BIOGRAPHICAL MEMOIRS

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ERNEST ARMSTRONG McCULLOCH

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Elected FRS 1999

BY TAK WAH MAK*

Campbell Family Institute for Breast Cancer Research, Princess Margaret Cancer Centre, 610 University Avenue, Room 9-406, Toronto, Ontario, Canada M5G 2M9

Ernest Armstrong McCulloch was half of the brilliant partnership that discovered haematopoietic stem cells (HSCs) and changed how we think about human tissue generation and regeneration. Based at the Ontario Cancer Institute (now the Princess Margaret Cancer Centre) in Toronto, the haematologist ‘Bun’ McCulloch, together with James E. Till, a physicist with a steel-trap mind, exercised their penchant for adventurous ‘big picture’ thinking in devising experiments to identify stem cells. This exceptional team was the first to demonstrate that HSCs have the dual capacity to self-renew and to differentiate into a vast array of mature haematopoietic cells. Their trainees, as well as investigators elsewhere, built on McCulloch and Till’s findings not only to isolate and characterize HSCs and progenitors derived from them, but also to devise therapies for certain blood disorders. Later in his career, Ernest focused on characterizing the malignant cells of human leukaemias and determining the effects of various drugs on leukaemic cell growth. The implications of Till and McCulloch’s work continue to be profound and underpin many significant breakthroughs in our knowledge of normal cellular physiology, pathophysiology, tumorigenesis and tissue transplantation. Indeed, regenerative medicine owes its very existence to the stem cell discoveries of McCulloch, Till and others. At times eccentric and demanding, but always well spoken, incisive and erudite, Ernest personified the outstanding research scientist cloaked in Canadian modesty. His legacy lives on in the bright therapeutic future emerging from the rigorous stem cell research being conducted in Canada and around the world.

* Tak.Mak@uhnresearch.ca

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Early days and education

Ernest Armstrong McCulloch was born in Toronto, Ontario on 21 April 1926. His parents were comparatively well off and he enjoyed a privileged upbringing. His maternal grandfather was James Armstrong, a wealthy businessman, and his maternal grandmother took a keen interest in Ernest’s education. In his personal notes written much later in life, McCulloch recounts an early memory in which he was routinely driven to a prestigious junior public school by a chauffeur in a Cadillac sedan. He notes that the chauffeur was often late, which caused him considerable distress but had no academic consequences. Ernest spent his high school years at Upper Canada College (UCC), a boy’s private school in Toronto where ‘elite’ English Canadians of that era sent their sons to grow up into gentlemen of influence. In his personal notes, Ernest recalls that many of his happiest memories of UCC were centred around the long-lasting friendships that began at this school. He also fondly remembers his involvement with the school magazine. He eventually became the editor of this publication, a position of some prestige that came with the title of ‘steward’ and the right to wear a ‘fancy blazer’.

As a student, Ernest was brilliant academically but had little interest in or aptitude for sports. Even the quintessential Canadian pastime, ice hockey, was boring to Ernest. This lack of interest disappointed his father, who had been very good at sports until he sustained a serious injury in France during the First World War. The one exception for the younger McCulloch was sailing, which he learned in his youth at the ancestral family cottage on Ahmic Lake in the Parry Sound district of Ontario (about 240 kilometres north of Toronto). He also grew to love walking and thinking in the quiet woodlands of this region, a habit he maintained later at his own cottage on Thunder Beach in the Georgian Bay area of Ontario.

Although the Toronto in which Ernest grew up resembled a slice of British high society, he later came to appreciate the increasing number of immigrants who settled in what is today one of the most ethnically diverse cities in the world. As an adult, he merrily commented on the transformation that the immigrants had wrought: ‘if you come to Toronto, you start your restaurants, and you preserve your culture – but the rule is that you have to share it. Toronto is much much better now’ (Sornberger, 2011, p. 23).

The origin of ‘Bun’

The nickname ‘Bun’ or ‘Bunny’ originated in McCulloch’s early childhood days. Partly because he was not overly fond of his first name, the term stuck with him for the rest of his life (despite his occasional mild protests). Most of his close friends addressed him as such in public and in private, with the notable exception of his long-time professional partner, James Till. Till always called McCulloch by his given name, Ernest, in public, but admits to using ‘Bun’ in private.

McCulloch attended the University of Toronto for his undergraduate education. A Renaissance man, he was described by his professors and peers as ‘charming, extroverted and very witty’. He had a great love for English literature and poetry, and could recite long passages of Shakespearian plays by heart. He was a voracious reader of works by Jane Austen, Dickens, Keats, Wordsworth, Tolkien and other such notables, a habit he maintained throughout his life. Despite his aptitude for the humanities, however, he opted to become a
physician in the family tradition (his father and two of his uncles were all doctors). Another motive for joining the profession was his feeling that ‘In being a doctor, you are your own boss’.

