

MEETING ABSTRACT

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# Pharmacological stimulation of murine and human hematopoietic stem cells

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## Background

Hematopoietic stem cell (HSC) transplantation is a standard procedure in the treatment of hematological disorders and also applicable to support aggressive chemotherapy in cancer. In practice, the clinical outcome is often limited by inefficient bone marrow (BM) engraftment or by low numbers of available stem cells. It would therefore be desirable to enhance engraftment by pharmacological stimulation. HSC require several signals for successful migration into the bone marrow. One of these signals is provided by stimulation of  $G\alpha_s$ [1]. Pretreatment with prostaglandin (PG)  $E_2$  enhances engraftment via activation of  $G\alpha_s$ -coupled  $EP_2$  and  $EP_4$  receptors [2]. Treprostinil is a stable analogue of prostacyclin/ $PGI_2$ , which acts via  $IP$ ,  $EP_2$  and  $EP_4$  receptors and is approved for treatment of pulmonary hypertension. Here we tested the hypothesis that treprostinil stimulates stem cell engraftment.

## Methods

Generation of murine bone marrow-derived HSCs: Undifferentiated HSC (lineage-negative,  $Lin^-$  cells) were isolated from murine BM, separated by MACS (magnetic-assisted cell sorting) and characterized by fluorescence-activated cell sorting (FACS). BM transplantation:  $Lin^-$  cells were pretreated *in vitro* in the absence and presence of 10  $\mu$ M treprostinil alone or in combination with 30  $\mu$ M FSK for 1 h at 37°C. The cellular threshold for successful transplantation was determined by titrating the number of HSCs required to allow for survival of lethally irradiated recipient mice. Engraftment and transplantation efficiency was determined by the analysis of white blood cell counts.

## Results

Treprostinil triggered a concentration-dependent accumulation of cAMP in murine  $Lin^-$  cells with an estimated  $EC_{50}$  in the range of 0.3  $\mu$ M. A treprostinil-induced cAMP accumulation was also observed in human HSCs, which were also shown to express the mRNA encoding  $IP$ ,  $EP_2$  and  $EP_4$  receptors. Treprostinil enhanced engraftment of HSCs; this conclusion is based on the following observations: (i) mice injected with treprostinil-pretreated  $Lin^-$  cells had significantly higher levels of circulating white blood cells as compared to those receiving vehicle-treated  $Lin^-$  cells ( $p < 0.05$ , unpaired t-test); (ii) when pretreated and untreated  $Lin^-$  cells were mixed to compete for BM reconstitution, the pretreatment with treprostinil increased transplantation efficiency 1.5–3-fold; (iii) *in vitro* pretreatment of HSCs with treprostinil reduced the minimum number of cells required to rescue a mouse; (iv) engraftment of HSCs was further enhanced when treprostinil was also administered after injection of the pretreated HSCs.

## Conclusions

Treprostinil is suitable for improving haematopoietic stem cell transplantation. The observations allow for designing a protocol to test the compound in a clinical trial.

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