



Ralph M. Steinman
1943–2011

BIOGRAPHICAL

Memoirs

*A Biographical Memoir by
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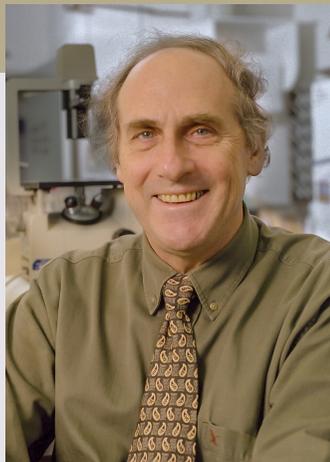
NATIONAL ACADEMY OF SCIENCES

RALPH MARVIN STEINMAN

January 14, 1943–September 30, 2011

Elected to the NAS, 2001

With his discovery of the dendritic cell—a class of blood cells that control cell-mediated immunity—Ralph M. Steinman created a revolution in the 200-year history of immunology. During a research career that spanned 40 years at The Rockefeller University, he defined dendritic cells as sentinels that capture pathogens, activate the immune system, and manage not only tolerance but also resistance to infection, transplantation, cancer, allergy, autoimmunity, and environmental toxins. He developed methods for their identification, isolation, and culture, demonstrated the pivotal role of their maturation in the control of tolerance and immunity, and began clinical studies of injected dendritic cells to induce immunity. Ralph often referred to dendritic cells as the “conductors of the immune orchestra.”



Photograph courtesy The Rockefeller University (1981)

Ralph Steinman

By Carol L. Moberg

Ralph was born in Montreal, Quebec, the second of four children. His father Irving (born Isador) and three of Irving’s siblings had immigrated to join family in Montreal after they were orphaned in Bessarabia (now within Moldova and Ukraine). Irving and his older brother rose from selling clothing on the streets to owning a department store in Three Rivers, Quebec. Ralph’s mother Anita (“Nettie”) Takefman was born in Montreal to Polish immigrants. She taught English as a second language in the city’s school system and operated a furniture outlet for new immigrants. After marrying, Irving and Nettie moved to Sherbrooke and opened Mozart Limited, a clothing, school-uniform, and small-appliance store. Nettie was a lively workaholic, serving, for example, into her 90s as a volunteer for the Jewish National Fund’s Israel programs. Her familiar saying, “You can’t waste your time,” had a strong influence on Ralph.

Although his parents wanted Ralph to study religion, and ultimately to take over the family business, his passion for science bloomed while in high school. Both a science whiz and athlete—an especially keen hiker and skier—he collected a molecular building set, graphic anatomy books, and dissection kits. He also built a model electric train

village, alive with connecting train lines, smoke-producing engines, and crossing barriers—a world foreshadowing the pathways and junctions he would soon explore with dendritic cells in the immune system. On fishing trips with his sister Joni, 11 years his junior, he adhered to a “catch and release” protocol; he made anesthetized dissections to teach her how living beings function, then sewed the fish back up and released them when they awoke and could swim away.

In his 1959 valedictory address at Montreal High School, Ralph traced a path he himself would follow. While noting the achievements of life-saving vaccines and medicines, he envisioned science and technology offering limitless opportunities “whose horizons resemble a multi-coloured rainbow, always beckoning us on to the tantalizing pot of gold.” He urged fellow graduates to be guided by their class motto, “Man gains strength as he goes,” and to confront problems with “steadiness, strength, and patience.”

Ralph obtained a B.S. degree with first-class honors in biochemistry from McGill University (1963). He also received the Major Hiram Mills Gold Medal in Biology, the Society for Chemical Engineering Award, and, for his literature studies, the Great Books of the Western World Prize. During medical training at Harvard Medical School he took a year off to do research, supported by a George P. Wislocki Fellowship, in the anatomy laboratory of Elizabeth Hay and Jean-Paul Revel, where he was introduced to cell biology and the subcellular organelles. Ralph’s thesis, “Studies on the Fine Structure of Developing Cilia,” which involved electron microscopy and tissue culture of the clawed-frog embryo, led to his first two publications. Graduating magna cum laude in 1968, he received the Leon Resnick Prize and John H. Parker Bequest for his research. Ralph was also chosen to give the Class Day lecture, in which he called for integrating more basic science into clinical training—“investigation and practice are one in spirit, method, and object,” he asserted.