McCulloch received his medical degree in 1948. However, his passions ran more to science than to medical practice, and he promptly decamped to London to join the Lister Institute for one year to pursue training in clinical investigation. The Lister Institute was a newly formed centre of study into vaccines and antitoxins that could be used for preventative medicine, and this experience sparked McCulloch’s interest in the immune system. In 1949, he returned to Toronto for additional clinical training in haematology at the Toronto General Hospital and Sunnybrook Hospital. He also took on various teaching duties at these institutions, as well as in the Department of Medicine at the University of Toronto. With his increasing interest in science, McCulloch saw fewer and fewer patients and shifted his focus more and more to pure research. In 1957, he joined the Biology Division of the brand new Ontario Cancer Institute (OCI) located at 500 Sherbourne Street in Toronto. The OCI had been established by the Ontario Government for the dual purpose of treating cancer patients and conducting medical research. McCulloch was the first Head of Hematology at the OCI, where he partnered with Alan Howatson to study how viruses contribute to tumorigenesis. However, he soon got sidetracked into pursuing an ambition that became a lifelong goal: to cure human leukaemia. It was at this point that he completely abandoned his clinical practice.

McCulloch launched his research career by examining the differences between normal and cancerous blood cells of patients who were undergoing radiation therapy at the OCI. At this time, in 1958, the Cold War was at its height, fear of nuclear catastrophe was palpable, and government funding was readily available for the study of radiation and its effects on the human body. McCulloch determined that he should carry out studies of irradiated mice to better understand the mechanisms underlying the effects of radiation therapy on human cells, but he lacked the requisite knowledge of the physics of radiation. Harold Johns, the head of the Physics Division at the OCI and one of the pioneers contributing to the invention of the cobalt-60 radiation therapy machine, would not allow mere biologists to use these machines unsupervised. Enter James E. Till of the OCI’s Physics Division. Till had studied at Yale University, one of the leading radiation therapy institutions in the USA, and was an expert in radiation physics. Till and McCulloch got to know one another at informal scientific meetings held in the basement of the home of Arthur Ham, then head of the OCI’s Biology Division. Ham was fond of promoting cross-disciplinary cooperation among OCI scientists by hosting these casual gatherings. Till remembered having enjoyed McCulloch’s presentations at these meetings and volunteered to be his ‘supervisor’ in the use of the radiation machine. Till and McCulloch then blended their complementary skills to form the perfect investigative partnership, and excelled at making insightful connections that became obvious to others only after they proved them. The rest is scientific history.

**THE DISCOVERY OF STEM CELLS**

McCulloch and Till are best known for their work in the 1960s on identifying haematopoietic stem cells (HSCs). Although it had been suspected since the beginning of the twentieth century that a type of stem cell existed for every tissue, it had proved impossible to identify such a cell and define it in any meaningful way. McCulloch and Till’s finding on its own was
thus a landmark discovery, but it also led later to the identification of cells with stem cell properties in many other adult tissues and sparked a revolution in thinking about how tissues are generated and renewed. Major breakthroughs in deciphering the mechanisms underlying the physiology and behaviour of normal and cancer cells can be traced back to the early work of Till and McCulloch. A key aspect of their results was the devising of methods of not only counting HSCs but also detailing their functions. They were the first to show that HSCs have the dual capacity both to self-renew (proliferate) and to differentiate into the various types of mature haematopoietic cells required by the body. The partnership subsequently went on to characterize the malignant cells comprising leukaemias and came up with methods of determining the effects of various drugs on leukaemic cell growth. The implications of their work continue to be profound and underpin many significant breakthroughs in our knowledge of normal cellular physiology, pathophysiology, tumorigenesis and tissue transplantation.

McCulloch and Till’s seminal experiments involved subjecting mice to lethal irradiation to replicate the effects of a nuclear bomb and destroy cells in the bone marrow. They compared the capacities of normal untreated mouse bone marrow cells versus irradiated bone marrow cells to regenerate haematopoietic cells in an irradiated recipient mouse. This approach was a new means of assessing the number of viable cells remaining in an irradiated bone marrow sample, replacing the previous two existing, but unreliable, methods that were based on either in vitro determinations or transplantation of tumour cells. In contrast, McCulloch and Till’s experiments were based on the observations that ‘marrow cells injected intravenously into lethally irradiated animals will permit the survival of a proportion of recipient animals and that the decrease in mortality is a function of the number of cells given’ (1)*. It turned out that it did not matter whether the transplanted marrow cells were irradiated in vivo or in vitro: the survival of the animal depended solely on the number of viable cells able to repopulate the marrow:

It is not known which cell type or types are capable of multiplication when transplanted into a new animal but it is unlikely that fully differentiated cells have this capacity . . . Further, the transplanted cells not only must divide and form clones but also must possess the capacity to differentiate into functional marrow in order to prevent the death of irradiated recipients. (1)

This was the first glimpse of the dual nature of what later became known as HSCs.

