Eva J. Neer

1937–2000

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Robert Neer,
Thomas Michel,
and Robert J. Lefkowitz

NATIONAL ACADEMY OF SCIENCES

EVA JULIA **NEER**

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Eva Julia Neer was a biochemist and a pioneer. She left an indelible mark on the field of signal transduction; she was fearless in challenging dogma, and her work established new paradigms in cellular communication through careful experiments and their rigorous interpretation. She was a role model for men and women alike and one of the first women to be named a full professor at Harvard Medical School. She died of breast cancer in 2000 at the age of sixty-two, leaving behind a legacy of discovery and inspiration and personal generosity. She will long be remembered and honored by her family and friends, her students and trainees, and her colleagues around the world.

By Robert Neer, Thomas Michel and Robert Lefkowitz

Early Life and Education

Eva Julia Augenblick was born on October 28, 1937, in Warsaw, Poland, the only child in a vibrant and intellectually rich household. Both her parents had advanced degrees and were fluent in Polish, German, Italian, French, English, Spanish and Portuguese. When Germany and Russia invaded Poland in 1939, the family fled the country and spent the war in Brazil. They planned to return to Poland after the war, but when the terms of the Yalta Agreement became public, they immediately applied for U.S. immigration visas. Their immigration was officially sponsored by Hilary Koprowski, a Polish friend educated as a physician but by then an eminent U.S. virologist. Koprowski had important influences on Eva's education and career choices.

Eva and her parents settled in New York City and later its suburbs, where she thrived in the public schools. She was an outstanding student at Bronxville High School and also skilled in graphic arts, with a group of intellectual friends who included future economist Fisher Black. Influenced by Dr. Koprowski's example and by Paul de Kruif's *Microbe Hunters*, Eva decided she wanted to become a biological research scientist. She was accepted at Radcliffe College, where she concentrated in biochemistry and was an

outstanding student. In the spring of her freshman year, she met and fell in love with Robert Neer, a Harvard College pre-medical student two years her senior. When he graduated from college and entered Columbia Medical School in New York City, Eva switched from Radcliffe to Barnard College, commuting daily from Scarsdale, where she lived with her parents. After a year, she and Bob married and lived near Columbia Medical School, a short commute to Barnard.

Following the guidance of Dr. Koprowski (later a National Academy of Sciences member), Eva decided to attend medical school to obtain a broad education in human biology, although not expecting to practice medicine. Barnard did not offer the pre-medical courses she wanted, and Barnard students were not then allowed to take those courses at the affiliated Columbia University. So she majored in English at Barnard while completing pre-medical course requirements with distinction at Harvard College's Summer School. She graduated from Barnard with honors and entered Columbia University's College of Physicians and Surgeons, one of eight women in a class of 108, a typical gender ratio in that era.

Eva engaged in three research projects before she completed medical school. As a college senior, she designed and completed an experiment that involved urine collections in mice, a technique her faculty mentor had never used. Eva acclimated each mouse to a large Buchner funnel topped by a metal screen and funneled its urine into a test tube, rinsing down the residue with distilled water. She got reproducible results, and a healthy respect for the challenges of animal research, to which she did not return for thirty-five years. The summer between college and medical school, Eva worked as a technician in Marjorie Zucker's platelet research lab at the Sloan Kettering Institute in Manhattan, counting platelets under a microscope, a tedious job before automated methods. She learned that some necessary aspects of research are boring, and even well-meaning lab directors cannot change that. In her third year of medical school, Eva won a cash prize as the best student in neurology (which she spent on a thirteen-volume *Oxford English Dictionary*) and worked in the laboratory of neurologist Lewis P. Rowland, who was investigating the chemical properties of muscle tissue in patients with myopathy. This work introduced Eva to the techniques of protein chemistry, which became a lifelong fascination, and she decided she wanted to become a protein chemist when she finished medical training.

Professional Career and Research

Eva graduated from Columbia's medical school in 1963 and began a medical internship at Georgetown University Hospital in Washington, D.C. There were two women in Eva's medical internship group, both Columbia graduates. Each completed her internship successfully while pregnant, with no extra time off.

