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LOS ALAMOS SCIENCE AND TECHNOLOGY MAGAZINE

About Our Name:
During World War II, all that the outside world knew of Los Alamos and its top-secret laboratory was the mailing address—P. O. Box 1663, Santa Fe, New Mexico. That box number, still part of our address, symbolizes our historic role in the nation's service.

About the LDRD Logo:
Laboratory Directed Research and Development (LDRD) is a competitive, internal program by which Los Alamos National Laboratory is authorized by Congress to invest in research and development that is both highly innovative and vital to our national interests. Whenever *1663* reports on research that received support from LDRD, this logo appears at the end of the article.

About the Cover:
With cyber attacks on American enterprises becoming increasingly common, cyber security experts at Los Alamos are deploying their latest and greatest defense, a software program called PathScan. When hackers invade a network, they move from one computer to another, creating a path through the network as they search for valuable data and ever-greater levels of access. PathScan, as its name implies, scans for such illicit paths. Unlike existing firewalls, which provide protection against unauthorized entry, PathScan catches intruders on the inside—but before they can do any damage.

Los Alamos Firsts

The First Cell Sorter

Imagine, as Los Alamos physicist Mack Fulwyler did in the mid-1960s, an instrument that could find the proverbial needle in a haystack, only the needles were certain living cells, and the haystack was a solution containing millions of other cells. Fulwyler turned imagination into reality and patented his "cell separator" in 1965. Cell biology hasn't been the same since.

The story begins at Los Alamos Scientific Laboratory in the early 1950s, in the days of atmospheric nuclear weapons testing. A team of Laboratory physicists had joined with chemists and biologists to develop methods to test for the presence of radioactive fallout in people and food products. But in 1963, with the limited test ban treaty in force, they turned to other biomedical measurement challenges, including DNA analysis, cancer cell detection, and blood cell characterization.

The team had acquired a Coulter Counter, a recently developed instrument that could measure the size of single cells in solution for automated blood analysis. The instrument forced a sample of cells in solution to flow past an electric sensing region, one cell at a time. As each cell passed, an electronic signal changed by an amount that was proportional to the size of the cell. The distribution of cell sizes gave important information on the distribution of cell types in the sample, which could then be linked to a diagnosis.

In studying this instrument, Fulwyler had the idea to isolate specific cells from the large population of cells to confirm their identities. He could use the electronic signals from the size analysis to trigger a mechanism that would divert specific cells from the fast-moving sample stream (thousands of cells per second). He didn't know what that mechanism would be, but knew that mechanical methods to physically separate individual cells were too slow.

Then Fulwyler read a paper describing the invention of an ink-jet printing device in which a stream of ink was vibrated to break it down into droplets. The droplets were charged according to an electronic signal and subsequently redirected by an electric field. Fulwyler had his answer: he would marry the automated cell-size analysis concept with the fast ink-jet printing technology. Cells suspended in a conducting fluid would be partitioned into fine droplets after size analysis. Then a charge would be applied to the droplets containing the cells of interest, allowing those droplets to be pulled out of the stream for collection and further study. The first paper, describing the cell sorter and its positive results when sorting mixtures of human and mouse blood cells of different sizes, appeared in the top-tier journal *Science* in 1965 and a patent was issued.

In the 50 years or so since Fulwyler built the first cell separator, the descendents of that original instrument have become ubiquitous in research and clinical laboratories all over the world. The development of flow cytometry (cell measurement) with cell sorting transformed cellular biology from a descriptive, qualitative science to a quantitative science. With the addition of fluorescent dyes that chemically light up specific cell molecules, researchers have gained the ability to ask questions about cell function—what a cell does, rather than just what it looks like. Today, flow cytometry provides insight into the complex cellular and molecular mechanisms that underpin diseases such as cancer and AIDS and helps elucidate the role of individual cell types in health, disease, and treatment.

—Babetta Marrone

Director of the National Flow Cytometry Resource (2008–2013) at Los Alamos National Laboratory