

# Remembering Ralph Steinman

Jacques Banchereau, Fern Cohn, Kayo Inaba, Bill Muller, Ira Mellman, Carl Nathan, Michel Nussenzweig, Anne O'Garra, Bob Seder, Gerold Schuler, and Alan Sher

As detailed in the Appreciation piece written by [Carol Moberg](#), Ralph's discovery and investigation of DCs constituted an enormous contribution to immunology. However, Ralph's influence extended far beyond the strictly scientific. Below, some of Ralph's closest colleagues and friends reflect on the long-lasting effects of his unwavering mentorship, enthusiasm, generosity, and friendship.

Also in this issue is a Perspective, originally commissioned by Ralph and written by [Robin Weiss and Peter Vogt](#). Ralph passed away before he could read this engaging piece, which celebrates the centennial of the publication in the *JEM* of the Nobel Prize-winning work of Peyton Rous. In addition to their Nobel Prizes, Ralph and Peyton Rous shared the distinctions of being long-time leaders of Rockefeller laboratories and editors of this journal.

### Michel Nussenzweig

When Zanvil Cohn introduced me to Ralph Steinman in 1977, he was working at the bench. Ralph continued to work during our 45 minute interview, at the end of which he told me that my ideas were from "outer space," and that I should drop them and come work with him on DCs. The next day I did, and it was one of the best decisions I ever made.

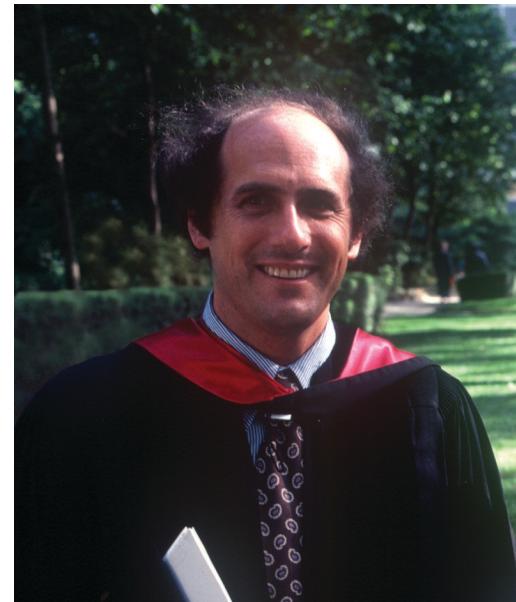
Those three years working together were among the most exciting in my career in science. We worked in a small room with Ralph's technician, Maggi Pack. Our routine was to spend the entire morning collecting and processing spleens, and talking about the experiments. There were always so many different possibilities for experiments, but never enough DCs. Despite the daily frustrations of difficult technical work at the bench, I was thrilled to be there and to spend the day talking to Ralph. He taught me how to do experiments, how to think about science, and how to be a mentor. Later, he also taught me how to be an editor of the *JEM*.

Others will comment on Ralph's tremendous determination, intelligence, and generosity. For me Ralph was above all a great friend and mentor. He will be sorely missed.

### Carl Nathan

One of my happiest memories of Ralph took place in a gilded ballroom at the Pierre Hotel on a beautiful September day in 2007 as I watched him receive the Lasker Award. His demeanor was serious as Joe Goldstein cataloged his contributions to immunology, but he lit up with a huge grin when Joe described Ralph's greatest interest: dancing with Claudia. Besides science, family was the driver in Ralph's life, both his wonderful first family—Claudia, Adam, Lesley, and Alexis—and his "second family" of colleagues, co-workers, and trainees.

What was my place in his second family? Ralph was my big brother from the moment I joined the Rockefeller faculty in 1977. The triple bonds of our shared progress through Harvard Medical School, residency at Massachusetts General Hospital, and membership in the Cohn laboratory led him to express life-long loyalty and generosity. When I needed guidance, he came into my office or invited me into his and told me what I needed to hear. When I needed support, he gave it unstintingly. For example, 20 years ago, 5 years after I moved to Cornell University Medical College, National Institutes of Health reviewers announced that they would not renew funding for the three separate MD-PhD programs that the Medical College maintained at the time: a Cornell–Cornell program, a Rockefeller–Cornell program, and a



Rockefeller University graduation, 1981. Photo by Alexander Babich.