McCulloch and Till then went on to examine the spleens of their transplanted animals (2). McCulloch had noticed that discrete, macroscopic nodules had developed on the spleen surface in surviving mice (Figure 1). Upon closer examination, these nodules were found to be filled with proliferating cells. It turned out that the nodules, which the team dubbed ‘spleen colonies’, were easy to count and could be used to quantitatively determine ‘the sensitivity to radiation of the proliferative capacity in vivo of normal adult mouse bone marrow cells irradiated in vitro’ (2). In other words, the number of nodules appearing on the spleen was directly proportional to the number of bone marrow cells originally injected into the lethally irradiated recipient. Rather than rashly labelling them ‘stem cells’, McCulloch and Till used the term ‘colony-forming units’ (CFUs) to describe the injected cells that were able to lodge in the spleen, proliferate and form nodules.

Andrew (Andy) Becker, a graduate student of Till’s, then joined the group and used the unique chromosomal breaks induced in cells by radiation to determine whether all

* Numbers in this form refer to the bibliography at the end of the text.
the cells in a spleen colony were originally derived from one founder CFU. Karyotypic examination confirmed that a spleen colony was indeed a clone. The conclusion was reached that ‘The spleen colony procedure may, therefore, be regarded as an in vivo single-cell technique, analogous to the well-known in vitro single-cell experimental systems’ (3). The team subsequently entered into a rewarding collaboration with Louis (Lou) Siminovitch, who was a senior staff member at the OCI and later distinguished himself as a prominent scientist in the field of genetics. This partnership yielded results demonstrating that CFUs within spleen nodules (now labelled CFU-S) had the property of self-renewal, but that some spleen colonies also contained varying numbers and types of differentiated haematopoietic cells (4). Because of the tremendous heterogeneity in cell composition among the nodules, the group concluded that colony-forming cells, which numbered only about 1 per $10^4$ nucleated haematopoietic cells, were capable of great proliferation, self-renewal and differentiation, but that how these properties were balanced during each colony’s growth could vary due to factors intrinsic to each HSC as well as elements in the immediate microenvironment. The McCulloch, Siminovitch and Till team next demonstrated that genetic factors were also involved in defining CFU-S properties. Through the study of two strains of mutant mice, one defective in stem cell renewal and thus incapable of robust haematopoiesis (W/Wv mice), and the other lacking a tissue microenvironment able to support stem cell proliferation and differentiation (SI/Sld mice), the team defined the autonomous natures of both the stem cell and its niche (5, 7).
All this work bolstered a key hypothesis developed by McCulloch, Siminovitch and Till, namely that: ‘During the development of a colony, a single colony-forming cell gives rise to more than a million progeny, a large majority of which are differentiated as judged by their morphology. Thus, the development of a colony involves processes of differentiation occurring among the progeny of a single cell’ (6). The team theorized that any CFU-S would either self-renew by dividing into two equivalent CFU-S cells, each with the capacity to form new colonies, or it would differentiate into mature haematopoietic cells that might undergo limited proliferation but would lose the capacity to establish new colonies. This groundbreaking theory completely changed researchers’ view of haematopoiesis and sparked parallel efforts around the world to identify the precursor cells of various haematopoietic lineages.

The tool of choice for this work was the clonal assay, and its use, not only in the McCulloch/Till labs but also in those of Donald Metcalf in Australia (Bradley and Metcalf 1966) and Leo Sachs in Israel (Ichikawa et al. 1966, Pluznik and Sachs 1966), led to the concurrent development of a method called the CFU-C (C for ‘culture’) assay, which primarily resulted in the growth of myeloid progenitor cells. Arthur Axelrad of the University of Toronto then established the CFU-E assay, an *in vitro* culture method to detect erythroid precursors (McLeod et al. 1974).

These endeavours eventually led to the discovery of several specific growth factors that became critical therapeutics utilized for the treatment of certain blood disorders. For example, erythropoietin, which was isolated by Eugene Goldwasser at the University of Chicago (Miyake et al. 1977), became the standard-of-care for the treatment of anaemia associated with particular chronic diseases, transplantation, or cancer chemotherapy. Similarly, myeloid growth factors became widely used in the treatment of infectious diseases, inherent neutropenia and post-chemotherapy neutropenia. Other growth factors that gained clinical application were granulocyte/macrophage colony-stimulating factor (GM-CSF), which was isolated by Nicola and Metcalf (Metcalf 1990, Nicola et al. 1983), and granulocyte colony-stimulating factor (G-CSF), which was first purified by Malcolm Moore at the Memorial Sloan-Kettering Institute in New York (Welte et al. 1985). Looking back, the discovery of the original CFU-S by McCulloch and Till was a key enabler of these clinical advances (Figure 2).

