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Obituary

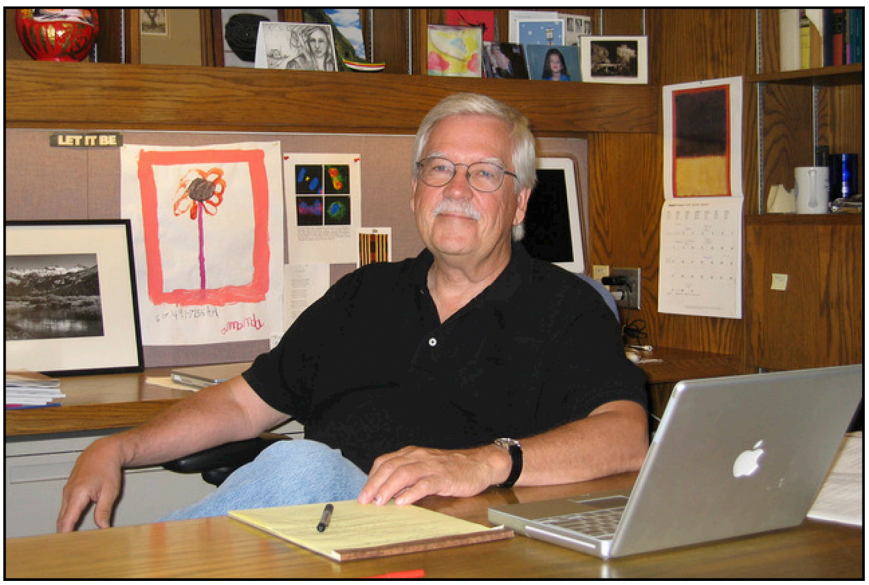
Raymond L. Erikson (1936–2020)

Raymond L. Erikson, discoverer of the SRC protein and a giant in the fields of signal transduction and cell proliferation control, died in Cambridge, Massachusetts on March 30, 2020 from complications of bladder cancer. He was 84 and professor emeritus in the Department of Molecular and Cellular Biology, Harvard University. A great scientist, generous colleague, dedicated mentor, devoted husband, and father, and brother, Erikson leaves an enduring legacy of landmark scientific contributions, generations of well-trained, highly influential investigators in their own right, and friends from all walks of life who were enriched by their personal connection with him.

Born into the jaws of the Depression in 1936, Ray grew up on a family dairy farm near the village of Eagle, Wisconsin, where he attended a one-room, two-student classroom. The first in his family to go to college, he arrived at the University of Wisconsin-Madison with the goal of becoming a high school agricultural sciences teacher. But these plans were waylaid when, inspired by his professor, James F. Crow, and fascinated by the new field of molecular biology, he discovered a love for "the science of biology." By his nature taciturn, Ray nevertheless spoke often—and passionately—about how his college experience had changed his life. That commitment to learning and education began at Madison but continued throughout his life to the ultimate benefit of the many undergraduates who attended his classes and his multiple graduate student and postdoctoral trainees.

Erikson graduated in 1958 and then continued at Madison for graduate studies at the famous McArdle Laboratory, receiving his PhD in 1963 under Waclaw Szybalski. During this time, Raymond had the great fortune to meet his first wife and long-time scientific collaborator, Eleanor "Jo" Erikson. Her scientific support was invaluable, and she would be his most important colleague for many years and friend for life. After leaving Wisconsin, he pursued postdoctoral training with Richard Franklin at the University of Colorado Medical School, where he studied RNA bacteriophages. Appointed to the University of Colorado faculty, his interests soon turned to the emerging field of RNA tumor viruses.

Erikson initially investigated viral RNAs and virus-associated small (4S, 5S, 7S) RNAs, advancing to the rank of professor.



