Stem Cell Network | Réseau de Cellules Souches
Powering Regenerative Medicine
Propulsons la médecine régénératrice

A Tribute from the Network

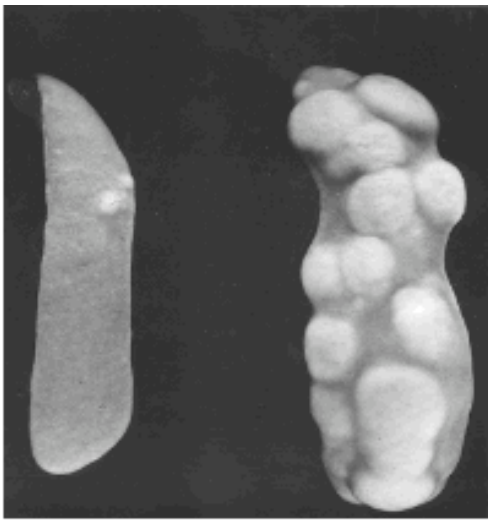
James Till and the Discovery of Stem Cells

By Dr. Ronald Worton, former student

Dr. James Till

It was 1965 when I enrolled in a University of Toronto PhD program in a new Department of Medical Biophysics, housed in the Ontario Cancer Institute (OCI) atop the Princess Margaret Hospital (PMH). The OCI was a unique place with physicians carrying out clinical research and physicists applying physics methodology to biological problems. My MSc degree from Manitoba was in radiation physics, so the Department Head assigned me to Jim Till as my thesis supervisor.

Radiation therapy was a big focus of cancer treatment at the PMH, and for leukemia the process involved total body radiation to kill cancer cells, followed by bone marrow transplant to replenish the blood-forming system. Jim had been attracted to the OCI because of his scientific interest in the nature of cell survival following exposure to ionizing radiation, and hematologist Ernest (Bun) McCulloch had joined the OCI to study radiation as a tool for leukemia therapy.



Dr. James Till and Dr. Earnest McCulloch

In 1961 Bun and Jim joined forces to study mice exposed to ionizing radiation followed by bone marrow transplantation. Jim would do the radiation measurements and Bun would examine the mice for signs of biological damage. Repeatedly, Bun observed that mice who received a lethal dose of radiation, but survived with a bone marrow transplant, had enlarged spleens that were covered in bumps. The spleen was a known site of hemopoiesis, so it was possible that the enlargement was due to transplanted cells dividing and making new blood cells within the spleen. Jim looked at the bumps and noted that they looked like colonies of cells typically seen in a culture dish during his experiments treating cell cultures with radiation, so he wondered if each bump might be a colony of cells. *This was not a eureka moment. If there was one, it came three years later.*

What this did stimulate was a lot of questions. Perhaps a bump is not a colony derived from a single cell, but rather a localized spleen microenvironment where conditions favor cell growth resulting in a bump.Or perhaps the bump was initiated by a cluster of cells becoming trapped in the spleen architecture, where they grew to produce a bump. Bun's questions centered around what might be in a bump. Is it really made up of cells, and if so what kind of cells? If they are blood cells, are they all of one type or are they of many types, characteristic of bone marrow?

Here are the 10 critical pieces of information leading to the stem cell model of hemopoiesis:

1. Bun did what a hematologist does. He examined histological sections through the bumps and found that each bump is made up of a mixture of immature and differentiated blood cells characteristic of those normally found in bone marrow.

2. Jim did what a physicist does and counted the number of bumps in recipient mice transplanted with variable numbers of bone marrow cells, and found a perfectly linear relationship between cells injected and bumps generated, consistent with each bump being derived from a single bone marrow cell.

3. Jim's student, Andy Becker, transplanted irradiated mice with marrow cells that had been lightly irradiated to produce unique spontaneous chromosome anomalies, and he found that most bumps had mitotic cells with normal chromosomes, but a few bumps had dividing cells with a chromosome anomaly, unique to that bump, and different from any chromosome anomaly in other bumps, proving a clonal origin for each bump.

4. Bun's student, Alan Wu, repeated the experiment, and showed that clones with a unique chromosome marker contained mitotic cells with erythroid, granulocytic and monocytic cell characteristics proving the multipotent differentiation potential of each colony forming cell.[1]

By 1963 it was clear that bumps were colonies derived from a single cell and made up of many types of blood cells found in bone marrow. Jim and Bun finally agreed to call the bumps "spleen colonies". The idea of a "stem cell" was an ill-defined concept of a cell with (i) extensive capacity for cell division, (ii) capacity for self-renewal to generate new stem cells, and (iii) capacity for differentiation into one or more cell types. Having demonstrated only number (iii) *Jim and Bun were not yet ready to call the initiating cell a stem cell, so they called it a CFU (colony forming unit).*

5. A colleague, Lou Siminovitch, suggested an experiment to test for self-renewal – a double transplant – first into a mouse to generate spleen colonies, then testing each colony for the presence of CFU in a second transplant. Sure enough, most spleen colonies contained many CFU proving self-renewal.