Sloan-Kettering–Cornell program. The reviewers said they would only consider funding a unified program. They ended the critique with the prediction that they didn't think we could bring it off. The Cornell administration charged me with trying to set this up. It went nowhere until Ralph stepped forward with his full and influential support, and the Tri-Institutional MD-PhD Program has thrived ever since. I can never repay Ralph's brotherhood, except by continuing to support the goals we shared with the passion he brought to his work.

And Ralph *was* a man of passions. He did not just believe, he believed passionately in the potential of DCs, in addition to the need to support

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younger scientists, the application of exacting rigor in scientific evaluation, the importance of moving beyond *in vitro* and animal models into human studies, and the key role in the scientific community of his beloved journal, the *JEM*. During our 30 years together on the editorial board, I saw no one work harder or do more behind the scenes to sustain the journal's philosophy and effectiveness than Ralph.

If I had to pick one word to summarize Ralph's personality and impact, it would be "generativity." Generativity describes all three of Ralph's greatest interests: family, education, and research. It was also his subject matter: DCs generate an immune response by educating other cells in their family. Ralph did what he studied.

Ralph gave a Harvey lecture in January 2010. In one of those decisions for which I will never forgive myself, I allowed another obligation to keep me from attending. Later, Julien Vaujourgeix, one of my postdoctoral fellows, told me about the lecture and said, "Now I know why I want to be a scientist!" No tribute could have pleased Ralph more, perhaps not even a Nobel Prize.

#### Bill Muller

Ralph had an uncanny ability to cut right to the heart of the matter, whether it was designing an experiment, summarizing a manuscript, critiquing a grant, or describing a movie plot. He could take the most complex data and distill the essence into one or two concise simple sentences that made one think, "That's so obvious! Why didn't I think of that?"

Ralph had the most amazing smile. It was radiant. It was genuine; he looked so relaxed when he was smiling. And he always seemed to be smiling, no matter how life was treating him. The smile was infectious and those around him found themselves smiling, too. Just to be around him made me feel better.

When people would ask about my relationship with Ralph, I used to say that I was his first graduate student, and the only one NOT to work on DCs. When I came back to Rockefeller as

an Assistant Professor in the same department in which I had trained, I knew I needed to establish my independence. It was hard to work down the hall from Ralph and not get caught up in DC mania. DCs were finally being accepted by the immunology community. However, I was determined to keep focused on my own research program. This worked well, or so I thought, for a decade. At that time Gwen Randolph and I were studying a funny subset of monocytes that, after transmigrating endothelium would cross back from the basal to the apical side. We discussed these data with Ralph. He suggested a few experiments. Sure enough, these cells turned out to be monocytes that differentiated into immature DCs and were crossing the endothelium from the abluminal to the luminal side, the way they would enter afferent lymphatic channels *in vivo*.

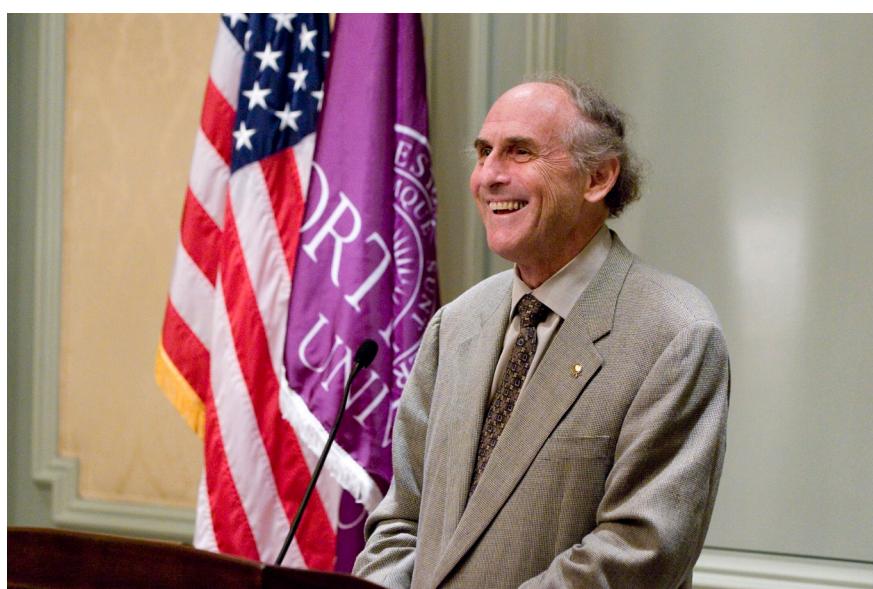
The lesson I learned from this is that there are two types of immunologists: Those who are studying DCs and those who don't realize they are studying DCs!