Eva's first son was born a month after she completed her internship, and she spent the next year at home with him. Because of her husband's appointment at the National Institutes of Health (NIH), she was able to take a physical chemistry course at NIH's night school during that year; she also studied Spanish at home, taught by a neighbor. She competed successfully for an NIH training fellowship and began studying hemoglobin chemistry with William Konigsberg in the Department of Biochemistry at Yale Medical School in Connecticut. Konigsberg and Guido Guidotti had together recently determined the amino acid sequence of hemoglobin at the Rockefeller Institute for Medical Research (now Rockefeller University), in New York City. Eva spent an extremely happy and educational year in Konigsberg's lab. Konigsberg and Eva's senior lab-mates Klaus Weber and Donna Arndt (later Arndt-Jovin) were deeply schooled protein chemists and taught her laboratory skills and intellectual standards she retained for a lifetime. At the end of the year, Eva was able to pack up her test tubes and move her hemoglobin experiments and NIH training fellowship to Guidotti's lab and mentorship in Massachusetts at Harvard College, while her husband completed medical training in Boston. Guidotti's lab was at that time pioneering the study of membrane proteins by developing methods to solubilize them, then characterizing them with the methods of physical chemistry.

When Eva finished the hemoglobin studies she had begun at Yale, Guido advised her to switch to membrane proteins and develop an independent research program. He also helped her apply for independent funding, despite Harvard College rules against it. In 1969, the American Heart Association awarded her a five-year Established Investigator Award to study adenylate cyclase and related membrane proteins. She postponed the award one year, which she spent at home with her newborn second son. In 1973-74, she published three consecutive single-author papers in the *Journal of Biological Chemistry*, describing the solubilization and physico-chemical characterization of adenylate cyclase and guanylate cyclase from several tissues and species. In these papers, Eva determined the buoyancy of enzyme-detergent complexes by comparing their sucrose density-gradient centrifugation parameters in H_2O versus D_2O, a clever technique recently developed in Guidotti's laboratory. Each paper acknowledges Guidotti's inspiration and

advice, but he refused as a matter of principle to be a co-author. These papers stimulated a chemical approach to membrane signaling proteins and started Eva's scientific career.

In 1972, Eva joined Harvard College's Board of Tutors in Biological Sciences, which had been devised years earlier by Professor John Edsall as a way for Harvard College and Harvard Medical School to share faculty expertise in biochemistry for mutual benefit and for the benefit of undergraduates. Membership involved individual tutorials throughout the academic year. Some of these students also spent a summer and part of their senior year working in Eva's lab, which often resulted in a scientific publication with the student as first author. She relished her contact with undergraduates and was a popular tutor.

In 1976, Thomas Smith, newly appointed chief of cardiology at Boston's Brigham and Women's Hospital, invited Eva to join his department as a basic scientist, although she was not working on the heart. This involved a transfer from the Department of Biological Sciences at Harvard College to the Department of Medicine at Harvard Medical School, with an adjunct appointment in the Biochemistry Department. Eva was initially a volunteer lab instructor in biochemistry at the medical school but stopped because the biochemistry course director ridiculed her suggestions to engage medical students intellectually. She reactivated her membership on the Board of Tutors in Biological Sciences at Harvard College and chaired the board in 1984-85, when its permanent chair was on sabbatical. She thus had a closer relationship with biochemists and students at Harvard College than with those at Harvard Medical School.

In the early 1970s, Eva began reviewing manuscripts for the *Journal of Biological Chemistry,* the field's leading publication. In 1978, she was invited to join the journal's Editorial Board, on which she served for 12 years. She also began attending the annual Gordon Conference on Second Messengers and Protein Phosphorylation, where she met the pioneers in this developing field and formed a network of lifelong scientific friendships. In 1988, she was vice-chair and in 1989 chair of this conference.

In 1976, Eva reported that GTP-activated adenylate cyclase had physico-chemical properties different from those of fluoride-activated adenylate cyclase.[1] In 1980, she reported that the size of adenylate cyclase increased substantially when it was activated by GTP,[2] implying that this activation involved combination with another macromolecule (subsequently identified by others as a GTP-binding protein). Eva spent most of the 1980s purifying and characterizing multiple GTP-binding proteins that modulate signals between cell surface receptors and other cell membrane proteins.[3, 4] These modulator proteins (known as G proteins because of their regulation by and hydrolysis of GTP)

became the focus and passion of the remainder of her scientific career. Her rigorous biochemical approach led to the discovery of a new class of G proteins (termed G_o, one of the most abundant signaling proteins in the brain, and established the existence of a large and complex family of G proteins.[5, 2] The purified G proteins isolated by Eva formed the basis of collaborative experiments with Robert Lefkowitz at Duke University (he was awarded the Nobel Prize in Chemistry in 2012). These studies used reconstitution of purified proteins to establish that the essential components of adrenergic receptor-mediated adenylate cyclase activation are structurally distinct: receptor, G protein, and adenylate cyclase were discrete molecular entities and each was required for receptor-mediated adenylate cyclase activation.[6]

