



Toronto General Hospital
University Health Network

MEDIA RELEASE: For immediate release

Healing the Heart with Bone Marrow Cells

'This is the first step in repairing the heart and in preventing the vicious downward spiral of heart failure in which the heart progressively thins and dilates, eventually causing death.'

(Tuesday, July 4, 2006, Toronto) – Researchers at the McEwen Centre for Regenerative Medicine at Toronto General Hospital have discovered the 'SOS' distress signal that mobilizes specific heart repair cells from the bone marrow to the injured heart after a heart attack.

While it has long been known that bone marrow cells have the ability to clear the dead tissue after a heart attack, what has not been known until now is the critically important role of bone marrow adult stem cells in repairing a damaged heart, restoring its function and enhancing the growth of new blood vessels.

"These cells act like generals in a battlefield, explained Dr. Shafie Fazel, cardiac surgery resident at TGH and lead author of the study entitled, "Cardioprotective c-kit+ cells are from the bone marrow and regulate the myocardial balance of angiogenic cytokines," published yesterday in *The Journal of Clinical Investigation*. "When damaged heart tissue sends out an 'SOS' distress signal, this subset of bone marrow cells mobilizes quickly and stimulates the growth of new blood vessels in the heart. This is the first step in repairing the heart and in preventing the vicious downward spiral of heart failure in which the heart progressively thins and dilates, eventually causing death." Despite advances in surgical procedures, mechanical assistance devices, drug therapy, and organ transplantation, more than half of patients with congestive heart failure die within five years of initial diagnosis.

"Cardiovascular diseases are the most important cause of mortality in Canada and the western world," said Dr. Ren-Ke Li, scientist at the McEwen Centre for Regenerative Medicine and Professor of Cardiovascular Surgery at the University of Toronto. "Each year, 70,000 Canadians suffer from a heart attack and many of them are left with crushing disabilities, mainly because the heart muscle is not able to regenerate after a heart attack. This study identifies the method the body employs to repair the heart and provides new therapies to stimulate cardiac regeneration and prevent heart failure in patients who have suffered a heart attack," noted Dr. Li, who is also a Canada Research Chair in Cardiac Regeneration. The research was performed in Dr. Li's laboratory.

Dr. Li's team used genetically-engineered mice in which bone marrow cells were modified to carry a green fluorescent marker allowing researchers to easily track them. The researchers demonstrated that these bone marrow cells are quickly mobilized to the damaged heart region following a heart attack. Once in the damaged area, the cells produce chemicals that trigger the growth of new blood vessels—an important step in repairing the injured heart.

The research also demonstrated that a specific molecule, called c-kit, which is located on the surface of a subset of bone marrow cells, plays a central role in this mobilization. The molecule c-kit is the 'switch' that needs to be turned on by the 'SOS signals' sent by the damaged heart. By binding to another molecule called the stem cell factor – much like a lock and key -- the "turned on" c-kit activates the bone marrow cells to migrate to the heart to help stimulate new blood vessel growth.

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"Heart failure affects one in five Canadians in a lifetime, and commonly occurs after a heart attack. The results of this study have the potential to benefit thousands of Canadians after a heart attack," said Dr. Peter Liu, Scientific Director of CIHR's Institute of Circulatory and Respiratory Health. "By understanding the functions of the c-kit cells and their involvement in heart repair, we can bring brand new treatments for heart attack to this dangerous situation." Dr. Liu is also the Director of the Heart & Stroke/Richard Lewar Centre of Excellence.

In the study, mice with defective c-kit bone marrow cells, could not mobilize these cells to race towards the injured site and regenerate the injured heart. Their heart function was dramatically impaired and, 42 days after a heart attack, their hearts dilated to twice the size of the normal mouse heart. However, the heart function of the c-kit defective mice could be restored to normal by restoring the c-kit cells in their bone marrow, confirming the importance of these cells in repairing the heart. This suggests that a similar treatment of an infusion of bone marrow cells after a heart attack may prevent progression of heart failure in patients who survived a heart attack.

The study may explain why some patients have mild heart attacks and others develop progressive and potentially fatal congestive heart failure. "We know that the number of c-kit positive cells decreases with age and that elderly patients don't recover from heart attacks as well as younger patients. The key for the older patients would be to find new ways to restore this particular subset of cells in their bone marrow," said Dr. Fazel.

"These findings have very important implications," noted Dr. Richard Weisel, Director of the Toronto General Research Institute, Professor and Chairman of Cardiac Surgery at the University of Toronto and co-author in this study. "Based on the knowledge we gained from this study, we can now design new strategies to enhance normal repair and regeneration for patients who suffered a heart attack." This concept is central to the exciting new field called regenerative medicine which aims to restore, repair and regenerate damaged organs rather than merely treating the symptoms of disease.

According to Dr. Weisel, "One treatment resulting from this discovery was to inject cells genetically modified to release large amounts of stem cell factor into the region of the heart injured by the heart attack. These cells increased the 'SOS' signals from the heart and enhanced the intrinsic regeneration of the heart and restored function nearly to normal. These results were recently published in *The Journal of Thoracic and Cardiovascular Surgery*."

This work was supported by The Heart and Stroke/Richard Lewar Centre of Excellence, the Heart and Stroke Foundation of Ontario (HSFO), the Canadian Institutes of Health Research (CIHR) and Physician Service Incorporated. Shafie Fazel received support from the McLaughlin Centre for Molecular Medicine and is a CIHR/HSFO TACTICS fellow (Tailored Advanced Collaborative Training in Cardiovascular Sciences) in the surgeon/scientist program at the University of Toronto.

About Toronto General Hospital, University Health Network

Toronto General Hospital is a partner in the University Health Network, along with the Toronto Western Hospital and the Princess Margaret Hospital. These teaching hospitals are affiliated with the University of Toronto. The scope of research at Toronto General Hospital has made this institution a national and international source for cardiovascular discovery, education and patient care, as well as for its innovations in transplantation, surgical innovation, infectious diseases, diabetes and genomic medicine. In addition, the Peter Munk Cardiac Centre at Toronto General Hospital trains more cardiologists and cardiovascular surgeons than any hospital in Canada.

About the McEwen Centre for Regenerative Medicine

The McEwen Centre for Regenerative Medicine was established in 2003 with a generous donation from Rob and Cheryl McEwen. Its mission is to be a catalyst for regenerative medicine research by facilitating collaborations and promoting research and awareness in the field of regenerative medicine. The McEwen's Centre ultimate goal is to accelerate the development of better, more effective treatments for life-threatening conditions such as heart disease, diabetes, respiratory disease and spinal cord injury. The McEwen Centre for Regenerative Medicine is fully affiliated with the Toronto General Hospital of the University Health Network.

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