Ralph was remembered by his fellow interns and residents Ronald Crystal, Thomas Pollard, and George Thibault at Massachusetts General Hospital for his inquisitiveness, optimism, and collaborative nature—traits that would define his later successes in science. He also was admired for his synthesis of often-complex patient cases into easily understood oral reviews.

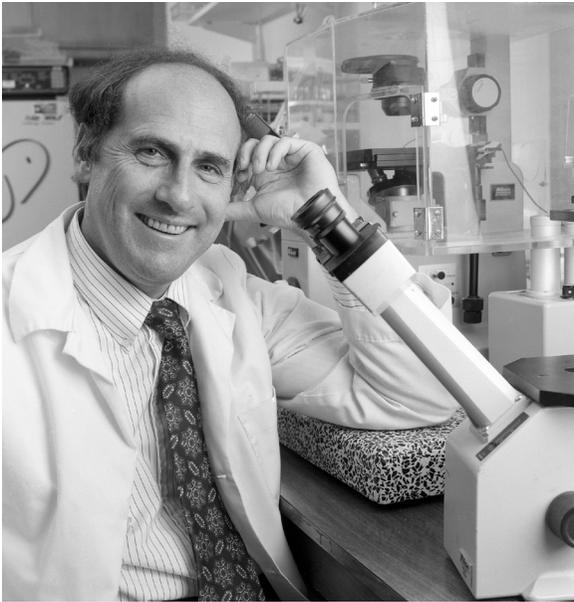
In summer 1969, Ralph met Claudia Hoeffel in the Hospital’s emergency room. He was an intern and she a medical social worker caring for an elderly woman with advanced cancer. Consistent with his lifelong passion for hiking and skiing, the couple took long weekend outings in New England’s mountains. Claudia quickly learned that Ralph’s

custom on reaching a mountaintop was to read copies of medical and scientific journals that he carried in his pack, along with chocolate bars. They were wed in 1971.

Contemplating research in medical science

Several events during his medical training in the late 1960s influenced Ralph's path to the cell biology of immunology. He was fascinated by the clonal selection theory of

MacFarlane Burnet, who posited that the immune system is comprised of a repertoire of clones, each with a distinct receptor for an antigen (Burnet 1957). While this theory defined antibody formation in terms of cell receptors, Ralph believed it still did not explain how an antigen provokes an immune response. Further, he read that James Gowans, who identified lymphocytes as mediators of transplant rejection, and Peter Medawar, the father of transplantation, both expressed uncertainty about where and how an immune response begins (Gowans 1965, Brent and Medawar 1967). Then, in a course on the "new cellular immunology" taught by Kurt Bloch at Mass General, Ralph was exposed to the idea that macrophages take up antigens and make a transforming RNA that instructs lymphocytes to produce a corresponding antibody.



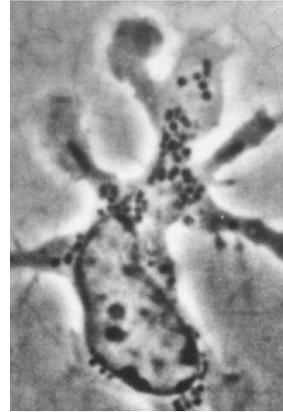
Ralph Steinman in 1992. (Courtesy of The Rockefeller University.)

At the time, the innate and adaptive immune systems were considered separate entities. Innate immunity involved Elie Metchnikoff's macrophages that internalize and kill microbes, while Paul Ehrlich's adaptive immunity involved lymphocytes that learn to produce specific antibodies to all known pathogens. The great questions of the day in immunology were: How does the adaptive immune system recognize the diverse world of pathogens? And how are these immune responses initiated? Robert Mishell and Richard

Dutton had shown that initiation of antibody responses in vitro requires lymphocytes and adherent cells, which they assumed to be macrophages (Mishell and Dutton 1967).