But a sabbatical at the Imperial Cancer Research Fund in the early 1970s changed his focus to the question of how Rous Sarcoma Virus (RSV) transforms cells. Classic experiments by the groups of G. Steven Martin, Peter Vogt, Peter Duesberg, and the late Hidesaburo Hanafusa had separated viral replication from transforming ability and localized a putative "sarcoma (*src*) gene" toward the 3′end of the RSV genome. The identification of temperature-sensitive (ts) mutants by the Martin, Vogt, and Hanafusa laboratories was particularly influential. These mutants replicate without transforming host cells at the non-permissive temperature but quickly induce transformation following shift to the permissive temperature. Remarkably, transformation is restored even in the presence of protein synthesis inhibitors. In concert, these findings argued that the putative *src* gene encoded a temperature-labile protein.

The next four years changed the history of cancer biology. In 1976, Stehelin, Varmus, Bishop, and Vogt prepared hybridization probes specific for the *Src* gene by using RNA from transformation-defective deletion (td) mutants of RSV to deplete viral sequences unrelated to transformation. Using this "viral src" (v-*src*) probe, they discovered that normal cells contained *src*-related sequences, providing the first evidence for what are now termed cellular proto-oncogenes. Key questions remained, however: what does v-*src* encode, is there a related c-SRC protein, and most importantly, how does v-Src transform cells?

These problems were as difficult to solve as they were tantalizing. Despite being a virus-encoded protein, v-Src levels in cells were much lower than those of proteins typically studied at the time. At a time when no mammalian gene had been cloned, much less sequenced, inferring the v-SRC sequence from the nucleotide sequence of v-*src* was inconceivable. Other modern techniques either didn't exist, were rudimentary, or were extremely expensive. For example, Erikson lab members

didn't buy radioactive methionine for cell labeling experiments; they made it by incubating bacteria with the much less expensive $^{35}HSO_4$ and purifying the hydrolysate. Likewise, synthesizing γ32P-ATP from ADP, radioactive orthophosphate, and an ATP-regenerating system was a legendary—and mandatory—right-of-passage for all Erikson trainees. Protein-A Sepharose beads could not be purchased. Instead, sometimes accompanied by an intrepid postdoc or student and usually on a Sunday to avoid risk to others, Erikson would prepare fixed *Staphylococcus aureus* for use in immunoprecipitations. There were no kits for *in vitro* translation (for that matter, there were no kits at all!); rabbit reticulocyte lysates had to be prepared *de novo*.

Nevertheless, Erikson and his colleagues adopted an ingenious, two-pronged approach to solve these daunting problems. First, a graduate student in the lab, Tony Purchio, established conditions for *in vitro* translation of RSV RNA, with the goal of identifying the putative protein produced by the 3′ end of RSV. In parallel, inspired by earlier approaches that identified SV40, polyoma virus, and adenovirus transformation antigens, Joan Brugge developed antisera from newborn rabbits bearing RSV-induced tumors. Using this "tumor-bearing rabbit serum" for immunoprecipitations, she identified a protein produced in RSV-infected, but not in uninfected or td-RSV-infected, cells. Remarkably, in 1978, the two approaches converged on the same molecule, p60-Src, as confirmed by peptide mapping (Brugge and Erikson, Nature 269, 346–348; Purchio et al., Proc. Natl. Acad. Sci. USA 74, 4661–4665; Proc. Natl. Acad. Sci USA 75, 1567–1571).

These seminal findings were rapidly confirmed by others, and the race was on to discover what v-Src does. Again, Erikson's group made the key discovery. Their finding that v-Src was a phosphoprotein (leading it to be renamed pp60), combined with the rapid reversibility and protein synthesis independence of ts-RSV transformation, led Erikson and Marc Collett, a new postdoc in the lab, to suspect that v-Src might be a protein kinase—but how could this be tested? Collett then performed an experiment that now seems elementary, but at the time it was revolutionary. He mixed v-Src immunoprecipitates with standard kinase substrates (casein and histones) and γ32-ATP. Neither casein nor histone underwent phosphorylation, but instead, Collett observed strong labeling of immunoglobulin heavy chains (and to a lesser extent, v-Src). Jo Erikson and Collett soon obtained identical results with *in vitro* translated v-Src, proving that the kinase activity was intrinsic to, and not associated with, the oncoprotein (Collett and Erikson, Proc. Natl. Acad. Sci USA 75, 2021–2024; Erikson et al., Nature 274, 919–921). Shortly thereafter, c-SRC was identified and found to have kinase activity using similar methodology (Collett et al., Proc. Natl. Acad. Sci. USA 76, 3159–3163). Collett's elegant "immune-complex kinase assay" was soon adapted by multiple laboratories to study many other protein kinases, lipid kinases, and even protein and lipid phosphatases.