#### Ira Mellman

I came from a genetics lab at Yale to do my postdoc with Ralph Steinman for reasons that had nothing to do with DCs or even immunology. In fact, I

was somewhat taken aback to learn that Ralph (and Zanvil Cohn) were more interested in immunology than they were in membrane traffic, given that the two of them had just published a series of seminal papers establishing that membrane internalized during endocytosis must recycle back to the plasma membrane. I learned later that they undertook these studies in an effort to determine if antigen-presenting cells could re-express captured antigens on the surface for presentation to T cells. They did not find evidence for this pathway, but at the time (and even now) there were really no effective techniques to monitor the dynamics of peptide–MHC complexes. Nevertheless, with these efforts, Ralph helped launch the new era of molecular cell biology and the initial discovery of endosomes a few short years later. To the non-DC community, these were profound contributions.

While I may be the only one of his past post-docs who came to the lab for reasons other than DCs, Ralph's influence eventually had its way with me, as it did with virtually everyone else with whom he came in contact. Back in my own lab, immunologic receptors (e.g., Fc $\gamma$  receptors) and macrophages figured prominently in basic studies of membrane traffic and endosomes. In fact, the



Investiture ceremony for Bill Muller, Ralph's former student. Chicago, 2008. Photo by Nathan Mandell.

study of endosomes rapidly turned to the study of antigen processing and presentation. And ultimately, Ralph's masterful scientific long-term plan to attract my attention in the direction of DCs paid off. Ralph called me one day to say that I was wasting my time with B cells and that he was sending off a technician from his lab to spend a summer at Yale growing DCs in the hope that their wiles would prove attractive to a group of nonimmunologists. After the technician left, Ralph himself carried cells up weekly on the train from New York. Shannon Turley and Philippe Pierre were in the lab at the time (Sebastian Amigorena had just left), and Ralph's plan worked like a charm.

I knew Ralph for 33 years. During that time, we managed to keep in close contact: working, collaborating, planning meetings, plotting strategies, solving the world's problems, complaining about work, and sharing family stories. In all that time, I never had a colleague or a friend in science who was more committed, energetic, motivated, kind, generous, honest, concerned, brilliant, funny, harried, serious, mirthful, loyal, or loving of his family. That Ralph is and will be deeply missed by me and many others is a plain fact. But it is also a fact that my experience with him was so concentrated and supersaturated a solution that enough substance and inspiration remains to last the rest of my life. This is a good thing because, sadly, it will have to.

#### Bob Seder

My first interaction with Ralph was in 1988 when I was a second year medical resident at New York Hospital/Cornell Medical Center doing a rotation in his laboratory. Ralph and his closest friend and colleague, Zanvil Cohn, shared all the laboratory space on the fourth floor of The Detlev Bronk Building. It was in these laboratories, which seemed outdated even in 1988 and have not appreciably changed over the last 20 years, that Ralph and his colleagues made such important discoveries. In my first meeting with Ralph, he described DCs as being "special" based on their striking potency for activating naive T cells.

This early finding was the antecedent for Ralph's later work focused on targeting DCs directly with vaccines to improve T cell immunity. I was fortunate to be intimately involved with this work almost 20 years later.

Ralph was unique in his ability to have a broad perspective for what was scientifically and potentially clinically important, yet maintain a profound understanding of the cellular and molecular basis for the underlying biology. Ralph used this broad, yet specific, expertise and committed himself to translational research in two major ways. First, as an editor of the *JEM*, he was instrumental in strongly encouraging submission of papers describing experiments with human tissues, allowing those doing this type of research to publish it in a high quality journal read by so many basic immunologists. Second, Ralph devoted much of his own efforts to what he called "Vaccine Science" to develop vaccines for infections including HIV, malaria, and tuberculosis, where T cells play a critical role.