Challenged by many unanswered questions, Ralph decided to work with Zanvil (“Zan”) Cohn, the founder of modern macrophage biology, at The Rockefeller University (Steinman and Moberg 1994). The laboratory had been founded by René Dubos, a renowned microbiologist who recognized the need to study the host during infection (Moberg 2005). Dubos was the mentor of James (“Jim”) Hirsch (Moberg and Steinman 2003) and Zan, two physicians devoted to studying phagocytes in infectious diseases.

The Cohn laboratory proved to be an ideal place for directly testing whether macrophages could trap intact antigens and present them to lymphocytes. Zan had spent a decade elucidating how macrophages identify, engulf (endocytose), destroy, and defend the body against pathogens. He and his colleagues are largely responsible for our current understanding of macrophages as “versatile elements of inflammation.”



Phase contrast micrograph of a dendritic cell from a mouse spleen with a large irregular shaped nucleus, multiple mitochondria, and elongated tree-like processes. (Steinman, 1974.)

Discovery of dendritic cells

Ralph spent his first two years as a postdoctoral fellow in Zan’s laboratory studying the endocytosis of proteins in peritoneal macrophages. He failed to find either antigen uptake or retention needed for an immune response. Instead, he discovered there was rapid recycling of vesicle membranes into and back out of the macrophages.

So he began to look for a different cell and ultimately turned to the spleen as a prime source of white blood cells in generating immunity. In 1972 he observed, by accident, cells with an unusual shape and movement. “There they were,” he later said, “these distinctive cells that just jumped out at you in a well-preserved state.”

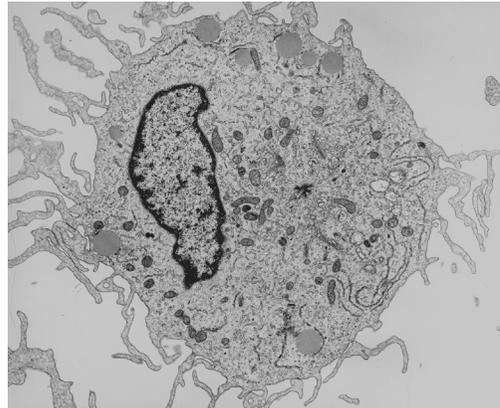
Zan’s wife Fern remembered that day very well. “Zan came home from the laboratory and announced, ‘Ralph made a very important observation today’....Ralph had come to Zan’s office to ask him to look into his microscope. Zan went to Ralph’s laboratory and looked through Ralph’s microscope, and saw what Ralph had just seen. It was their very first view of what they were later to call the dendritic cell” (Cohn 2011). Ralph later remarked, “We felt right away that we had found something new”.

With a rare opportunity to name this newly discovered cell, Ralph was impressed by the cells' long slender projections and graceful movements. He initially called them "claudia-cytes" in reference to the lanky arms and legs of his wife Claudia, who was his long-time ballroom-dancing partner. Ultimately, he named them dendritic cells (DCs), a term derived from the Greek word for tree.

The laboratory's vast experience with macrophages and their cell markers gave the researchers great appreciation of DCs' distinctiveness. Jim and Zan had never seen it, Ralph recalled, and they had seen every kind of white cell from every part of the body and from many species. Unlike macrophages, the DCs were elongate with unusual stellate or tree-like processes that were constantly forming and retracting. However, the world was not ready to recognize dendritic cells as different from macrophages simply on the basis of morphology. Moreover most immunologists were not familiar with the more sophisticated methods of microscopy used to identify dendritic cells.

Zan's laboratory, on the fourth floor of the Bronk Laboratory building, was in close proximity to immunologist Gerald Edelman and cell biologists Keith Porter, George Palade, and Christian de Duve, who were pioneering tools of cell fixation, centrifugation, and electron microscopy (Moberg 2012). Their methods inspired Ralph to further identify the unusual spleen cells and to compare phase-contrast images with electron micrographs. With micro-cinematography, Ralph and Jim observed dendritic cell behavior that was dynamic, unlike that of the sedentary macrophages.

