

# Researchers find NSAIDs help push stem cells into bloodstream prior to transplantation

March 14 2013, by Bob Yirka

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(Medical Xpress)—A team of researchers at Indiana University's School of Medicine has found that giving meloxicam, a non-steroidal anti-inflammatory drug (NSAID), to people and baboons boosts the number of haematopoietic stem cells that enter the blood stream from bone marrow. This, the team writes in their paper they've had published in the journal *Nature*, may help cancer patients recover their ability to create new blood cells following chemotherapy.

Haematopoietic stem cells are precursors to blood cells that reside in bone marrow—they are harvested from healthy donors or from patients themselves prior to undergoing chemotherapy. Chemicals used to treat cancers such as leukemia or non-Hodgkin's lymphoma, destroy such stem cells, thus, patients who undergo treatment require a transplant of new cells from a donor or re-transplantation of cells harvested prior to treatment, so that their body can once again produce [blood cells](#).

Currently a drug called filgrastim is used to cause more of the stem cells to leave the bone marrow and enter the blood stream where it can be collected for later transplantation. It works by inhibiting a lipid called prostaglandin E<sub>2</sub>, which among other things has been found to inhibit movement of stem cell movement from bone marrow to the [blood stream](#). Unfortunately, not all patients respond well to filgrastim and that's why researchers have been looking for other drugs that can perform the same function. In this new effort, the researchers have

found that NSAIDs (which include most aspirin-like pain relievers) are also able to coax stem cells from the bone marrow into the bloodstream. The team focused on meloxicam because it has the fewest negative side-effects of the group.

The research team has been able to study how meloxicam works with actual patients in field trials because it's a drug that has already been approved for use in patients for other purposes. They found that administering the drug to both people and [baboons](#) increased the number of haematopoietic [stem cells](#) found in the blood and therefore may be a good replacement for patients who don't respond well to filgrastim. They also suspect that using both drugs might prove an even better approach as they've seen hints with baboon testing that doing so provides a synergistic effect. The team plans to next begin testing that approach in a new set of trials.

**More information:** Differential stem- and progenitor-cell trafficking by prostaglandin E<sub>2</sub>, *Nature* (2013) [doi:10.1038/nature11929](https://doi.org/10.1038/nature11929)

### **Abstract**

To maintain lifelong production of blood cells, haematopoietic stem cells (HSCs) are tightly regulated by inherent programs and extrinsic regulatory signals received from their microenvironmental niche. Long-term repopulating HSCs reside in several, perhaps overlapping, niches that produce regulatory molecules and signals necessary for homeostasis and for increased output after stress or injury. Despite considerable advances in the specific cellular or molecular mechanisms governing HSC–niche interactions, little is known about the regulatory function in the intact mammalian haematopoietic niche. Recently, we and others described a positive regulatory role for prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) on HSC function *ex vivo*. Here we show that inhibition of endogenous PGE<sub>2</sub> by non-steroidal anti-inflammatory drug (NSAID) treatment in mice results in modest HSC egress from the bone marrow. Surprisingly,

this was independent of the SDF-1–CXCR4 axis implicated in stem-cell migration. Stem and progenitor cells were found to have differing mechanisms of egress, with HSC transit to the periphery dependent on niche attenuation and reduction in the retentive molecule osteopontin. Haematopoietic grafts mobilized with NSAIDs had superior repopulating ability and long-term engraftment. Treatment of non-human primates and healthy human volunteers confirmed NSAID-mediated egress in other species. PGE2 receptor knockout mice demonstrated that progenitor expansion and stem/progenitor egress resulted from reduced E-prostanoid 4 (EP4) receptor signalling. These results not only uncover unique regulatory roles for EP4 signalling in HSC retention in the niche, but also define a rapidly translatable strategy to enhance transplantation therapeutically.

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