Ralph directly trained or played a major role in the development and success of a very large number of accomplished, first-rate investigators around the world. As a board member of Keystone he promoted the idea for the short talks by young investigators at plenary sessions. Over the past few years, he spent a substantial amount of time establishing The International Society for Dendritic Cell and Vaccine Science, "a web-based society to promote collaboration of dendritic cell biologists and vaccine scientists." A highlight of Ralph's vision of integrating the biology of DCs and Vaccine Science was DC2010: Forum on Vaccine Science. Antonio Lanzavecchia, Federica Sallusto, Markus Manz, and Giorgio Noseda organized this meeting, which took place September 26–30 in Lugano, Switzerland almost exactly one year prior to his passing. It was a wonderful scientific program with outstanding basic and clinical talks on the role of DCs. Ralph was the closing speaker, as was fitting.

Over the past several years, Ralph remained very private and rarely talked about his illness. I would ask periodi-

cally about how he was doing, purely out of courtesy, and he would then describe things in precise detail and sometimes wonderment about how some of the treatments were going, especially the potency of anti-CTLA-4. However the majority of our conversations focused on data, his family, and an obligatory and uninterrupted 10 minutes on the perils of research funding. Having known Ralph for over 20 years, I was fortunate to get to know his wife Claudia and daughter Alexis very well. They are warm, engaging, outgoing, and understanding of the constant intrusions by so many of us into Ralph's time. Ralph was always in a good mood when he was with his family, which also includes Adam and Leslie, their respective spouses, and of course his precious grandchildren.

Ralph was tireless, rigorous, demanding, courageous, humble, and determined. I speak for so many of his colleagues in saying that he was also incredibly loyal. He emphasized our strengths and was honest yet respectful and supportive of our weaknesses. Although the Nobel Prize is certainly the highest scientific honor, and well deserved and appreciated, the greatest prize for Ralph and his legacy will be for the scientific community to dedicate themselves to developing successful vaccines to prevent HIV, malaria and tuberculosis and help treat cancer. His scholarship, mentorship, and friendship will be missed in a way that words cannot convey. As such, it is not just DCs that were "special."

#### Gerold Schuler

Ralph changed my life in many ways. My time with him was just wonderful. The scientific findings we made and the training I received have obviously helped me in my career. However, he also impressed and influenced me very deeply as a caring and understanding human being, especially because his family was so important to him. I consider myself lucky that Ralph was my teacher, mentor, and friend. I miss him and hope to see him again in other spheres. Ralph, thank you for all you gave me.

**Alan Sher**

Ralph Steinman leaves a legacy that extends beyond his groundbreaking discovery of DCs and the numerous seminal contributions to immunology of his group at Rockefeller. To the many of us who were fortunate to have interacted closely with Ralph, he served as a model of scientific leadership to which we all might aspire. His dedication to the field of immunology extended beyond advocating for DCs and vaccines, his own areas of research interest. He was also vocal in his opposition to trends in the field that he believed to be misdirected or unfruitful. As a senior editor of the *JEM*, he was uncompromisingly rigorous but at the same time notably generous in his encouragement of submissions by authors able to make a convincing argument for the significance of their findings. Above all, Ralph was a personable and extremely positive colleague and mentor who encouraged the very best from all of us, but in particular from younger scientists struggling to make their name in the field. Ralph Steinman left us with many professional and life lessons but his last, on how to confront death with enormous courage and dignity, was to the me the most moving and powerful. In the end, the Nobel was merely the final triumph in the life of a man who was already a laureate not only in his outstanding research accomplishments and dedication to the translation of science for the betterment of humanity but also for his personal integrity. Thanks, Ralph, for your friendship and support and for leaving us with this inspiring legacy!

**Anne O'Garra**

Ralph Steinman was already very famous as the father and discoverer of DCs by the time I met him. He was modest, and always had a persistent excitement with other people's new findings, especially those related to DCs. I got to know Ralph, first in the 1990s when we co-organized (together with Jacques Banchereau) the first of a few Dendritic Cell Keystone Conferences, and then through the *JEM* Board, which I joined

in 2004. He was the most effective conference organizer, thoroughly reviewing each abstract, attending every single talk, taking detailed notes, and, importantly, engaging with and encouraging young researchers. He was the most diligent reviewer and editor I have ever met, always concerned about publishing new findings and reacting against overzealous reviewers, who either nit-picked or asked for too much. As he used to say "publishing manuscripts is an evolving process – we cannot have all the answers in the one paper, there will always be some unanswered questions, but science must go forward." I learned a lot from Ralph and will miss him sorely, both as a friend and as a mentor.

