

### Erythropoietin receptor is detectable on peripheral blood lymphocytes and its expression increases in activated T lymphocytes (reply)

We have read with interest the letter of Lisowska *et al.*, submitted to *Haematologica* in response to our manuscript "Macrophages as novel target cells for erythropoietin" by Lifshitz *et al.*, published in *Haematologica* in June 2010. In their commentary, Lisowska *et al.* claim that: (1) we have neglected to acknowledge their longstanding contribution in the field of erythropoietin as an immunomodulator, and that (2) we have failed to cite their very recent findings that lymphocytes express EPO-Rs.

We consider it important to respond to their comments and to clarify the relevant points.

1) We have certainly not "passed over the publications of Lisowska *et al.* concerning immunomodulatory action of recombinant human erythropoietin (rHuEPO) from over the last 12 years" as the authors claim. The scientific work of this group is well recognized by our team and has, in fact, been cited in our previous publications.<sup>1,2</sup> In the article by Prutchi-Sagiv *et al.* 2005,<sup>2</sup> we have cited four of their publications<sup>3-6</sup> clearly mentioning the contribution of these authors to the field of "EPO as an immunoregulator".

Regarding the study of Lisowska *et al.* demonstrating EPO-Rs on lymphocytes,<sup>7</sup> we did not cite it, simply because it was published after our manuscript in *Haematologica* had already appeared in the press.

Specifically, the issue of EPO-Rs on lymphocytes deserves proper clarification. In the study by Prutchi-Sagiv *et al.*, 2006<sup>1</sup> we could not determine EPO-R expression on lymphocytes, although we have used most critical methodologies of both PCR and antibody binding, applied on isolated lymphocytes. In our article on these findings we did cite two publications<sup>3,4</sup> of Lisowska *et al.*, reporting on the effect of rHuEPO on cytokine secretion from the lymphocytes. However, it should be noted that in their studies the effect of rHuEPO on cytokine secretion was demonstrated on a heterogeneous cell population (whole blood cell cultures), derived from chronic renal failure patients treated with hemodialysis. Additionally, in both Prutchi-Sagiv *et al.*, 2005 and 2006<sup>1,2</sup> we have cited the studies of Bryl 1998 and 1999,<sup>3,4</sup> with respect to their data demonstrating that EPO has the "ability to restore the imbalance of cytokines by decreasing the production of TNF- $\alpha$  and IL-6, resulting in values characteristic of the healthy state".<sup>1</sup>

2) In view of the fact that we could not detect EPO-Rs on lymphocytes and yet the immunomodulatory effects of EPO were obvious, we have proposed a mechanism whereby the effects are exerted *via* other immune cells, such as dendritic cells and macrophages.

3) The citation in the current manuscript<sup>8</sup> concerning our inability to detect EPO-R on lymphocytes, thus referred to our own previous studies as described by Prutchi-Sagiv *et al.*<sup>1</sup> This is a legitimate citation, given the fact that the focus of this manuscript was specifically on the function of EPO-R expressed on macrophages.

In summary then, we did refer to publications referred to in Lisowska *et al.*, as far as they were pertinent to our studies and findings, and there was no point in citing them in the particular study which focused on macrophages.<sup>8</sup>

Drorit Neumann,<sup>1</sup> Sara Prutchi-Sagiv,<sup>1</sup> Lilach Lifshitz,<sup>1</sup> and Moshe Mittelman<sup>2</sup>

<sup>1</sup>Department of Cell and Developmental Biology; <sup>2</sup>Department of Medicine, Tel Aviv Sourasky Medical Center; <sup>1,2</sup> Tel Aviv University, Sackler Faculty of Medicine Tel Aviv, Israel

Correspondence: Drorit Neumann, Department of Cell and Developmental Biology, Tel Aviv University, Tel Aviv, 69978, Israel. Phone: international +972.3.6407256; Fax: international +972.3.6407432; E-mail: histob6@post.tau.ac.il

Key words: erythropoietin, receptor, lymphocytes.

Citation: Neumann D, Prutchi-Sagiv S, Lifshitz L and Mittelman M. Erythropoietin receptor is detectable on peripheral blood lymphocytes and its expression increases in activated T lymphocytes.(reply) *Haematologica* 2011; 96(03):e14. doi:10.3324/haematol.2011.040030

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at [www.haematologica.org](http://www.haematologica.org).

Financial and other disclosures provided by the authors using the ICMJE ([www.icmje.org](http://www.icmje.org)) Uniform Format for Disclosure of Competing Interests are also available at [www.haematologica.org](http://www.haematologica.org).

### References

- Prutchi-Sagiv S, Golishevsky N, Oster HS, Katz O, Cohen A, Naparstek E, et al. Erythropoietin Treatment in Advanced Multiple Myeloma is Associated with Improved Immunological Functions: Could it be Beneficial in Early Disease? *Br J Haematol.* 2006;135(5):660-72.
- Prutchi-Sagiv S, Neumann D and Mittelman M. Erythropoietin as an Immunotherapeutic Agent: New Uses for an Old Drug? *Med Hypoth Res.* 2005;2:587-96.
- Bryl E, Mysliwska J, Debska-Slizien A, Rachoń D, Bułło B, Lizakowski S, et al. The influence of recombinant human erythropoietin on tumor necrosis factor alpha and interleukin-10 production by whole blood cell cultures in hemodialysis patients. *Artif Organs.* 1988;22(3):177-81.
- Bryl E, Mysliwska J, Debska-Slizien A, Trzonkowski P, Rachoń D, Bułło B, et al. Recombinant human erythropoietin stimulates production of interleukin 2 by whole blood cell cultures of hemodialysis patients. *Artif Organs.* 1999;23(9):809-16.
- Debska-Slizien A, Rutkowski B, Manitus J, Zdrojewski Z, Szolkiewicz M, Bullo B, et al. [Influence of erythropoietin on immunological system of patients with chronic renal failure]. *Pol Merkur Lekarski.* 2003;15(88):326-7;discussion 327-9.
- Trzonkowski P, Mysliwska J, Debska-Slizien A, Bryl E, Rachoń D, Mysliwski A and Rutkowski B. Long-term therapy with recombinant human erythropoietin decreases percentage of CD152(+) lymphocytes in primary glomerulonephritis haemodialysis patients. *Nephrol Dial Transplant.* 2002;17(6):1070-80.
- Lisowska KA, Debska-Slizien A, Bryl E, Rutkowski B and Witkowski JM. Erythropoietin receptor is expressed on human peripheral blood T and B lymphocytes and monocytes and is modulated by recombinant human erythropoietin treatment. *Artif Organs.* 2010;34(8):654-62.
- Lifshitz L, Tabak G, Mittelman M, Gassmann M and Neumann D. Macrophages as novel targets for erythropoietin. *Haematologica.* 2010;95(11):1823-31.