Weizmann Wonder Wander

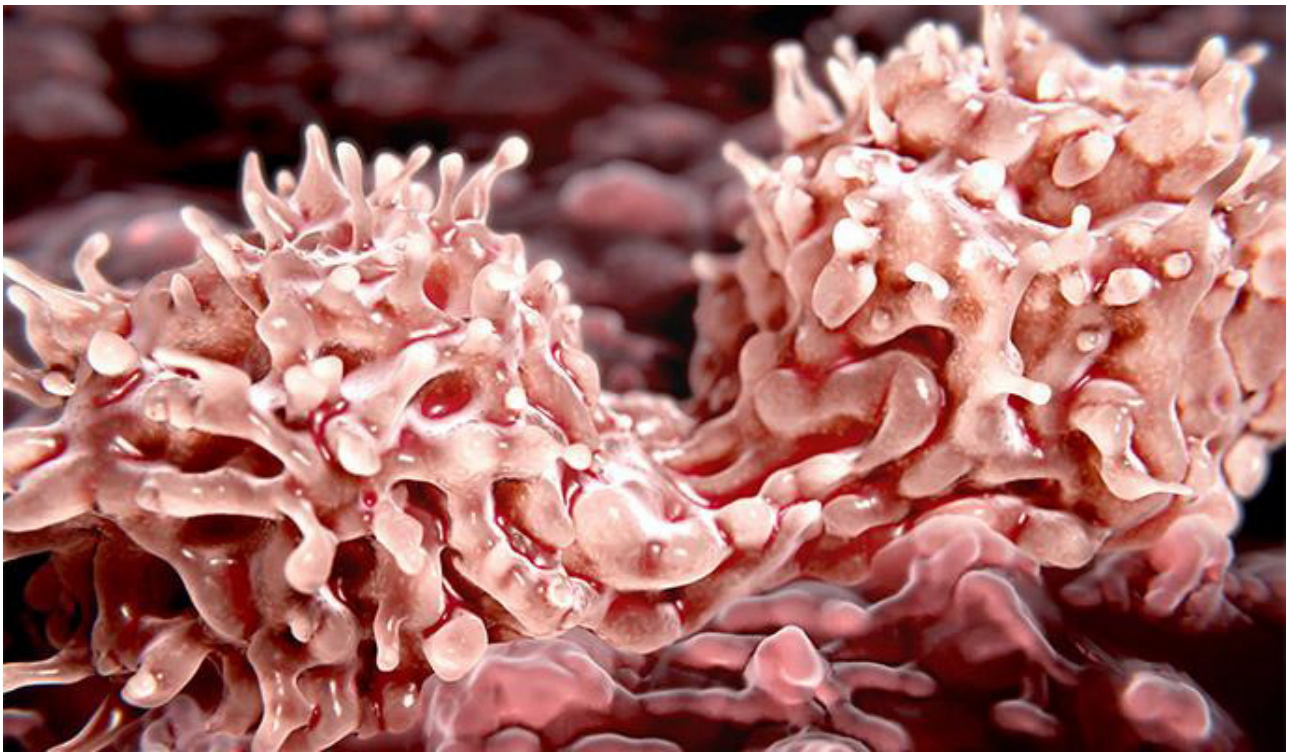
**News, Features and Discoveries from the Weizmann Institute of Science**

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

# The Dark Side of the Bone

## Discovery of stem cell light and darkness cycles may advance bone marrow transplantation

09.10.2018 | Also in: Life Sciences, Biochemistry, Disease, Drugs & Diagnostics, Immunology, Molecular and Cell Biology, Stem Cells



The blood-forming stem cells in the bone marrow divide (above) and differentiate one way in the morning, another at night

Bone marrow replenishes the blood daily with billions of short-lived mature cells, all the while maintaining a full pool of immature stem cells. Researchers at the Weizmann Institute of Science, in collaboration with colleagues in Brazil and elsewhere, have now found that in meeting this challenge, **the marrow follows daily cycles of light and darkness *(https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(18)30387-4)***. This discovery, reported in *Cell – Stem Cell*, suggests that adjusting the timing of stem cell harvesting to these daily cycles may help increase the success of their transplantation.