Another important outcome of Till and McCulloch’s work was the realization that cells of the thymus and lymph nodes could be derived from the same clone as normal haematopoietic colony-forming cells (8). This result linked the immune system to the haematopoietic system and suggested that a stem cell that was similar to the CFU-S, but was perhaps more primitive, was responsible for generating both lymphoid and myeloid progenitors. In 1969, McCulloch and Till’s team achieved physical separation of HSCs and demonstrated that individual HSCs differed intrinsically in their capacity for self-renewal (9). Others, including Irving L. Weissman and colleagues, went on to isolate the elusive HSCs through increasingly sophisticated enrichment techniques that culminated in HSC purification in the late 1980s (Spangrude et al. 1988). It is now generally accepted that a cell type known as the long-term HSC (LT-HSC) is capable of generating both lymphoid and myeloid lineage cells.

The practical value of the above discoveries later became apparent with the use of human bone marrow transplants to restore a patient’s own failed haematopoietic system. Even before Till and McCulloch (and others) carried out their tissue transplantation experiments in mice, E. Donnall Thomas had been pioneering techniques of bone marrow transplantation in humans (Thomas et al. 1957). Reiner Storb, a member of the original Thomas bone marrow transplantation group, publicly acknowledged that their life-saving procedure was influenced
by the work of Till and McCulloch, as well as by that of Dirk van Bekkum of the Netherlands, D.W.H. Barnes and John Freeman Loutit in the UK, and Joan M. Main and Richmond Prehn of the USA. The clarity of Till and McCulloch’s description of a single stem cell in a hierarchical blood system greatly facilitated the understanding of the principles behind transplantation and spurred subsequent work in this field. As more and more applications of McCulloch and Till’s work evolved over the next decade, they mused, ‘Our experience provides yet another case study of both the value of fundamental research and the importance of serendipity in scientific research’ (11) (Figure 3).

The landmark discoveries of McCulloch and Till not only established models for elucidating mechanisms of HSC functions and aided in bone marrow transplantation but also
set the stage for investigations of how non-haematopoietic tissues are regenerated after injury. The key issue was and remains: what factors drive a given stem cell to undergo self-renewal as opposed to differentiation? As early as 1964, based on their studies of CFU growth in murine spleen, Till, McCulloch and Siminovitch postulated that the decision of an HSC or early differentiated progenitor to proliferate rather than differentiate was stochastic in nature (6). In other words, HSC cell fate decision-making was somewhat random rather than instructional in character. This concept has served as the backbone for many studies in a wide variety of tissues over multiple decades. As observed by Sir John Bell of the University of Oxford: ‘Although the concepts of tissue repair and regeneration and development had existed as individual entities before 1961, the concept that you had discrete cell populations that populated and self-renewed, which was ultimately their breakthrough, changed the way everybody thought about that particular discipline’ (Sornberger 2011, p. 42).

Till and McCulloch’s method of quantitatively following HSC differentiation into mature haematopoietic cells of a broad range of functions also primed the testing of the notion that a stem cell of a particular tissue might be able to differentiate into cells of another lineage, a concept known as ‘plasticity’. This idea of stem cell plasticity fascinated McCulloch and was frequently the subject of furious debate within his lab and at staff retreats. Lineage infidelity in oncogenesis was by then a well-recognized phenomenon (Golub et al. 1999), and so might also apply to normal cells. By the early 2000s, evidence had accumulated that HSCs could give rise to muscle and liver cells, among other tissue types, and that, conversely, progenitor cells in some tissues bore surface markers often associated with HSCs (Wulf et al. 2001). In 2005, Weissman’s group elegantly employed highly purified HSCs to show that, at least
for haematopoietic cells entering the brain, no detectable switching to the neuron lineage occurred, making the likelihood of plasticity under these circumstances remote (Massengale et al. 2005). In his commentary on this paper in Nature Medicine (11), McCulloch emphasized the degree of purity of the HSCs used by the Weissman team to cement the argument that, at least in this situation, HSC plasticity could not be documented. The idea of lineage plasticity within normal tissues became the subject of intense research in the later stages of McCulloch’s career and remains controversial to this day.

FOCUS ON LEUKAEMIA

In the 1970s, McCulloch’s lab became focused on dissecting the cellular components and regulatory mechanisms of human leukaemia, particularly acute myeloid leukaemia (AML). His group put forward a model for AML development that stated: (i) myeloblastic leukaemias originate from pluripotent HSCs; (ii) after genetic transformation, a single altered stem cell expands in the patient; (iii) the clone developing from this stem cell shows increased genetic instability and clonal evolution; and (iv) abnormal stem cells retain the capacity for differentiation along different pathways, leading to heterogeneity among leukaemic cells (10). Much effort was then expended during the 1980s and 1990s both to validate this model and to examine the sensitivity of normal progenitor cells and leukaemic blasts to various chemotherapy drugs. Numerous genes governing normal and abnormal stem cell behaviour were identified during the course of these studies, as were the effects of various growth and hormonal factors that influenced stem cell differentiation. In addition, this work was the prelude to the identification in 1994 of tumour-initiating cells in AML by John Dick’s group, which was at the time located at the Hospital for Sick Children in Toronto (Lapidot et al. 1994). Although McCulloch moved away from the bench in his twilight years, his team and its ‘offspring’ continued and continue to study stem cells, both normal and malignant, and still regularly make significant scientific contributions to these fields.