In the mid 1980s, Tom Smith invited David Clapham to bring his cell membrane patch-clamping expertise to the department. He and Eva and their colleagues Diomedes Logothetis and Yoshi Kurachi soon began studying the effects of Eva's purified GTP-binding proteins, and their sub-units, on cell membrane ion channels. In 1987, they reported in *Nature* that purified beta-gamma subunits of GTP-binding proteins activate the muscarinic K^+ channel in the heart.[7, 8] This was unorthodox: until then, only alpha subunits of these heterotrimeric proteins had been shown to stimulate or inhibit the function of cell-effector molecules. Beta-gamma subunits of GTP-binding proteins were thought to function only by masking (and thereby inactivating) the alpha subunits. Another U.S. patch-clamping laboratory disputed their findings[9] and reported in over a dozen papers that it was the alpha subunit alone (at sub-picomolar concentrations) that activated this channel.[10, 11] Throughout the difficult years of this sometimes bitter controversy, Eva relied on data rather than acrimony to make her points.[12-18] She was honest and forthright and inspired those around her to be the same. Other laboratories eventually entered the field, and by 1994 it was accepted that beta-gamma activates this channel and alpha does not. It is now clear that Gβγ activates as many effector molecules as Gα does.

Eva lecturing in 1988, in the middle of the G protein b-γ controversy. At the Uehara Symposium in Tokyo. (Photo provided by authors.)

While this controversy was at its height, a Harvard Medical School committee was considering Eva's promotion to full professor. They deferred action until the controversy appeared to be tilting in her favor, and in 1990 she was promoted to Professor of Medicine. This was very unusual for women in the school's largest department. The same year, she was invited to join two informal Medical School clubs that until then had been all-male. After her death in 2000, the Harvard Medical School dean told a *Boston Globe* obituary writer, "Eva Neer broke Harvard Medical School's glass ceiling."

Eva celebrating her promotion to full professor at Harvard Medical School Photo taken at Eva's home in Cambridge, MA in 1990. (Photo provided by authors.)

In November 1988, when this controversy and her promotion were both unresolved, routine mammography led to the discovery that Eva had early breast cancer. She did not want her promotion to be awarded or denied because of this diagnosis, nor did she want it to influence the scientific controversy in which she was involved. Because of this, and because treatment was highly likely to cure her early cancer, she kept the diagnosis secret from everyone but her family; David Clapham; the head of the cardiology unit Tom Smith; and the chair of her department, Eugene Braunwald. She also asked her husband to tell the chair of his department. All respected her privacy. Her breast surgery occurred during Thanksgiving vacation and her radiation therapy began during Christmas vacation. All her therapy occurred at a hospital different from her workplace. She had standard chemotherapy on Fridays, symptoms over the weekend, and returned to work on Mondays. She cut her hair before she lost it, transitioned to a wig during a brief Florida vacation, and managed to escape the notice of her colleagues at work and abroad, her neighbors at home, and her friends at parties. Periodic reappraisals showed no signs of cancer.

In the early 1990s, Eva began collaborating with Jonathan Seidman in Harvard Medical School's Department of Genetics on several projects and soon decided she needed to learn techniques of molecular biology herself. She persuaded Seidman to accept her as a scientist-in-training in the afternoons, while she continued to run her own lab in the mornings. She found the experience stimulating but humbling. She was accustomed

to students, technicians, and postdocs asking her how to do things in the lab; now she had to ask them how to do everything. But working closely with her postdoctoral fellow Thomas Michel and with others in her lab, she soon mastered these powerful new experimental approaches[5, 19] and began comparing membrane protein-protein interactions before and after mutation of selected amino acids.[20] She identified distinct Gα genes[19] and later produced genetically modified mice with mutant cardiac G-proteins.[21, 22] Characterizing their cardiac physiology took Eva back to her college days, the last time she had studied live animals.

Throughout her career, Eva successfully competed for federal research grants, and she received a coveted Merit Award from the NIH. Her parents did not live to admire Eva's 1996 election to the Polish Institute of Arts and Sciences of America (sponsored by Dr. Koprowski), her 1997 election to the American Academy of Arts and Sciences, her 1998 elections to the U.S. National Academy of Sciences and the U.S. Institute of Medicine (now named the National Academy of Medicine), or her basic science research prizes from the American Heart Association (1996) and the Federation of American Societies for Experimental Biology (1998).

Mentorship and Advocacy for Women in Science

In addition to her impressive scientific accomplishments, Eva developed a broad reputation as a superb teacher and thoughtful mentor for Harvard College undergraduates, Harvard medical students, and her own research fellows. In 1992, she became associate director of the medical school's Walter B. Cannon Society, which put her in close and informal touch with one-quarter of the school's students. In this capacity, she initiated a journal club to engage medical students intellectually and confirmed her long-standing belief that most medical students delight in such an environment. A natural communicator, she had no trouble interesting students in the three-dimensional structure of G-proteins. In 1998, she was invited to speak to the entire senior class on their student research day. Her lecture described her work with G-proteins but was illustrated at critical points with works by Brueghel, Rubens, and other classical painters, in a popular multicultural tour-de-force. With broad knowledge of literature and the arts, Eva found fascination and joy in all facets of her world. She was scholarly, scientific, and witty—an arbiter of scientific, cultural, and literary knowledge and taste.

