Effects of MSC-NTF cells on T and B regulatory cell function in ALS

RALPH KERN, REVITAL ARICHA, HAGGAI KASPI, YAEL GOTHELF & CHAIM LEBOVITS

Brainstorm Cell Therapeutics, New York, NY, USA

To the editor,

We read with interest the publication, "The involvement of regulatory T cells in amyotrophic lateral sclerosis and their therapeutic potential," by Giovannelli et al (1). This is a timely and important review of the potential role of T regulatory cells in ALS and how these cells may relate to ALS disease progression and patient survival. The authors review several clinical trials specifically targeting T regulatory cells. We would like to bring to the authors' attention our own observations on the effects of autologous mesenchymal stem cells secreting neurotrophic factors (MSC-NTF cells) on B and T regulatory function and how this is being evaluated in ongoing ALS clinical trials.

MSC-NTF cells (NurOwn®) are autologous, mesenchymal stem cells (MSC) induced by a culture-based approach to secrete higher levels of neurotrophic factors (NTF) while retaining their intrinsic immunomodulatory activity. The pharmacodynamic effect of a single intrathecal administration of MSC-NTF cells on CSF inflammatory biomarkers was confirmed in a randomized placebo-controlled phase 2 ALS clinical trial (2) and is being evaluated in a fully enrolled 200 patient phase 3 ALS randomized clinical trial (NCT03280056).

We studied the immunomodulatory properties of MSC-NTF *in vitro* by evaluating their interference with IFN-γ production by T cells in response to PHA stimuli and their induction of B cells' IL-10 secretion. In addition, the effect of MSC-NTF cells on induction of regulatory T or B cells was evaluated using flow cytometry. ELISA was used to measure IL-10 and IFN-γ secretion.

We found a significant ($p < 0.0001$) decrease of IFN-γ secretion by peripheral blood mononuclear cells (PBMC) in the presence of MSC-NTF cells (see Figure 1).

When co-cultured with PBMC, MSC-NTF cells induced CD4 + CD25 + FoxP3+ T regulatory cells.

MSC-NTF cells co-cultured with B cells induced $CD24^{hi}CD38^{hi}$ B regulatory cells, and increased IL-10 secretion (See Figure 1).

As suggested by the authors, T and B regulatory cell function may be an important therapeutic approach in ALS. We have previously demonstrated that a single MSC-NTF treatment increased circulating Tregs in a phase 2a ALS open label study (3). IL-10 has effects on microglial function and influences disease onset in the mouse SOD1 ALS model (4). Recently it has been suggested that B regulatory cells may induce the formation of IL-10 expressing T cells in mice with autoimmune neuroinflammation (5), and IL-10 secreted by both T and B regulatory cells may impact microglia and cytokine networks (6). In addition, adoptive transfer of IL-10+ B regulatory cells has the potential to decrease myeloid-derived macrophages in the central nervous system in a transgenic mouse amyotrophic lateral sclerosis model (7).

We appreciate the thoughtful review and look forward to evaluating T regulatory cells and their correlation to clinical outcome in Brainstorm's fully enrolled phase 3 clinical trial evaluating repeat intrathecal dosing of MSC-NTF cells in ALS patients (NCT03280056).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Correspondence: Ralph Kern, Brainstorm Cell Therapeutics, New York, NY, USA. E-mail: rkern@brainstorm-cell.com

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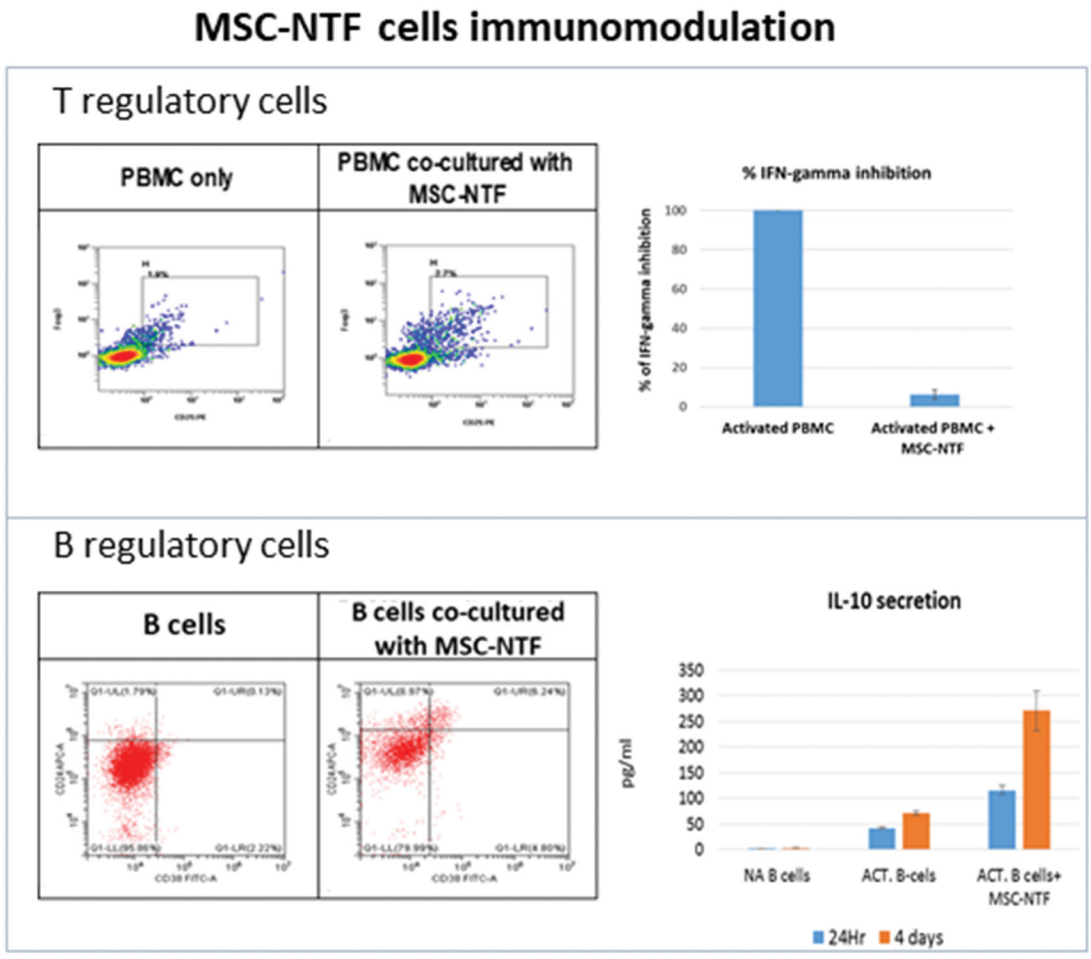

Figure 1. MSC-NTF cells immunomodulation: Upper panel (left)- Representative FACS analysis of double positive FoxP3 and CD25 cells in a gate of CD4 cells showing an increase of T regulatory cells after co-culture of PBMC with MSC-NTF cells. Upper panel (right)-inhibition of IFN-g secretion by PBMC after 4 days co-culture with MSC-NTF cells ($p<0.0001$). Lower panel (left) Representative FACS analysis of CD24hiCD38hi B regulatory cells showing an increase of B regulatory cells after co-culture of B cells with MSC-NTF cells. Lower panel (right)- Induction of IL-10 secretion by B cells after 24 hours or 4 days co-culture with MSC-NTF cells ($p < 0.001$ for both).

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