REVERED TEACHER

Professor McCulloch was not only a great scientist but also a great teacher. Although he was occasionally piercing in gaze, eccentric in manner, and clear in his refusal to suffer fools gladly, most trainees emerging from his lab found the experience to be invaluable. Those who conquered their trepidation and whose work survived his keen scrutiny say that he inspired them with his enthusiasm for science and pushed them to think above and beyond the confines of their immediate projects (Figure 4).

McCulloch encouraged translational thinking before the term was coined, urging his colleagues and trainees to relate their findings in the laboratory to problems in the clinic, and to collaborate widely to obtain fresh points of view. He was the epitome of an original thinker. He easily applied insights from one field to another, and often came up with ‘out of left field’ ideas that drove his colleagues and students to say ‘Now why didn’t I think of that?’ He set a fine example for his trainees, personifying scientific passion tempered with wisdom, and research precision enlivened with courageous insights. A favourite mantra was ‘You cannot eat breakfast all day’, a reference to the need to maintain a broad research horizon and sample intriguing problems from various fields. McCulloch stressed the importance of integrity, both
personally and scientifically, and was always unduly modest about his considerable talents and achievements. He taught his trainees to be generous with their time and materials, and constructive in their comments on others’ work. Numerous high-profile scientists now working around the world benefited from his mentorship and to this day attempt to carry on his tradition of razor-sharp observation and counterintuitive thinking.

The list of alumni who have passed through the McCulloch/Till lab reads like a Who’s Who of Canadian biomedical science: Andy Becker, Alan Bernstein, Ronald Buick, Allen Eaves, Connie Eaves, Victor Ling, Norman Iscove, Hans Messner, Rick Miller, Mark Minden, Bob Phillips, Don Sutherland, Ronald Worton, Allen Wu and Gillian Wu, among others. I am very honoured to count myself among this group. Other prominent Canadian researchers have studied with McCulloch/Till alumni, including John Dick, who discovered AML stem cells (Lapidot et al. 1994); Pamela Ohashi, a prominent immunologist well known for her work on the molecular basis of thymic selection and immune tolerance (Sebzda et al. 1994); and Gordon Keller, a renowned developmental biologist who discovered a common precursor for haematopoietic and endothelial cells (Choi et al. 1998). Through these individuals and their trainees, the McCulloch/Till approach to science, with all its imagination and rigour, has been passed down to the current crop of graduate students and postdoctoral fellows. Below are the thoughts of some trainees of either McCulloch, Till or their alumni, many of whom are giants in their fields in their own right. I start with my own recollections of my time with McCulloch.

Tak Wah Mak: How I remember McCulloch

I joined the Till and McCulloch group about a dozen years after their discovery of haematopoietic stem cells. I regret having missed the excitement of those seminal first findings
but I was exceedingly lucky to be carried along in the ongoing momentum of their research. I fondly remember the leukaemia meetings that McCulloch and Till held at the McCulloch family enclaves at Thunder Beach and Ahmic Lake. We would sail, watch the water and discuss our science, thinking about biology while basking in the freedom of the great outdoors. So many great collaborations and ‘mini-Eureka’ moments had their foundations in those meetings (Figure 5).

Often in science, when a seminal discovery is associated with more than one leader in a field, discussions are triggered as to who contributed what. I have found it a very difficult task to tease apart the influence of McCulloch versus Till in their shared breakthroughs. They were both such modest individuals, who maintained the utmost respect for each other, and one steadfastly refused to claim credit at the expense of the other. Nonetheless, they had very different personalities and highly dissimilar scientific backgrounds. While Jim Till was the physicist with the steel-trap analytical mind who crossed over into biology, McCulloch was the ‘big picture’ thinker who liked to venture into unknown territory. Together they would look at any scientific problem in a wider context and apply to it a vigorous and quantitative analysis.
What struck me most about McCulloch’s thinking was his ability to seek out a paradigm shift (and use that term) long before it became a ‘thing’ in our modern society. McCulloch was always looking for the opposite to the obvious as an alternative way of understanding a conundrum, and actively rooted out dogma and entrenched concepts that might actually be wrong and thus limit scientific progress.

McCulloch was also a friend and admirer of the iconic Canadian philosopher and public intellectual Marshall McLuhan. McLuhan is known, among many things, for his promotion of the concept of using tetrads to analyse four key questions in relation to communications media. What does a particular medium: (i) enhance, (ii) make obsolete, (iii) retrieve that has been rendered obsolete, and (iv) flip into when pushed to extreme? (McLuhan and McLuhan 1988). McCulloch was fond of transposing the concept of McLuhan tetrads to scientific explorations. He contended that our understanding of each paradigm of science is governed by the same principles and undergoes the same transformation. I have often wondered if Bun’s successful deliberations in science were guided by these imperatives.

