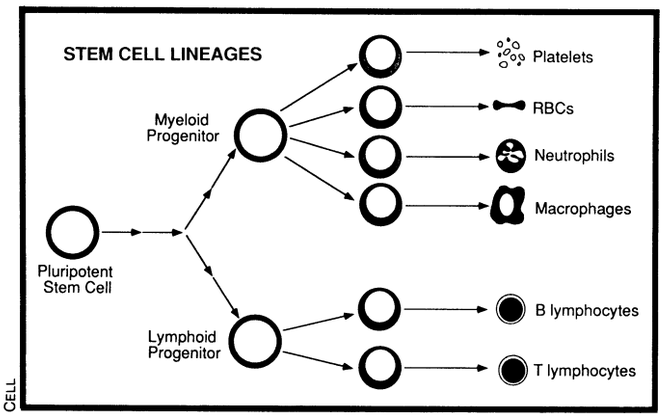
Blood Cells Traced to a Common Ancestor

After years of sifting through thousands of bone marrow samples, California researchers announced this week that they have identified a candidate "pluripotent" human blood cell — the elusive, primordial cell thought to serve as a fount replenishing red and white blood cells throughout a person's life.

The pluripotent blood cell has been the Holy Grail of hematology because it may hold the key to cures for a host of genetic disorders, leukemias and immune-system diseases such as AIDS. But the purported discovery has already generated controversy among hematologists, some of whom question the thoroughness of the experiments that led to the new finding.



Pluripotent cells produce myeloid cells in the marrow and lymphoid cells in the thymus or marrow. Myeloid daughter cells differentiate into platelets, red cells or infection-fighting neutrophils or macrophages. Lymphoid daughters become B or T lymphocytes, key immune-system cells.

Irving L. Weissman, a noted immunologist at Stanford University, reported the discovery at the 15th Bristol-Myers Squibb Symposium on Cancer Research, held in Seattle. Weissman told the conference that he and his colleagues at SyStemix Inc., a biotechnology company he founded in Palo Alto, Calif., had isolated a human pluripotent cell that can generate nearly every type of human blood cell when transplanted into the bone marrow of mice lacking an immune system. He claims that the cell is the most basic known "stem" blood cell, from which arises the family tree of more specialized blood cells.

To track down the pluripotent cell, the researchers used a series of antibodies against cell-surface proteins that identify the "cluster of differentiation" (CD) of each specific blood cell type. Blood cells that perform different jobs — such as antibody-producing B-cells, or invader-gobbling macrophages — wear different CD-protein uniforms, which are assigned a number as they are found by immunologists. Moreover, just as lieutenants' uniforms differ from those of generals, blood cells don new uniforms as they mature and are promoted to new roles.

Because Weissman and his colleagues reasoned that blood-cell precursors must persist throughout life, they began their quest among a set of bone marrow cells that had already survived for months in their laboratory. They eventually narrowed their search to a subset of slow-growing cells that stained weakly with the dye rhodamine — an indication that the cells' energy-producing mitochondria were merely idling.

When the researchers added these human marrow cells, one by one, to connective-tissue cells taken from mouse marrow and grown in the laboratory, they found one type of cell that could give rise to all major blood-cell varieties. These cells stuck to a mixture of labeled antibodies that detected the CD34 protein and another protein — called Thy1 — that is present on T-cells, white blood cells that mature in the thymus. The same cells also lacked a set of CD proteins, collectively known as the lineage determinants (Lin), normally found on mature blood cells. Weissman's group named the precursor cells $Thy1^{+}Lin^{-}CD34^{+}$.

To prove that these cells could give rise both to lymphoid cells (produced in the lymph nodes, thymus or spleen) and to myeloid cells (made in the bone marrow), the researchers injected some of the cells into the bone marrow of immunodeficient mice, and others into human thymus tissue transplanted into a second group of immunodeficient mice (SN: 9/24/88, p.198). The first group of mice developed human white blood cells that normally arise from marrow, the researchers found, while the second group developed a normal collection of human T-cells.

The researchers conclude that the $Thy1^{+}Lin^{-}CD34^{+}$ cells — which represent only 0.05 to 0.1 percent of all human marrow cells — must be pluripotent. "These were the only cells that worked [to replenish the white blood cells of immunodeficient mice], so we think they must be candidate human stem cells," Weissman says.

Hematologist Malcolm Moore calls that claim "outrageous." The development of an antibody to detect human Thy1 "is the only original thing I see in this report," says Moore, who studies blood development at Sloan-Kettering Cancer Center in New York City. "They can't really prove that they have pluripotent cells until they show that the cells can produce a full complement of normal blood cells in human patients given a bone marrow transplant." He notes that Weissman and other colleagues performed this definitive experiment in mice when they reported finding the mouse pluripotent blood cell in 1988 (SN: 7/9/88, p.20).

John E. Dick, a stem-cell researcher at the University of Toronto, notes that other researchers have already shown that cells bearing CD34 but lacking Lin can grow for months among marrow connective-tissue cells in the laboratory. He asserts that Weissman's group will have to demonstrate that descendants of their candidate cell can outlast other blood cells in mice or humans.

Weissman agrees that the acid test will be a clinical trial in people who already require a marrow transplant, but he says his group has shown that injected $Thy1^{+}Lin^{-}CD34^{+}$ cells live "for months and months" in immunodeficient mice — the next-best model. He told SCIENCE NEWS that "at least one" U.S. hospital that routinely performs marrow transplants has given his group permission to use the newly identified cells in clinical tests, but he declined to say when the first trial will begin.

Last week, SyStemix received a U.S. patent for the cells and for the means of purifying them. The company plans to develop and market the cells for transplantation into the marrow of leukemia victims or cancer patients whose stem cells have been killed off by intensive chemotherapy. Because the cells are not sufficiently differentiated to recognize their recipient as "foreign," Weissman says he does not expect them to cause graft-versus-host disease, a deadly outcome of some marrow transplants.

He also envisions using transplants of pluripotent cells to restore AIDS patients' CD4 cells, the T-cells that are the main targets of the AIDS virus. "The [pluripotent] cells might return AIDS patients to a much earlier stage [of the disease] that could be controllable with the conventional therapies that are available right now," he suggests. Weissman predicts that scientists could also engineer the pluripotent cells to contain normal copies of genes whose defects cause diseases. — *C. Ezzell*