It took six years for Ralph to get pure populations of DCs and to begin comparing these cells' immune-response functions with those of other cell types. Christian de Duve's expertise in density-gradient centrifugation was key to Ralph's purification methods in 1979. This procedure was laborious and the DC yield was poor, so very few laboratories attempted to reproduce his research. As a result, Ralph and his colleagues had DC studies to themselves for almost 15 years. During this time, the laboratory's nurturing environment provided the independence and creativity needed



Transmission electron micrograph of a dendritic cell showing numerous thin processes and many mitochondria. (Moberg, 2012.)

to prove DCs were distinct. Zan and Ralph never waived from their belief that this accidental discovery was a true breakthrough—a paradigm shift—that would change the basic concepts of immunology.

By 1975, Ralph had produced three publications describing the morphology, quantitation, and tissue distribution of DCs, along with some functional properties *in vitro* and *in vivo*. At this point, Ralph received an NIH R01 grant, titled “Characterization of Lymphoid Dendritic Cells,” with the objective “to document and to elucidate their association with developing antibody-secreting cells and with germinal centers.”

The first clue to dendritic cell function came in 1978, when Ralph and Maggi Witmer-Pack performed the mixed leukocyte reaction (MLR), an assay used to measure the primary immune response for tissue typing of patients undergoing organ transplantation followed by rejection. Surprisingly, they found that DCs were 100 times more potent in stimulating the response than unfractionated spleen cells and concluded that DCs were the key stimulators of this reaction.

Now confident that there were ways to distinguish the dendritic cells from macrophages and other leukocytes, Ralph renewed his NIH grant in 1978 and changed its title to “Properties of Mouse Dendritic Cells and Macrophages.” (This was also the year he became a United States citizen.) Little did anyone know at the time that this grant would fund 40 years of productive research and account for nearly half of Ralph’s 400 papers. With every renewal of the grant, the DCs’ unique properties, potency, functions, locations, and movements continued to distinguish them from macrophages. This cumulative research, which showed how DCs control the human immune system, set a new platform for immunology.

The MLR conclusion reached by Ralph and Maggi was not accepted by most immunologists who still believed that the major antigen-presenting cells were macrophages. This assay did not define the precise nature of the antigens or the reacting cells, and methods did not then exist to distinguish dendritic cells from other cells and determine their role in cell mixtures. Thus Ralph found it very difficult to convince anyone—whether at scientific meetings or even in the Rockefeller community—that this was a distinct cell type. Some close colleagues thought that he “was out on a limb” or “chasing an artifact” and so early in his career. Despite the attacks at a frontier in science, he accepted there were always many unclear, contradictory ideas where researchers do not agree on how to proceed or even know what is important. “Being a scientist,” he said, “is like being a transplant. You’re always at risk of rejection.” So he persevered during a difficult decade, trusting his data and pushing experiments ever deeper to acquire new knowledge of DCs.

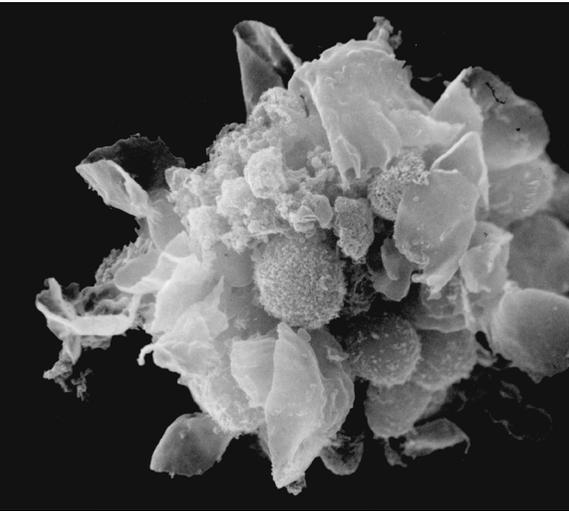
Antigen presentation and molecular markers