James Edgar Till: How I remember McCulloch

The collaboration between Ernest Armstrong McCulloch (EAM) and myself began almost by accident. It was not carefully planned. We both were members of the founding research staff at the new (in 1957–58) Ontario Cancer Institute (OCI) in Toronto. The OCI initially had two research divisions. One was the Physics Division, of which I was a member. The other was the Division of Biological Research. EAM was a member of the latter division, which was headed by Arthur Ham, the author of a popular textbook of histology that was used by many medical schools. The Physics Division was headed by Harold Johns, a pioneer in the field of medical physics in Canada. A priority in the early days of the OCI was to help the new staff members to get to know each other. For this reason, Arthur Ham hosted a series of meetings at his home at which members of the research staff introduced themselves and spoke about their research interests. I recall that I found EAM’s presentations quite interesting. This memory played a crucial role in the initiation of our collaboration. Later on, at the end of a staff meeting of the Physics Division, Harold Johns noted that EAM wanted to make use of an irradiation unit developed by the Physics Division for experimental purposes. Johns had a rule that a member of the Physics Division needed to be involved in any uses of the irradiation unit. He asked for a volunteer. After a brief pause, I said: ‘I’ll volunteer’. It was my memory of EAM’s earlier presentations that had prompted me to speak up.

We soon found that we both enjoyed working together. My role quickly evolved from provision of technical expertise about radiation sources and radiation dosimetry to full involvement in the planning and conduct of experiments. A catalyst in this transition was an error in dosimetry for which I was responsible. When the error was found, I went (somewhat shamefacedly) to EAM and confessed. His reaction was noteworthy in two ways. Firstly, I think he was pleased that I was willing to confess to making an error. Secondly, I think he was secretly delighted to learn that physicists, just like all other humans, could make a mistake. I therefore feel that my error played a key role in breaking the ice. We both believed that we could trust each other and could freely express divergent points of view. As an illustration, I can remember EAM once saying: ‘If Jim and I disagree, we know that the correct answer is somewhere else’. This level of trust played an absolutely crucial role in our very fruitful and enjoyable collaboration.
Ron Worton: How I remember McCulloch

I joined the lab of Jim Till as a PhD student just after he and his partner, Ernest McCulloch, had identified spleen nodules in irradiated mice. At the beginning, I was afraid of Dr McCulloch because I felt that his thinking was so far ahead of my own. It was only after I had generated my first substantial results that I gathered the courage to present my data to him. He listened, agreed on my work’s importance and rapidly began to suggest future experiments – dozens of them. This was my first personal encounter with the brilliant intellect of Bun McCulloch.

My next memorable encounter occurred when I wrote my first stem cell paper. I had used gravity sedimentation techniques to show that the stem cells identified by the spleen colony assay were totally different from the cells that formed colonies in cell culture. Of course, my first draft contained much unnecessary detail that only I deemed to be vital. When Bun asked if I would like to know how he would write up my results, I said yes. He picked up his Dictaphone and in the next 20 minutes paced the floor while reducing my pedantic prose into a punchy and dramatic account. I was transfixed by this valuable lesson and it completely changed how I wrote subsequent papers (although I never did learn to dictate one in 20 minutes).

I hope that the current generation of stem cell scientists will reflect on Till and McCulloch’s original experiments, carried out long before ‘stem cell’ was a household term. Bun and Jim were true pioneers whose work changed how we think about the human body and how it develops and is maintained. Bun can rest knowing that he truly made a difference. (With excerpts from Worton 2011.)

Connie Eaves: How I remember McCulloch

Bun had a deeply insightful intuition about science that was enormously captivating to his trainees but often scary to the more established. His amazing sense of humour and unforgiving obsession for truth were also remarkable and inspirational. Perhaps his most endearing characteristic, however, was his ability to articulate complex ideas in words that embraced every level of understanding without the need to overstate or self-proclaim, and were often peppered with quotes from the English literature that most of us forgot before we left high school. His unique partnership with Jim Till enabled this duo to become giants in forecasting principles of cell behaviour that remain a cornerstone of our current understanding of normal and malignant cell populations. I am enormously grateful and proud to have received their amazing mentorship.

Irving Weissman: How I remember McCulloch

When I think of Bun McCulloch, I am struck afresh by the originality of his discoveries, and how he unerringly hit the central point initially with his observations and secondly with the experiments they engendered. I am also drawn to the way he and Jim Till built a team that not only worked together to open up the field of HSC/progenitor cell biology but also attracted and/or trained the next generation of scientists that turned Toronto into a centre of basic research in this area as well as a leader in its application in biomedicine. I have written elsewhere that, in my view, most investigators would have missed the importance of the ‘bumps on the spleens’ of bone marrow-injected irradiated mice, much less have guessed the significance of the fact that each bump contained a variety of myeloid and erythroid cell types (Weissman 2011, Weissman 2014). Few others would have appreciated that a single cell might
have been the origin of a spleen bump, that within this bump were bump-forming cells and that each bump was a clone. Most would not have thought that sometimes a clonal progenitor could give rise to myelo-erythroid cells as well as to lymphocytes, and that the phenotypes of mice bearing the W/Wv and Sl/Sld mutations provided direct evidence of stem cell and niche cell activities. These discoveries were certainly central to my own scientific direction, and, if you look at where the field is today, they were also pivotal to the research paths of the current leaders in HSC/leukaemia biology everywhere. Imagine if Till and McCulloch had dismissed the bumps on their mouse spleens as an artefact!

