Howard Grey 1932–2019

On 23 December 2019, Howard Grey died at age 87 from a lung infection picked up during a river cruise in Europe, which likely turned deadly due to his advanced lung cancer. The decision to go on this trip exemplified Howard's rational approach to life and science. When diagnosed with cancer three years earlier, Howard dryly observed that he expected to die within the next few years anyway, and that, rather than undergo aggressive treatments, he wanted to do what he enjoyed most — traveling and spending time with family.

Howard was born on 16 August 1932 in Queens, New York. Losing his parents in a plane crash when he was an 18-year-old college freshman reinforced his naturally reserved character and shaped his legendary frank mentoring style. After a BA in Chemistry from the University of Pennsylvania and an MD from New York University, he was an intern at Johns Hopkins. There, he met a lively nurse named Hilda Kassoff, whom he married on New Year's Eve in 1957. During his internship, he realized that he was more suited to the in-depth reasoning required by research than to day-to-day patient care. His first steps were under the mentorship of Frank Dixon in Pittsburgh and at the Scripps Clinic and Research Foundation in La Jolla. After a short stint as an assistant professor at Rockefeller University in the mid-60s, working in collaboration with Henry Kunkel, he returned to Scripps in 1967. His remarkable studies, conducted before proteins could be sequenced, revealed many key features of immunoglobulins, including their structure, their disulfide bridges and domains, and different antibody classes and subclasses.

In 1970, Howard joined the faculty of the University of Colorado Medical Center in Denver, where he served as Head of the Basic Immunology Division from 1978 to 1988, and expanded his research interests to include the structure of MHC molecules. Seminal papers he coauthored with Peter Creswell, Jack Strominger and Ralph Kubo showed that the small subunit of HLA antigens is β 2-microglobulin. He also became interested in how antigens are recognized by T cells. Studies from the 1970s by Philip Gell, Baruj Benaceraff and Kimishige Ishizaka suggested that, while B cells depend on the three-dimensional structure of antigens, T cell reactivity is dictated by an antigen's primary sequence.

Credit: La Jolla Institute for Immunology

Because small peptides that lack a stable 3D structure are likely to be formed following uptake of native or denatured antigens by cells, this led Howard's demonstration, in collaboration with Philippa Marrack and John Kappler, that peptides generated by trypsin treatment of a protein antigen could activate antigen-specific T cells.

By 1985, Howard's group in Denver and Emil Unanue's laboratory in Saint Louis had convincingly demonstrated that the basic function of MHC molecules is to present peptides for recognition by T cells. Howard's observations radically advanced our understanding of T cell recognition and profoundly influenced vaccine design and the definition of correlates of protection and disease. They also earned him prestigious accolades, including the William B. Coley Award and being named an outstanding alumnus from NYU Medical School, culminating in his induction to the National Academy of Sciences in 1999.

When I joined Howard's lab in 1985, I was lucky to be involved in many of these seminal studies and to develop a strong personal relationship with Howard, influenced by the fact that my parents had died in my early 20s as well. The Greys welcomed me into their family, and their

youngest son Harry and I became close friends. I was the best man at Harry's wedding, and when I married several years later, Howard himself was part of the wedding party.

In 1988, Howard left Denver for San Diego to cofound the biotechnology company Cytel, focused on the development of novel peptide drugs to modulate the immune system. Those were early years for the biotech industry. Thus, Howard was also an innovator and pioneer, in terms of translational research, who realized the great potential of basic immunology for translational applications. Cytel became publicly traded on the Nasdaq exchange in 1991, and Howard remained Cytel's vice president for research and development until 1994, when he decided to return to the basic immunology research he so dearly loved.

Howard became division head of immunochemistry at the La Jolla Institute for Immunology (LJI) and was appointed president in 1996. He recruited outstanding faculty, solidified LJI's relationship with several important academic business partners and initiated the Institute's move to its current home in the University of California San Diego's Science Research Park.

After Howard stepped down in 2003 at age 71, he continued to play a pivotal role in LJI's Division of Vaccine Development for the next ten years, focusing on what he liked most about science: discussing the design and interpretation of experiments and providing razor-sharp feedback. Howie created a special place dedicated to scientific interaction, where ego was checked at the door and it did not matter who was right or wrong; it was okay to say stupid things, and, if he was wrong, he was the first to admit that his hypothesis did not stand up to the experiment. He demanded high standards, but the standards were the same for his trainees as for himself, and his feedback was always constructive. Particularly in this day and age, we will miss having a space where interactions are fair, honest, incredibly intelligent and constructive. This is how we, his friends, trainees and colleagues, remember him, and this is his legacy that will live on. □

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