

nature

International weekly journal of science

Search This journal go Advanced search

## Article

Nature advance online publication 6 February 2008 | doi:10.1038/nature06685; Received 26 November 2007; Accepted 16 January 2008; Published online 6 February 2008

## Haematopoietic stem cell release is regulated by circadian oscillations

Simón Méndez-Ferrer<sup>1</sup>, Daniel Lucas<sup>1</sup>, Michela Battista<sup>1</sup> & Paul S. Frenette<sup>1,2,3</sup>

1. Mount Sinai School of Medicine, Department of Medicine and Department of Gene and Cell Medicine, New York, New York 10029, USA
2. Black Family Stem Cell Institute, New York, New York 10029, USA
3. Immunology Institute, New York, New York 10029, USA

Correspondence to: Paul S. Frenette<sup>1,2,3</sup> Correspondence and requests for materials should be addressed to P.S.F. (Email: [paul.frenette@mssm.edu](mailto:paul.frenette@mssm.edu)).

**Haematopoietic stem cells (HSCs) circulate in the bloodstream under steady-state conditions, but the mechanisms controlling their physiological trafficking are unknown. Here we show that circulating HSCs and their progenitors exhibit robust circadian fluctuations, peaking 5 h after the initiation of light and reaching a nadir 5 h after darkness. Circadian oscillations are markedly altered when mice are subjected to continuous light or to a 'jet lag' (defined as a shift of 12 h). Circulating HSCs and their progenitors fluctuate in antiphase with the expression of the chemokine CXCL12 in the bone marrow microenvironment. The cyclical release of HSCs and expression of *Cxcl12* are regulated by core genes of the molecular clock through circadian noradrenaline secretion by the sympathetic nervous system. These adrenergic signals are locally delivered by nerves in the bone marrow, transmitted to stromal cells by the  $\beta_3$ -adrenergic receptor, leading to a decreased nuclear content of Sp1 transcription factor and the rapid downregulation of *Cxcl12*. These data indicate that a circadian, neurally driven release of HSC during the animal's resting period may promote the regeneration of the stem cell niche and possibly other tissues.**