**Gordon Keller: How I remember McCulloch**

The discoveries that Ernest McCulloch made together with his colleague Jim Till over a half a century ago launched the modern era of stem cell biology. Their concepts of stem cell behaviour and function have stood the test of time and continue to influence the field today. I was very fortunate to be able to do my postdoctoral training at the Ontario Cancer Institute at a time when the impact of their findings was a driving force in the field of haematopoiesis. The critical thinking that McCulloch and Till brought to stem cell biology greatly influenced us all at the time, and set a high standard that has guided many of us throughout our careers.

**John Dick: How I remember McCulloch**

When I was a postdoc in the 1980s, an important lesson I learned from McCulloch was to let the past guide my future so as not to ‘reinvent the wheel’. My mentors, Bob Phillips and Alan Bernstein, punctuated our weekly lab meetings with observations such as ‘Well, in the 1960s, Till and McCulloch carried out such and such experiment’. Thus, I was prevented from entering many a blind alley. Although I did not interact extensively with McCulloch during this period, he was the head of the OCI and an imposing figure whose research rigour loomed large over my training. There was always the fear that McCulloch would ask a killer question, exposing one as not knowing enough background about one’s project. Formally or informally, McCulloch spoke with precision, in sentences strung together logically to create full paragraphs, without pause or misplaced word. He instilled in me the need to always be prepared for public speaking and to present clearly.

My direct interactions with McCulloch came years later after my lab had obtained evidence for the existence of a leukaemic stem cell. I sent him my draft manuscript because I was making historical claims and I wanted to be certain of their accuracy. He was generous with his time and incisively told me to focus only on my most important message. I felt this message should be the cell-of-origin question, but McCulloch held that the formal proof of a cellular hierarchy in AML was the key. He was right and his advice greatly helped me to sharpen my paper.

After I established my own lab, I often told my trainees that what we were doing was replicating in the human setting the approaches that McCulloch and Till had already developed in the mouse. All my students needed to do was read their original papers and use them as their guide. Indeed, questions like ‘What makes a stem cell a stem cell and how do you measure them?’ remain as fresh today as 50 years ago when first posed by Till and McCulloch (Figure 6).
RIPPLE EFFECT

The following is the perspective of 11-year-old Ethan Cairns, who, when tasked by his teacher with writing an essay about a prominent Canadian, chose the team of McCulloch and Till. In his essay entitled ‘Two stem cell scientists walk into a bar . . .’, Ethan set out a short but highly entertaining biography of his selected researchers. Below is his reflection on how their success affected him personally.

‘I have always known how important science is because both my parents are scientists. When I was given this school assignment to write a biography of a famous Canadian, I wanted to do someone that not many people knew about. At first I thought about profiling Frederick Banting, but as I scrolled through the Google results for “Famous Canadian scientist”, I noticed Dr McCulloch’s name. My dad told me that Dr McCulloch had taught Dr Tak Mak, who heads the lab in which my dad works. I started to research Dr McCulloch and
noticed three important things. One, Dr McCulloch worked with Dr James Till for most of his career, making it impossible to talk about one without the other. Two, Dr McCulloch was very influential and charismatic. He taught many students to follow in his footsteps, creating a whole new generation of stem cell scientists. Three, I really liked Dr McCulloch’s research approach. When he noticed colonies on the spleens of his experimental mice, he didn’t just jot the observation down and forget about it. He pursued this lead to its ground-breaking conclusion and secured his place in history. After doing my project on Drs McCulloch and Till, I feel that I have a much deeper understanding of and interest in science and medicine, and I am leaning towards studying a scientific discipline at university.

And so McCulloch and Till can take credit for kick-starting the scientific passions of yet another generation of Canadian researchers.

**DEDICATED COMMITTEE MEMBER**

Ernest McCulloch was not only a great scientist and teacher but also a believer in collaboration, collegiality and giving back to the research community. He served on countless scientific advisory committees at the international, national, provincial and local levels, and was on the editorial boards of numerous peer-reviewed scientific journals. He held leadership positions at the OCI and at the Institute of Medical Science at the University of Toronto, and he served as President of the National Academy of Science of the Royal Society of Canada. He was unfailingly loyal to the OCI, remaining on its faculty for life and writing a book about its history at the original 500 Sherbourne Street location.