But the SRC story had one final twist. Collett and Erikson, using the standard methodology at the time, had found that the amino acid phosphorylated by SRC co-migrated with phosphothreonine. But in a remarkable discovery (underpinned by careful attention to buffer pH!), in 1980, Tony Hunter and Walter Eckhart found that SRC is actually a tyrosine kinase. Shortly thereafter, Stanley Cohen's group reported that the epidermal growth factor receptor (EGFR) also has tyrosine kinase activity, uniting the fields of viral oncology, normal and malignant cell proliferation, and growth factor action.

There are now countless examples of reversible phosphorylation events that control cell proliferation, but all bear the intellectual footprints of Ray Erikson's discovery of SRC. His pivotal work was recognized with multiple major awards, including the 1982 Albert Lasker Basic Medical Research Award, the 1983 General Motors Cancer Research Foundation Prize, the 1994 Hammer Prize for Cancer Research, and many others. He also was a long-standing American Cancer Society Research Professor and a member of the National Academy of Sciences and the American Academy of Arts and Sciences. The Raymond Leo Erikson Professor of Life Sciences at Harvard University is named in his honor.

In 1982, Ray joined the faculty of Harvard University, but the excitement of the days of the discovery of SRC and its kinase activity never subsided, and Colorado always held a special place in his heart. At Harvard, Erikson led a new generation of researchers to a series of other major discoveries. His group identified, purified, and/or cloned MEK, S6K, and RSK, the latter with Jo Erikson and Jim Maller, and made multiple contributions to our understanding of their regulation (Crews and Erikson, Cell 74, 215–217; Erikson, J. Biol. Chem. 266, 6007–6010). Work initiated while he was a postdoctoral fellow in Ray's lab led Dan Simmons and his laboratory to identify a v-Src-induced gene as a novel isoform of cyclooxygenase, ultimately leading to COX2 inhibitors (Xie et al., Proc. Natl. Acad. Sci. USA 88, 2692–2696). Another v-Src-induced gene, initially named serum-induced kinase, was subsequently found to be related to the polo-like kinase and renamed PLK2 (Simmons et al., Mol. Cell Biol. 12, 4164–4169). Ray reasoned that PLK kinases likely had important actions in cell cycle control, and in the 21st century, his group contributed to understanding the molecular details of their actions in centrosome biology and cytokinesis (Liu and Erikson, Cell Cycle 2, 424–425).

Ray was at least as proud of his many successful trainees as he was of his own laboratory's accomplishments. Those of us who had the privilege to be his graduate students or postdocs recognize several keys to his success as a mentor. Every morning, he would make the strongest coffee in the world. The hardy souls who drank that coffee never were tired even after long hours in the laboratory, although some of us do blame him for our lifelong caffeine addiction. Although he always stood ready to give advice if asked, he expected trainees to manage their own projects and think deeply about their results. He expected—and elicited—serious effort from laboratory members, but he never insisted on specific work hours. As he frequently said, "It's your career." He exemplified scientific integrity and despised scientific fads, flash, puffery, and prima donnas. He liked good ideas, but he loved beautiful experiments.

Ray Erikson's scientific contributions were monumental, but his interests extended beyond the laboratory. He was a prolific reader of literature, loved the theater, enjoyed good food and wine, and traveled widely. Paris and Santa Fe were particular favorites. But most important to him was his family. He spent time each summer running his family farm in Wisconsin, allowing his younger brother Gordon and sister-in-law Karen to go on vacation. He was married to his wife Donna for 31 years and viewed his daughter Amanda as his greatest contribution to the world.

Another mentor once said that one could only judge a scientific career when it was over. By any standard, Raymond L. Erikson had a remarkable career. Perhaps the Lasker Award citation said it best, "he was a pioneer's pioneer." He will be sorely missed.

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