Much of the uncertainty was resolved in a series of experiments in the 1980s, beginning with a key finding by Michel Nussenzweig, at the time Ralph's graduate student, who showed that DCs capture, process, and present foreign antigens to activate MHC-restricted antigen-specific cytolytic T lymphocytes. Again, as was the case for the MLR experiments, DCs were orders of magnitude more potent than macrophages or other leukocytes in stimulating these responses (Nussenzweig 1980b). Michel also developed the monoclonal antibody 33D1, the first molecular marker for DCs that distinguished them from other immune cells. This allowed for their selective depletion and established critical roles in antibody and mixed-leukocyte responses. Another of Ralph's students, Wes Van Voorhis, identified DCs in human blood and developed a monoclonal antibody

that killed monocytes but not DCs. These experiments provided evidence that DCs also exist in humans and set the stage for later immunization experiments.

Kayo Inaba arrived in the laboratory in 1981 and began a lifelong collaboration with Ralph in DC research. Her Ph.D. thesis at Kyoto University independently described a non-macrophage in the spleen that could function as an accessory cell. She subsequently demonstrated, together with Ralph, a role for DCs in stimulating naive B cells to produce antibodies capable of binding sheep red-blood cells and protein antigens. Once helper T cells were activated by DCs, they could drive B cell clonal expansion and antibody production. Analyzing these T cell/DC clusters showed that DCs provide a "microenvironment" for T cell activation

and the generation of cellular immunity. These experiments led to the recognition of two stages to every immune response, an afferent stage (when DCs prime T cells) followed by an efferent stage (when activated T cells propagate immunity).



Scanning electron micrograph of a cluster of several spherical T-cells covered with microvilli enveloped by smooth, leaflike dendritic cell membranes. (Nussenzweig, 1980a.)

Moving to in vivo research, Ralph, Kayo, and postdoctoral fellow Nikolaus Romani studied dendritic cells in mice. DCs were incubated in vitro with foreign proteins and bacteria and then injected into the animals, with the result being an expansion of T cells that recognized the specific peptide antigens generated by MHC molecules from the infused DCs. In parallel, high expression of the CD11c integrin was recognized as a marker for dendritic cells, and Ralph and other investigators developed methods to obtain large numbers of monocyte-derived DCs from the bone marrow of mice and humans. These important studies led to the availability of DCs in large numbers, triggering an explosion of research in many laboratories around the world.

At this point (1990) Ralph and Jacques Banchereau established the International Symposium on Dendritic Cells in Fundamental and Clinical Immunology. This weeklong biannual congress promotes the collaboration of dendritic-cell biologists and vaccine scientists, while strongly encouraging the participation of junior investigators.

Soon after antibodies to DCs became available, Ralph and colleagues systematically investigated their location in the body. They found that the cells migrate through all the tissues and are present at all the interfaces between the body and environment. In other words, DCs are perfectly positioned to act as sentinels and to capture antigens whenever and wherever they enter the body.

Maturation

Another important discovery during the mid-1980s about DCs was that they do not exist in just one state. They need to be activated by signals from incoming pathogens or other activated immune cells, for example, by organ transplantation and contact allergy. With Gerold Schuler and Nikolaus Romani, Ralph found that cells in an *immature* state express antigen-capture and pattern-recognition receptors that can induce activation. In the *mature* activated state, the cells migrate to the local lymph node to join networks of dendritic cells that contact migrating T and B cells. In addition to presenting antigen, the DCs orchestrate the adaptive immune response by activating effector T cells that leave the dendritic cell network in the lymphoid organs and patrol the body for invading pathogens.

A key concept to emerge from this work was that different DCs express different gene profiles. Depending on the molecular nature of the structure that triggers DC maturation, different versions of T cell-activated immunity are launched.

Endocytic System

As mentioned above, Ralph's initial experiments with Zan Cohn quantified the endocytic activity of macrophages during antigen uptake. Among other things, they found that macrophages are specialized for continual antigen scavenging and destruction. By contrast, when Ralph later studied endocytosis in DCs with Ira Mellman, they found that DCs process antigens to generate peptides that are presented to different subsets of T cells. This discovery revealed a new role for DCs as messengers that link the innate and adaptive limbs of the immune system.