Dr. Karin Golan in the laboratory of **Prof. Tsvee Lapidot *(http://www.weizmann.ac.il/immunology/Lapidot/)*** of the Immunology Department and her colleagues wanted to

reveal how the production of stem cells in the bone marrow is aff ected by the body's cues for light and darkness. After measuring the numbers of stem cells in the marrow of mice over 24 hours, the scientists discovered that there are two peaks in the production of these cells: at 11 am and 11 pm. The peaks served differ ent purposes and were created by different mechanisms.

## The timing of transplants matters

During the daylight morning peak, large numbers of stem and progenitor cells, which proliferated by cell division, were maturing and differentiating into the diff erent cell types required for replenishing the blood. At the same time, bone marrow blood vessels became more permeable, facilitating the exit of the differentiated cells into the circulation.

During the darkness evening peak, in contrast, a bigger population of cells in the bone marrow acquired the characteristics of undifferentiated – that is, unspecialized – stem cells. When these cells were transplanted into recipient mice, they were engrafted in the bone marrow and reconstituted it more than twice as efficient ly as cells collected during the morning peak.

Dr. Karin Golan and Prof. Tsvee Lapidot revealed a clock governing the production of blood cells

About an hour after the mice started being exposed to light, and an hour after darkness, they had increased levels of two substances in their bone marrow: the neurotransmitter norepinephrine (NE) and an immune system molecule called tumor necrosis factor (TNF), which is normally known to cause cell death and inflammation. When the scientists blocked NE and TNF or conducted experiments in genetically engineered mice that do not have these molecules, the stem cell peaks failed to occur, suggesting that NE and TNF are essential for the production of undifferentiated stem cells and mature

blood cells. “We have discovered a previously unknown mechanism by which stem cells are replenished in the bone marrow,” Lapidot says.

## Reversing the peaks with melatonin

In the morning, under the influence of light, the increase in NE and TNF levels was greater than at night, and this in turn enhanced the levels of molecules called reactive oxygen species, which stimulate stem cell diff erentiation and migration. In the evening, following one hour of darkness, the smaller increase in NE and TNF levels caused a relatively smaller increase in reactive oxygen species, while triggering the production of the major sleep hormone melatonin, which suppresses stem cell differentiation. In fact, the scientists found they could reverse the peaks with melatonin treatment: When they injected melatonin into mice, the typical evening peak, in which large numbers of undifferentiated stem cells are produced , occurred in the morning.

“Our results suggest that the timing of the stem cell harvest may affect the success of bone marrow transplantation,” Golan says. Study findings also suggest that in human patients, it might be possible to increase the success of transplantations by pretreating bone marrow donors with melatonin, or with other molecules found to regulate the light and darkness cycles of stem cell production.

This study was conducted in collaboration with **Prof. John Dick** ***(http://www.jdstemcellresearch.ca/)*** of University Health Network, Toronto, Canada; **Prof. Irit Sagi** ***(http://www.weizmann.ac.il/Biological_Regulation/IritSagi/)*** of Weizmann’s Biological Regulation Department; **Prof. Regina Markus** ***(http://www.iea.usp.br/en/persons/researchers/regina-pekelmann-markus)*** of the University of São Paolo, Brazil; and **Prof. Steffen Jung** ***(http://www.weizmann.ac.il/immunology/jung/)*** and Dr. Biana Bernshtein of Weizmann’s Immunology Department.

*Prof. Tsvee Lapidot's research is supported by the Helen and Martin Kimmel Institute for Stem Cell Research, which he heads; the Dr. Beth Rom-Rymer Stem Cell Research Fund; the Henri Gutwirth Prize; the Felix and Silvia Schnur Endowment Fund in Stem Cell Research; and Asher Pertman and Wayne Pertman. Funding for this project was provided in part by the Brazil Sau-Paulo FAPESPE-Weizmann collaborative grant, created by the University of São Paulo and the friends of Weizmann in Brazil (Amigos de Weizmann) headed by Mr. Mario Fleck. Prof. Lapidot is the incumbent of the Edith Arnoff Stein Professorial Chair in Stem Cell Research.*