

This Week's Citation Classic

Till J E & McCulloch E A. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. *Radiat. Res.* **14**:213-22, 1961.

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The authors describe 'a technique for the measurement of the number of cells in a bone marrow suspension capable of continued proliferation.' It involves 'the formation of colonies of proliferating cells' which, in irradiated mice, 'appear as gross nodules in the spleen.' [The SCI[®] indicates that this paper has been cited over 1,125 times since 1961.]

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"This paper was a report of work carried out in collaboration with Ernest McCulloch; my name appeared first on the paper simply because it was my turn. We thought the paper was a pretty good one, but certainly I for one did not expect it would be cited so often.

"The basis for the interest in this paper is that it described a method for detecting and counting pluripotent stem cells of the blood-forming system. The method is based on the ability of such stem cells, at least in mice, to multiply and differentiate to form localized colonies of descendants in the spleen of an irradiated mouse. These 'bumps on the spleen' had been described before, but in words such as 'local areas of regeneration.' A key contribution of our work was the realization that the 'bumps' could be regarded as 'colonies,' and that it was possible that the 'colonies' originated from single cells. Andrew Becker, in a subsequent publication, showed this view to be a reasonable one.¹ This established the validity of the method as an assay

for the cell of origin of the colonies; this assay could then be used to study the properties of these cells. In the beginning, we were careful to avoid assigning an identity to these as yet uncharacterized cells, and only referred to them by the operational term 'colony-forming units' (CFU). This CFU terminology has persisted and proliferated, and I am sure it now confuses the uninitiated, since several kinds of different CFU have been described and are named in different ways using the term CFU with various prefixes or suffixes.

"When the colonies were examined, they were found often to contain more than one kind of differentiated cell. Subsequent work, especially by Alan Wu, provided evidence that these different cell types could be derived from the same CFU.² This provided reasonably strong evidence that the CFU were pluripotent in their potentiality for differentiation. The question was an important one to settle, because it had been debated by several generations of hematologists. Does the blood-forming system of the adult contain pluripotent (or only unipotent) stem cells? For the mouse, the answer was yes, pluripotent stem cells are still present in adult life.

"If we were indeed detecting pluripotent stem cells using the spleen colony assay, then the colonies should themselves contain new stem cells. In a rather important series of experiments initiated by Louis Siminovitsh, this was shown to be the case.³ CFU were capable of self-renewal, in that the colonies to which they gave rise contained significant numbers of new CFU. These properties, a capacity for extensive proliferation including self renewal, and a capacity to give rise to several types of differentiated descendants, are the essential properties of pluripotent stem cells."

1. Becker A J, McCulloch E A & Till J E. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. *Nature* **197**:452-4, 1963.
2. Wu A M, Till J E, Siminovitsh L & McCulloch E A. A cytological study of the capacity for differentiation of normal hemopoietic colony-forming cells. *J. Cell Physiol.* **69**: 177-84, 1967.
3. Siminovitsh L, McCulloch E A & Till J E. The distribution of colony-forming cells among spleen colonies. *J. Cell Physiol.* **62**:327-36, 1963.