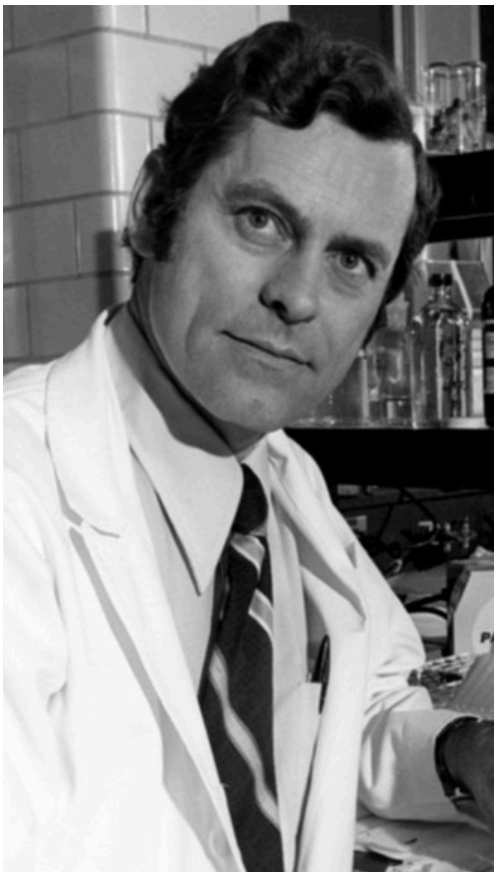
6. A simple extension of the Siminovitch experiment was to collect cells from the secondary spleen colonies and transplant yet again to a third recipient, generating the third generation of spleen colonies. After three passages, each one generating spleen colonies containing over a million cells and a few hundred new CFU, it was clear that CFU had extensive proliferative capacity. *Jim and Bun, with Lou, finally agreed to call them stem cells. It was 1964.*

7. The Siminovitch experiment to prove self-renewal revealed that the extent of self-renewal in a spleen colony was highly variable, with some colonies containing hundreds or thousands of CFU and some containing very few or none.This led Jim to analyse the frequency distribution and fit it to a stochastic model, strongly suggesting that a stem cell's decision to self-renew or differentiate was a random process. A competitor had suggested that replication or differentiation of stem cells was determined by its microenvironment in the marrow or spleen, and he called it a "hemopoietic inductive microenvironment" or HIM. Jim called his model "hemopoiesis engendered at random" (HER). *He always said that he preferred HER to HIM.*

[1] *The original publication contained an error in highlights #3 and #4, attributing Alan Wu's research to proving a single cell origin for each bump. The content has now been corrected.*

When I entered the lab, other researchers had just developed methodology to culture bone marrow cells in dishes where they would form colonies of differentiated myeloid blood cells. Jim jumped on this and began his own experiments to determine the nature of these colonies and their origin. The challenge posed to me was to determine if spleen CFU (CFU-S) were the same or different from culture CFU (CFU-C). Noting the great success in separating macromolecules by density or by sedimentation rate, Jim suggested a similar approach to separating cell types from each other.

8. In 1967 I used density gradient centrifugation to show that CFU-S and CFU-C had distinct density profiles, and then used sedimentation at unit gravity through a sedimentation chamber (developed by a summer student named Alan Bernstein) to show that CFU-S and CFU-C were also different in size, establishing that CFU-C was not a CFU-S type stem cell.



Dr. James Till

9. Alan Wu, meanwhile, showed that spleen colonies derived from a chromosomally marked stem cell contain CFU-C that generate cultured colonies with the same chromosome anomaly, proving that CFU-C may be derived by differentiation from CFU-S. *This is the basis for the textbook depiction of pluripotent "stem cells" giving rise to unipotent "progenitor cells".*

10. In an extension of Alan's experiment, he also found the same chromosomal marker in cells of the thymus and in immunologically competent lymph nodes, strongly suggesting that the immune system is derived from the same stem cell as the hemopoietic system, or the two systems are derived from a common precursor to the spleen colony forming cell.

By 1970 the stem cell discovery story was largely over. Jim and Bun spent the next decade applying the cell culture technique to the study of human leukemias and to the various factors that control hemopoietic cell proliferation and differentiation.

By 1980 Jim realized that he needed a new direction and began collaborations with clinical researchers, biostatisticians, and methodologists. His first paper examined the need for new approaches to designing clinical trials, including the potential use of quality-of-life measures. Subsequently, his publications focused on measuring patients' quality of life, such as eliciting their values for outcomes of treatment options, and measuring cancer patients' desire for information and participation in decision making.

With the advent of the internet, Jim became an outspoken advocate for open access publishing, chairing a CIHR committee that resulted in their open access policy of 2008. With the internet becoming a source of patient information Jim began to advocate for standards in the creation, assessment and communication of evidence to foster rational decision making by patients. There is no better evidence for realization of this goal than the 2021 induction of his former PhD student, Annette O'Connor, into the Canadian Medical Hall of Fame for her pioneering work on "Patient Decision Aids" that provide evidence-based information on options and outcomes with implicit methods to clarify personal values. Jim was not involved in Annette's internationally acclaimed work, but she claims that his advice, direction, encouragement and support (1982-86) sparked her career-long research interest in helping patients make informed values-based decisions with their practitioners.

A giant has left this world after decades of scientific and humanitarian studies to make the world a better place. And you might like to know that he was also the one to demonstrate that sweeping the ice in front of a curling rock makes it travel 3-6 feet further. He was an active curler to age 88 when he was forced to stop by covid.

Acknowledgement: *I thank Annette O'Connor for her assistance in reviewing Jim's publications after 1980, something I could not have done on my own.*

Dr. Ronald Worton is the Emeritus CEO and former Scientific Director of the Ottawa Hospital Research Institute, with a distinguished 37-year career in medical research. Renowned for his groundbreaking work on Duchenne muscular dystrophy, he also served as the founding Scientific Director of Canada's Stem Cell Network. His contributions to science and health research have been recognized with numerous accolades, including the Gairdner Award and the Order of Canada.