Other studies on endocytic receptors expressed by DCs, which Ralph performed with Michel Nussenzweig, introduced yet another area of inquiry: how to increase the immunogenicity of proteins by exploiting specific pathways for antigen uptake. The research began with biomedical student William Swiggard who isolated the DEC-205 protein. After being cloned by Wanping Jiang in Michel's laboratory, DEC-205 became the first endocytic receptor identified on DCs, and it was specifically expressed by one of the two major DC subsets. For the first time it became possible to selectively target vaccine proteins to DCs in vivo through the DEC-205 receptor by fusing the proteins with the anti-DEC-205 monoclonal antibody.

Tolerance

The importance of DCs extends beyond their ability to activate T cells and initiate immune responses to foreign antigens. Beginning in 2000, Ralph collaborated with Michel and his Ph.D. student Daniel Hawiger to use DEC-205 to target antigens to DCs in situ. They discovered that in addition to initiating immunity, DCs also play a role in controlling immune tolerance. The researchers focused on two different ways to deliver the same antigen. When the antigen was incorporated into anti-DEC-205 and targeted to immature DCs without a maturation stimulus, it was processed by DCs and presented to T cells, but the T cells were silenced (or tolerized). In contrast, when the same antigen was delivered with a maturation stimulus, the outcome changed from tolerance to immunity.

Before these discoveries, DCs in lymphoid tissues were thought to be in a mature immunogenic state, but the new results led to the opposite interpretation. Dendritic cells in the steady state continually capture harmless self-antigens, dying cells, and environmental proteins. In the absence of an activation signal, these self-reactive cells are silenced, thus preventing autoimmunity or the body's aversion to self-destruction. This finding led to

the search for methods of antigen-specific silencing of immunity, which might treat such autoimmune diseases as multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and rheumatoid arthritis.

Contributions of DCs in pathogenesis and prevention of disease

From the beginning, Ralph planned to explore the role of DCs in medicine. He believed that microbe- and tumor-related pathways found in mouse models of disease did not reliably replicate those in humans. Moreover, he advocated research that would be directly applicable to diagnosis, prevention, and treatment of human disease.

Regarding infectious diseases, Ralph studied DC function in the context of HIV-1, SIV, EBV, influenza, and dengue viruses. He found DCs provide the necessary factors to capture HIV-1 and present the virus to T cells that transmit the infection. With Christian Munz, he discovered that humans harbor a critical Epstein-Barr nuclear antigen, once thought to be ignored by the immune system, and they uncovered its role in resistance to malignancies in healthy carriers (Gurer, 2008). Thus, HIV and EBV illustrated two poles of DC function—pathogenesis and protection, retrospectively.

In vaccine biology, Ralph explored two novel strategies to stimulate innate immunity. One was active immunization against advanced cancer. With Madhav Dhodapkar, he developed ways to remove dendritic cells from a melanoma patient, charge them with specific antigens, and infuse them back into the patient. The expanded and sustained T cell response was a proof-of-concept study that was approved by the U.S. Food and Drug Administration and soon taken up by many other laboratories (Moberg 2011).

The other vaccine strategy harnessed major features of dendritic cells—location, formation, presentation, and maturation of subsets—in situ. It involved engineering disease-relevant antigens into monoclonal antibodies and targeting them directly to particular DC-specific receptors. These vaccines were applied to malaria and HIV-1. The resulting T cell-mediated immune response to targeted antigens was stronger, more efficacious, and more protective than with nontargeted antigens.

While he was always thinking on many levels at once, Ralph brought numerous scientists from other fields into his laboratory and expanded DC research to encompass these researchers' interests. Like Zan Cohn and Jim Hirsch before him, Steinman was a strong supporter of women in science. In 2011, the last scientists in his laboratory (14 women and 6 men) were broadening the scope of DC-targeted vaccines. One focused on the protein langerin, a newly found specific marker on a set of DCs, and on its potential for

vaccine targeting. Among the human pathogens studied for vaccines in mouse models were bubonic plague and Leishmania. Other scientists in the laboratory studied dendritic cells in the demanding locales of the aorta, brain, and intestine to learn how they might contribute to such clinical conditions as atherosclerosis, brain cancer, and mucosal immunity in HIV. Still others initiated preclinical studies in mice to test whether adjuvants would provoke DCs into activating the disease-fighting T cells.