Eva was equally successful at home. She had a joyous marriage and two happy and successful sons, maintained a beautiful and welcoming home, and was a solicitous

Eva at home in the kitchen Cambridge, MA 1992.
(Photo provided by authors.)

daughter to her lively widowed mother. She was also an excellent cook, noting many similarities between cooking and biochemical research.

In 1996, the Trustees of Harvard Medical School's two largest teaching hospitals (Massachusetts General Hospital and Brigham and Women's Hospital) jointly asked Eva to create and chair a small committee to investigate the underrepresentation of women in senior academic positions at both institutions and report to the Trustees directly. Her committee's report documented unequal representation of women at senior academic levels but not at starting academic levels. It also documented very unequal representation of female speakers at departmental academic conferences (including departments chaired by women), which Eva considered a lost opportunity to train female researchers to speak before audiences elsewhere. The committee also found that women in junior academic positions often made career choices that prioritized work schedules and funding over major scientific importance, with short-term social and economic benefits but long-term harm to their academic advancement. The report was unable to compare salary levels for female versus male hospital researchers, because no hospital department would surrender salary data, even anonymized salary data, to her committee.

In late 1996, Eva developed mild swelling of her hand and arm on the same side as her prior breast surgery. Imaging studies revealed a mass along the lateral ribs, invisible to a mammogram, and an abnormality at the bottom of her spine. Biopsy of each revealed breast cancer, recurrent after eight years. Breast cancer metastatic to bone or other distant locations was then incurable. Eva divulged this situation to the same small group as before, had supplemental radiation therapy, and took chemotherapy and a bone-protecting drug until her death 38 months later. During this time she again cut her hair before she lost it, wore a wig, and spent every evening and night with her right arm in a pneumatic compression sleeve to minimize swelling. One day she woke with swelling of her left leg, traced to obstruction of the main vein in her upper thigh by a spontaneous clot, a common complication of cancers. Thereafter she wore tight elastic stockings daily to reverse and conceal the leg swelling, and took anticoagulants to prevent clot recurrences.

Despite these challenges, she continued to work full time, pursuing the structure and function of Gβγ.[20, 23, 24] She published three scientific papers in 1997, six in 1998, and three in 1999. After the crystal structure of the Gβγ complex was revealed by the Sprang and the Sigler laboratories, she characterized the sites of interaction of the protein with Gα and phospholipase Cβ, and, in collaboration with Temple Smith, provided key insights into the structures of proteins like Gβγ.[23-25] She also worked on G-proteins in cardiac cells by producing transgenic mice with modified G-protein function,[21, 22] posing compelling questions about the mechanisms of heart failure.

In May 1998, liver metastases developed, and she began to inform a few work colleagues of her illness. She still told none of her friends and neighbors. "I cannot bear to see the pity in their eyes," she said. In late 1999, she developed intermittent symptoms and her liver function deteriorated alarmingly. By January 2000, she was slightly jaundiced, although only her more medically sophisticated colleagues noticed. As the jaundice deepened and all her liver functions dwindled, she continued to work full-time at her lab and work at home on scientific manuscripts, manuscript reviews, and personnel recommendations. Two days before her death, she missed a day of work because she was in a hospital acute care unit with an infection. In accordance with her wishes, she died at home surrounded by her family. The announcement of her death was a shock to most of her colleagues and all her friends and neighbors, who never imagined she was terminally ill. At her death, six manuscripts were ready or nearly ready for submission.

Renowned for her intellect, her tough, probing questions, and poignant retorts in scientific discussions, Eva's face always shone, with warmth in her smile and a sparkle in her eyes. She taught her students and colleagues to work hard, to care passionately about science and each other, and always to see the world with joy. Few people take on the future with so much spirit, energy, and determination. Not every life is as fulfilled as Eva Neer's; she had a career of significance and accomplishment, a lifelong joyous marriage, and two wonderful and successful children. She enriched all who came close to her. Her passion, wit, and intellectual achievements live on to inspire all those fortunate to have known her. The annual keynote lecture for the Harvard Medical School–MIT MD–Ph.D. program is aptly named the Eva Neer Lecture, and the honorees of this prestigious lectureship help annually to sustain the legacy of this extraordinary scientist and humanist and friend.

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