

In Memoriam

Cynthia Chambers, Ph.D.



Dr. Cynthia Chambers, AAI '00, died on December 19, 2004, after a decade long battle with cancer. She was 44 years old. Her untimely death was an enormous loss for the immunology community, as well as a personal loss for those of us fortunate enough to have been her colleagues and friends.

Cynthia began her immunology career at the University of Toronto, obtaining both M.Sc. and Ph.D. degrees. As a graduate student in Nobumichi Hozumi's laboratory, she investigated the patterns of cytokine production by T cell clones generated from atopic versus non-atopic individuals. These studies demonstrated that only T cell clones from atopic individuals were able to promote IgE production by B cells following *in vitro* culture. To further investigate the effects of distinct patterns of T cell cytokine production *in vivo*, Cynthia used retroviral-mediated gene transduction of murine hematopoietic stem cells and human peripheral blood lymphocytes to express the cytokines IL-4 or IL-6 in chimeric mice. The technical tour-de-force represented by these studies, among the earliest reports using retroviral-mediated gene transfer of hematopoietic stem cells, is typical of Cynthia's general approach to science. She continually exhibited an overall fearlessness at tackling even the most challenging problems, regardless of the technical difficulties that needed to be overcome.

After completing her Ph.D. degree, Cynthia joined Jim Allison's laboratory at the University of California at Berkeley. Her postdoctoral studies focused on determining the function of the T cell inhibitory receptor, CTLA-4. To begin to elucidate this problem, she chose the rigorous approach of developing mice that genetically lacked CTLA4. These mutant mice, generated simultaneously by both her and several other labs, had a dramatic phenotype in which they developed early in life a fatal lymphoproliferative disorder characterized by massive polyclonal T cell activation. Initially, this disorder was attributed by other investigators to a failure of central tolerance in the thymus purportedly leading to the maturation of autoimmune T cells. However, Cynthia's careful analysis of her CTLA-4^{-/-} mice demonstrated that T cell development actually proceeds normally in the absence of CTLA-4. This insight was critical in shifting the focus of CTLA-4 research to determining the role of this receptor in mature peripheral T cell activation and homeostasis. Another important aspect of Cynthia's postdoctoral research was her dissection of the differential role of CTLA-4 in resting CD4⁺ versus CD8⁺ T cells. Using *in vivo* antibody depletion of individual T cell subsets in neonatal CTLA-4^{-/-} mice – another remarkable technical tour-de-force – Cynthia demonstrated that CD4⁺ T cells, but not CD8⁺ T cells, were required for the development of the characteristic lymphoproliferative disorder observed in these mice. This finding provided a seminal piece of information indicating that CTLA-4 plays an essential role in regulating CD4⁺ T cell homeostasis, a role not required in resting CD8⁺ T cells. Finally, Cynthia also examined the kinetics of CTLA-4 action, and demonstrated that CTLA-4 engagement has a much more profound effect on the responses to secondary versus primary T cell stimulation.

In 2000, Cynthia joined the Department of Pathology at the University of Massachusetts Medical School, in Worcester, MA. As an independent investigator, she continued her studies of the functional role of CTLA-4 signaling in T cell activation, especially the molecular basis of CTLA-4 function and the cellular basis of trans-regulation of autoreactive CTLA-4 deficient T cells. In addition, she also began to blaze trails into exciting new areas of research, including the investigation of a novel and interesting gene expressed in hematopoietic stem cells that was identified by a screen using gene-trap technology in murine embryonic stem cells. Her research programs were asking fundamental questions and her experimental approaches were both creative and rigorous. Unfortunately, her untimely death took away from us a highly talented scientist who would have continued to contribute new insights into central problems in Immunology.

In addition to her scientific accomplishments and numerous honors, Cynthia was a valued colleague and a beloved mentor, and her loss will be felt deeply by all the faculty, staff, students, and postdoctoral fellows she interacted with. She had the wonderful capability of being both extremely rigorous and intellectually critical, while simultaneously demonstrating enthusiasm and support. Cynthia was always fully engaged in any activity she participated in, whether it was a seminar, a journal club, or a friendly scientific discussion in the hallway. Her incisive mind pushed those around her to perform to the maximum of their abilities, and as a consequence, her presence raised the level of the science being done in each environment she was a part of. Cynthia's sense of humor and her playfulness will also be sorely missed. Her passing is truly a loss for us all.

Donations may be directed to the Cynthia Chambers Memorial Fund at the Cancer Research Institute.

-- Leslie Berg, Ph.D., and Kenneth L. Rock, M.D., University of Massachusetts Medical School