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**What’s in a name?**

The Ontario Cancer Institute (OCI) was established by the Ontario government at 500 Sherbourne Street in Toronto in 1952. It was designed to perform a dual function: to undertake cancer research and to treat cancer patients. However, there was considerable stigma attached to the word ‘cancer’ at the time, and some patients (and their family members) were uncomfortable in revealing the true identity of their diagnoses. To provide a bit of cosmetic cover, the clinical operations were cleaved off in 1958 into an entity called the Princess Margaret Hospital (PMH). The research divisions remained under the OCI designation. In 1995, both the PMH and the OCI operations moved to larger buildings at 610 University Avenue. In 1998, the PMH became part of the University Health Network, which merged the oncology services of the PMH, Toronto General Hospital and Toronto Western Hospital. In 2012, with cancer no longer a dirty word, the OCI name for the research divisions was dropped and the group rejoined the PMH as both were subsumed into the Princess Margaret Cancer Centre. This centre is now recognized as an international leader in cancer research and innovative treatments.

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**FAMILY MAN**

Last, but definitely not least, a complete biography needs to make mention of Ernest McCulloch’s passion for his family. He was married for nearly 58 years to Ona, with whom...
he had five children: Paul, Michael, James, Robert and Cecilia. As these children, now adults, state: ‘Dad greatly loved our mother, and was greatly loved by her. He was also much loved by his children and grandchildren. We miss him greatly. His like may not be seen again in our lifetimes.’

The family enjoyed time together at their own cottage on Thunder Beach (affectionately dubbed Mirkwood Forest) and every August at the ancestral family cottage on Ahmic Lake. McCulloch’s favourite cottage pursuits were teaching his children to sail, canoe and swim, and to chop wood and build a respectable fire. He would take long nature walks with them on local trails through the woods, taking a particular interest in trees that appeared to be blighted by virus. A subject for a grant during his retirement, he would say. Alas, the trees will not benefit from his attention to their plight (Figure 7).

THE McCULLOCH LEGACY

The year 2011 marked the 50th anniversary of the first publication of Till and McCulloch’s work on HSCs. The University of Toronto and the Princess Margaret Hospital jointly planned
an event to be held on 11 February 2011 to celebrate this anniversary, stating that it would be ‘a great opportunity for the research community to pay homage to their achievement and to highlight Toronto’s ongoing excellence in stem cell research’. Sadly, McCulloch did not live to enjoy the event, passing away on 20 January 2011. His legacy in terms of scientific possibilities is thrilling: the much-hyped field of therapeutic stem cell transplantation has promise that is real, if not yet quite realized. Regenerative medicine is under concrete development, and the targeting of cancer stem cells as a means of combating malignancies is under active investigation. All of these research fronts are contributing to the ongoing stellar stem cell research in McCulloch’s hometown of Toronto. McCulloch would be proud (Figure 8).

HONOURS, AWARDS AND APPOINTMENTS

1969  Gairdner Foundation International Award (with James Till)
1974  Member of the Royal Society of Canada
1982  Professor, University of Toronto
1988  Officer of the Order of Canada
1991  Thomas W, Eadie Medal (with James Till)
1991  Senior Scientist Emeritus at the Ontario Cancer Institute
Ernest Armstrong McCulloch

1999 Fellow of the Royal Society
2004 Member of the Canadian Medical Hall of Fame
2005 Albert Lasker Award (with James Till)
2006 Member of the Order of Ontario
2007 National Cancer Institute of Canada Diamond Jubilee Award (with James Till and John Dick)
2010 Member of the Canadian Science and Engineering Hall of Fame

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SOURCES

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Ernest Armstrong McCulloch’s personal notes, prepared before 20 January 2011

AUTHOR PROFILE

Tak Wah Mak

Tak W. Mak is the Director of the Campbell Family Institute for Breast Cancer Research at the Princess Margaret Cancer Centre in Toronto, Canada. He is best known as the leader of the group that first cloned the genes of the human T-cell antigen receptor. His team also pioneered the creation of many strains of genetically altered mice that proved critical to unravelling intracellular programmes governing the development and function of the immune system, as well as inflammatory responses. In addition, these mutants enabled the dissection of signal transduction cascades in various cell survival and apoptotic pathways, as well as the identification of genes involved in tumorigenesis and metastasis. Most recently, his laboratory has studied signalling pathways that sustain the tumour cell phenotype,
focusing on genes involved in cancer cell metabolic adaptation. Dr Mak first encountered Ernest McCulloch and James Till when he joined the Ontario Cancer Institute in 1973 as a postdoctoral fellow. He became a senior scientist at the OCI in 1975 but spent a year in 1980 learning molecular biology in the lab of Howard Temin at the University of Wisconsin. Upon his return to the OCI, he joined McCulloch’s team researching leukaemias and began to examine human T-cell development. His interest in T-cell receptors soon burgeoned and led to his landmark discovery. ‘McCulloch and Till were behind me when most folks thought my ideas were outlandish.’ Dr Mak is very grateful to them for their faith in him.

Photo: McCulloch and the author in the Princess Margaret Hospital Research Atrium in 1997 (University Health Network Photography Department).

REFERENCES TO OTHER AUTHORS


Ernest Armstrong McCulloch


**BIBLIOGRAPHY**

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