Success in mouse models with anti-cancer and anti-viral immune responses encouraged Ralph to try this latter approach in humans. Together with physician-scientist Marina Caskey at The Rockefeller University Hospital and Tibor Keler at Celldex Therapeutics, Ralph initiated clinical trials of immune responses to a DC-targeted vaccine against the p24 HIV protein.

Beyond experimental science

Ralph was a tireless, curious, demanding, courageous, humble, and, most of all, determined scientist. His uncanny ability to cut to the heart of the matter at hand—whether in designing experiments, reviewing a manuscript, critiquing a grant, or describing a favorite movie plot—always came through. As at Harvard, he was known for taking complex data and distilling their essence into a couple of concise and thought-provoking sentences. He was also an effective conference organizer who thoroughly reviewed each abstract, attended every talk, took voluminous notes, and engaged researchers with tough questions.

Ralph was devoted to two families. One centered on his wife Claudia, son Adam (and his wife Jenny), and twin daughters Alexis and Lesley (and her husband Joe). The other was an even larger family of colleagues and students. Mentoring nearly a hundred postdocs and students over his long career, Ralph urged efficiency, flexibility, and collaboration while being thorough, strict, and interested in the minutest details of experiments.

He encouraged the learning of new techniques and, when indicated, altering directions; he felt that stagnation is an enemy that could prove fatal in the competitive and rapidly changing environment of research. Ralph had a few favorite sayings: *Work never ceases unless you stop it*, *Ideas are cheap*, and perhaps most memorably, *Don't tell Mother Nature what to do. Go back and do the experiment*. Then he always sent lab members off with a cheerful, *Get going, and have fun!*

As much as Ralph enjoyed composing poems for laboratory celebrations, he also devised epithets to describe the numerous dendritic cells' functions. We in turn all marveled how much each epithet applied equally to the Ralph we knew so well. He was a “novel cell”

(innovative operator), “accessory cell” (close collaborator), “antigen presenter” (initiator of experiments), “sentinel” (ever alert for new facts and postdocs), “orchestrator” (lab chief with flare and fun), “Trojan horse” (supporter and dispatcher of a hundred graduate students and postdocs), “controller” (rigorous mentor), and “nature’s adjuvant” (generous friend). The most surprising epithet he coined was “Cinderella of the immune system... whose slipper, like its wearer, had to be rescued from years of oblivion” (Steinman 2000). Ralph was the Prince Charming whose Cinderella DCs rose from obscurity to achieve recognition and significance.

One of Ralph’s most satisfying allegiances was as editor of *The Journal of Experimental Medicine* (1978–2011). He helped transform it from an all-Rockefeller editorial board and a mid-century focus on immunology into a modern world-class journal. The new outside editors were active investigators who held weekly meetings to discuss the merits of manuscripts and to judge the soundness of their critiques. As the journal neared the beginning of its second century, Ralph pressed for a return to its historical balance of papers focused on the physiological and pathological relevance of research.

Moreover, he campaigned to move the coverage of immunology beyond in vitro studies and animal models to research on human subjects. This was a significant departure from the journal’s original mission to publish from all areas of scientific medicine *except* clinical research. In several editorials, Ralph argued that human studies would provide a more systemic understanding of the manifestations and characteristics of disease. As he was learning about HIV in his own laboratory, the therapeutic procedures and theories of its pathogenesis were already calling for a return to the clinical setting.

As editor of *The Journal of Experimental Medicine* and several other journals, Ralph was uncompromisingly thorough and efficient in reviewing manuscripts. Papers had to convey conceptual advances, compelling data, and broad findings. He believed that publishing is an evolving process, as one paper could not have all the answers, so for science to go forward there would always need to be follow-ups and new approaches to address the unanswered questions. Thus he was notably generous in encouraging submissions by authors who could make a convincing argument for the significance of their work.