**Jacques Banchereau**

I met Ralph nearly 20 years ago. At the time, our laboratories had concluded that GM-CSF was critical for the generation of DCs in vitro, both in mice and humans. This was the beginning of a long friendship and collaboration centered on his original discovery that those DCs were an essential element of the immune system. DC meetings were launched, starting in Annecy, France, in 1994. At last, the scientific community had realized that these "dendritic cells" were not just funny macrophages! Ralph and I did not miss a DC meeting for the next 16 years.

Ralph was a true friend and the most insightful and generous collaborator, as he never refrained from being sincere. My decision to leave industry (Schering-Plough/DNAX) and join the American academic system to build the Baylor Institute for Immunology Research in Dallas did not entice Ralph, as he was worried about the funding of human studies. Yet, this gave us the opportunity to work together on a program project aimed at using DCs to induce tumor-specific immune responses in cancer patients. This project eventually got funded and allowed us to demonstrate the therapeutic value of DCs generated by culturing monocytes with GM-CSF and interferon- $\alpha$ . Eventually Ralph used these very cells for his own therapy! I will never forget those

long grant writing days with Ralph, Karolina Palucka, Joseph Fay, and Madhav Dhodapkar. What a privilege to be able to discuss DCs with Ralph and, during the breaks, learn from him how to dance salsa!

Though Ralph spent most of his life designing and performing the most elegant mouse studies, he was the strongest supporter of human immunology and was highly engaged in the field in many ways. After all, with Madhav Dhodapkar and Nina Bhardwaj, he was among the first to inject human DCs into volunteers and to demonstrate their immunogenicity in humans. In recent years, Ralph spent countless hours promoting this field. As an advisor to the Dana Foundation, he established grants to support investigators dedicated to human immunology studies. He led the Dana Foundation to establish an Award in Human Immunology Research given in collaboration with the American Association for Immunologists (AAI) every year at the AAI annual meeting. I have been a privileged recipient of this precious prize. Ralph also spent considerable time with the National Cancer Institute to encourage the development of cancer immunotherapy with an emphasis on cancer vaccines, of which he was an ardent advocate. He was impatient to see faster progress and increased funding for this field. As if to compensate, he slept short nights, ran in the early mornings, and kept an amazing pace during his long working hours. And he never hesitated to take time from his busy schedule to help his friends. He traveled south to Texas countless times to support the Baylor Institute for Immunology Research, as well as the MD Anderson Immunology program in Houston. There, he encouraged us to move forward with our studies on human lupus and cancer and with the development of HIV clinical trials. We owe it to this remarkable scientist and friend to "keep up the good work," as he used to tell us, always with a smile.

**Kayo Inaba**

I first met Ralph at the Naito Foundation International Symposium on Self-Defense Mechanisms, Role of

Macrophages, held in Tokyo November 2–4, 1981. That was Ralph's first visit to Japan. I had started my research into DCs and macrophages in 1978 at Kyoto University, following Ralph's discovery of dendritic cells with Prof. Zanvil A. Cohn in 1973. At that time, no one believed that DCs could be a unique cell type that could initiate and regulate immune responses. I joined Ralph's laboratory in 1982, and stayed for 26 months. After I returned to Kyoto, we continued to collaborate professionally in our research. On a personal level, our respective families kept in close contact. I am privileged to have such long-standing relations throughout all these years.

Ralph's amazing mind has always commanded my greatest admiration and respect. During his extraordinary career, he trained many excellent students and post-docs from many countries, including Asian countries such as China, Korea, and Japan. He was always encouraging and enthusiastic and excited about findings, even those of others. Every time we met him, he asked "What's new today?"

Ralph passed away after a four and a half year battle with pancreatic cancer. Ralph was passionately involved in science until the last days of his life. The news of Ralph's passing left me with a profound sense of grief, not only because I believe he himself deeply

regretted the "loss" of his own life but also because Ralph's passing will be a great loss to the field of immunology. I sincerely pray for him to rest in peace.

#### Fern Cohn

I remember the day very clearly. Zan came home from the laboratory and announced, "Ralph made a very important observation today." Then followed the details. Ralph had come to Zan's office to ask him to look into his microscope. Zan went to Ralph's laboratory, 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.