

Thomas Alexander Waldmann (1930–2021)

Life in science has an aspect like dominoes. You always have a project that's incomplete and where you have planted the seeds of an orange tree and you want to harvest it" — so said Thomas Alexander Waldmann in 2015 in an interview for the American Association of Immunologists Oral History Project (<https://www.aai.org/About/History/AAI-Awardees/ThomasAWaldmann>), communicating his insatiable drive to expand scientific knowledge and improve therapeutics.

Tom's remarkable career at the US National Institutes of Health (NIH) spanned more than 65 years. Born in New York City on 21 September 1930, he was the only child of a Czech immigrant father and Hungarian immigrant mother. After his father lost his engineering job during the Great Depression, the family moved several times before settling in Chicago, where Tom attended high school and the University of Chicago. He then attended Harvard Medical School, was a medical intern at Massachusetts General Hospital, and arrived at the NIH in 1956 as a 'Yellow Beret' Clinical Associate in the Metabolism Branch of the National Cancer Institute (NCI). Tom's best friend, Sherman Weissman (Yale University), was a graduate student at the University of Chicago and joined Tom as a medical school classmate and Clinical Associate at the NIH, with each being best man at the other's wedding. Tom married his soulmate, Katharine ('Kiffy') Spreng Waldmann, who was his medical resident when he was an intern and who pre-deceased Tom by just over a year after 62 years of marriage.

Tom became a tenured Senior Investigator in 1959 with what he considered to be relatively limited research experience. He said that he never had a true mentor but learned from conversations in the corridors and cafeteria and from his technicians and fellows. In the 1950s, immunology was a backwater field: the function of lymphocytes was unknown, and key molecules that mediate the immune response were not defined, but Tom was driven by the power of the polio vaccine in eliminating epidemics and the potential of harnessing the immune system. In 1971, Tom became Chief of the Metabolism Branch, which in 2014 was renamed the Lymphoid Malignancies Branch; he served as its head until 2019, when he became Chief Emeritus.



Credit: US National Institutes of Health

Tom's first studies were on erythropoietin, funded by a US\$50 grant he received as a medical student. At the NIH, he studied patients with macroglobulinemia, multiple myeloma, protein-losing enteropathies, hypogammaglobulinemia and immunodeficiencies, including ataxia telangiectasia and Wiskott–Aldrich syndrome, in part with colleagues Warren Strober and R. Michael Blaese. Tom studied leukemias and lymphomas, in part with Samuel Broder, and immunodeficiencies as experiments of nature to elucidate critical immune functions, studying patients with decreased numbers of T or B cells or defective immune function. Moreover, he studied the turnover of albumin and gamma globulin, identified the short half-life of IgG in myotonic dystrophy, studied disorders of lymphatics and described primary intestinal lymphangiectasia, which is also known as 'Waldmann's disease'.

Tom recruited Jay Berzofsky in 1976. Stan Korsmeyer arrived as a Fellow in 1979, with Tom then collaborating with Phil Leder on immunoglobulin gene rearrangements. Such studies of pre-T cell and pre-B cell leukemias provided information on the maturity of the cells and the effectiveness of therapy. Warner Greene also arrived in 1979, and I arrived two years later, with our use of the monoclonal antibody anti-Tac,

developed by Takashi Uchiyama while in Tom's lab, to clone the human IL-2 receptor α -chain. Louis Staudt was recruited in 1988, which further strengthened the branch. Through collaborations, recruitments, and his own investigations, Tom steadily transformed the Metabolism Branch into a center that used state-of-the-art approaches to basic science related to human immunology and disease and applied findings to patient care.

In later years, Tom had three major focuses. First, he studied HTLV-I-associated adult T cell leukemia (ATL) and showed that ATL was a malignant transformation of regulatory T cells, and he worked to advance therapy for this devastating disease. Second, he co-discovered IL-15 as a factor distinct from IL-2 that was produced by an ATL cell line. Third, he developed humanized anti-Tac (daclizumab) with Cary Queen and brought it to the clinic, and immunotoxins conjugated to this antibody were generated by Ira Pastan's group. Tom's lab showed that IL-15 is presented mainly in trans by its private IL-15R α chain, in contrast to IL-2, which acts mainly in cis. Despite sharing IL-2R β and the common γ chain (γ_c), these cytokines are distinct — for example, in their effects on activation-induced cell death. Moreover, IL-15 expands natural killer cell populations, especially CD56^{bright} natural killer cells, favors the formation of memory CD8⁺ T cells and promotes antibody-dependent cellular cytotoxicity. Tom orchestrated the production of IL-15 by good manufacturing practice and performed the first in-human trials with this cytokine. He believed that rational combination therapy with IL-15 would be effective, involving antibodies, CD40 ligand and checkpoint inhibitors.

Overall, Tom's meteoric accomplishments related to cytokines, ranging from basic science to human clinical trials, led to his election to the National Academy of Medicine, the National Academy of Sciences and the American Academy of Arts and Sciences and his winning a multitude of prestigious awards and delivering more than 100 named lectureships. In 2011, the Foundation for Primary Immunodeficiency Diseases established the Thomas A. Waldmann Memorial Award for Excellence in Human Immunology as a tribute to him.

In person, Tom was soft-spoken and could even seem shy, but on the podium, he was dynamic and a master communicator with slides so clear that he never needed a

laser pointer. In the past year, he intensively reviewed the IL-15 literature, reading or re-reading many papers to remain the absolute expert on that cytokine, while he continued his quest to plant new seeds and harvest ripe fruit to the very end, co-authoring more than 20 published manuscripts in 2020 and 2021. Tom was incredibly devoted to the NIH, serving on many important committees, including being the key advisor related to clinical

investigators for the Central Tenure Committee. He worked hard, was a highly cultured scholar and had more than 870 publications, but for Tom, family always came first, and he was a dedicated and proud father and grandfather. Tom was remarkable — with his passing on 25 September 2021, our field has lost a kind and generous colleague and friend, sage advisor and mentor, and extraordinary intellectual force.

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