While he spent most of his time designing and performing elegant experiments, Ralph was also an enthusiastic cheerleader for dendritic-cell biology. In that spirit, he was deeply engaged in several scientific advisory capacities. As advisor to the Dana Foun-



50th Birthday celebration for Ralph Steinman. Left to right, Ralph, Claudia Steinman, Fern Cohn, Zanvil Cohn. (Photograph courtesy of Lawrence R. Moberg ©1993.)

dition, he initiated its award in Human Immunology Research (renamed in 2012 AAI-Steinman Award for Human Immunology Research). He spent considerable time with the National Cancer Institute to encourage the development of cancer immunotherapy with emphasis on vaccines. Following the paths of René Dubos, James Hirsch, and Zanvil Cohn as an active board member of Trudeau Institute, Ralph supported its evolving research in immunology. In 1987, he helped launch and became a cofounding director of the Tri-Institutional M.D./Ph.D. Program at Rockefeller, Weill Cornell Medicine, and Sloan Kettering

Institute. As a passionate defender of DCs in immunology, Ralph was a leading speaker at scientific meetings, giving more than 150 honorary, keynote, and plenary lectures after 1990.

Ralph was a member of the National Academy of Sciences (2001) and the National Academy of Medicine (2002). He received honorary degrees from the University of Innsbruck (1998), Vrije Universiteit of Brussels (1999), University of Erlangen (2006), and Mount Sinai School of Medicine in New York (2008). His numerous awards included the Emil von Behring Prize (1996), Rudolf Virchow Medal (1997), Max Planck Award (1998), Robert Koch Prize (1999), Gairdner Foundation International Award (2003), Novartis Prize in Basic Immunology (2004), New York City Mayor's Award for Scientific Excellence (2004), Debrecen Prize in Molecular Medicine (2006), Albert Lasker Award for Basic Medical Research (2007), Albany Medical Prize (2009), A. H. Heineken Prize for Medicine (2010), and Nobel Prize in Physiology or Medicine (2011). Very few knew that Ralph used prize money from these awards to fund travel for junior scientists in his laboratory to attend international immunology meetings.

Ralph was diagnosed with advanced pancreatic cancer in 2007. He immediately decided to prove that dendritic cells would work in treating the disease and used himself as the experimental subject with his own cells. In addition to conventional chemotherapy, he tried eight experimental treatments in all, one at a time, including three cancer vaccines

made with his own dendritic cells. The first vaccine used irradiated cells from his tumor that were engineered to attract and activate dendritic cells. The second vaccine loaded his dendritic cells with RNA extracted from his tumor; it was then injected back into him with hopes of destroying the tumor. The third loaded his dendritic cells with peptide antigens from the surface of his tumor so that the T cells might recognize these cancer antigens and coordinate an attack. None of these approaches cured Ralph, but they energized him and perhaps extended his life for four productive years.

Moreover, Ralph was heroic in how he handled his disease while continuing his experiments and publications. He appeared at many international meetings and received multiple prizes. It was all about living life on his own terms and not wasting energy with things he thought were unimportant. Aware that his remaining time on Earth was limited, Ralph took control of what he did with the choices that were left. He remained optimistic, ebullient, engaged, and unrelenting. The pace during those years created an intense atmosphere in the laboratory, as all of its members became firmly dedicated to adding knowledge about dendritic cells. Their dedication to DC research continues to flourish today in many laboratories around the world.

In his final weeks of life, Ralph gave specific directions about what should be done to ensure the future of every person in the laboratory. He bade his family to keep mourning to a minimum. He also expressed his wishes for a memorial service that would dispense with classical music and instead feature a salsa dance band.

Three days after his death, Ralph was awarded the 2011 Nobel Prize in Physiology or Medicine for his discovery of the dendritic cell and its role in adaptive immunity. The committee decided to grant his award posthumously because they assumed he was alive when their decision was made (The Nobel Foundation 2011). The Nobel Prize lecture in Stockholm was given by his close colleague Michel Nussenzweig (Nussenzweig 2011). Ralph's wife Claudia Steinman accepted the award from Sweden's King Carl XVI Gustaf at the Nobel Prize ceremony. The honor affirms Ralph's perseverance in opening a new frontier in immunology and medical science.

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