Leo Lefrançois 1956–2013

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Leo Lefrançois, Chairman of the Department of Immunology and Director of the Center for Integrated Immunology and Vaccine Research at the University of Connecticut Health Center, passed away on 20 July 2013 while on a hiking vacation in Italy with his wife and friends. In life as in science he was adventuresome and fearless, always pushing the envelope. He will be sorely missed by his colleagues at the University of Connecticut, by friends all over the world and by his family.

Leo earned his PhD at Bowman Grey School of Medicine for work on vesicular stomatitis virus in Doug Lyles' laboratory before joining my group as a postdoctoral fellow at the Scripps Research Institute in La Jolla. Like many other laboratories at the time, we set about immunizing animals with cultured T cell clones and screening for clone-specific or anti-idiotypic monoclonal antibodies that would hopefully identify the T cell antigen receptor. We never obtained the specificity we sought, but Leo did make several monoclonal antibodies reactive to determinants expressed by terminally differentiated cytotoxic T lymphocytes that were clearly not reactive to the desired T cell antigen receptor. I told him to drop that research and get back to screening, but he wisely persisted and turned it into a *Nature* paper! On the basis of that episode, Leo established a maxim for students and postdoctoral fellows: "Ignore your advisor...but your idea had better be good." From the start, he was his own man, with the confidence and strength to go his own way.

Leo then went to Upjohn in Kalamazoo, Michigan, where he pursued his interests in the 'late' differentiation antigens expressed by cytotoxic effector T cells, and that led him to explore the gut mucosa and the intraepithelial lymphocytes that express these determinants. That led in turn to his discoveries about the other type of T cell found at high frequency in the gut: those T cells that express the $\gamma\delta$ T cell antigen receptor. In 1992, after 5 years at Upjohn, Leo returned to academia, joining the faculty at the University of Connecticut Health Center. This provides an answer to a question frequently asked by students finishing their degree and by postdoctoral fellows at the end of their stint: "Is there life in academia after biotech?" If you are like Leo Lefrançois, then yes, it is possible to come back. Leo was a native of Bristol, Connecticut, and although he had worked all around the USA, his final workplace at the University of Connecticut meant his net travel from home was only 10.8 miles.

What followed from 1992 to the present was a sustained period of brilliant discoveries emanating from the Lefrançois laboratory at the University of Connecticut and a continued commitment to his department in encouraging and assisting junior faculty. Leo's group identified interleukin 7 (IL-7) as the essential cytokine for the survival of peripheral T cells under homeostatic conditions, even though it

is not needed for their explosive growth after stimulation with antigen. Later work from the laboratory showed that IL-7 and IL-15 are required for the generation and long-term maintenance of memory T cells. One of Leo's greatest contributions came from an analysis of the distribution of memory CD8⁺ T cells. Through the use of tetramer staining to quantify T cells specific for a viral or bacterial infection, his group showed that so-called 'effector-memory cells' survived in large numbers in non-lymphoid tissues such as liver, lung and even fat pads. At this stage, it was not clear whether these tissue memory cells were resident in the tissue or were part of the circulating pool of memory T cells and were just passing through the tissue. That set up a brilliant experiment in which they joined the circulatory systems of congenically distinct mice by parabiosis and monitored the mixing of naive T cells and specific memory cells over time. Memory T cells in many nonlymphoid tissues reached equilibrium with kinetics similar to the rate at which they mixed in the blood, but in some tissues, such as the brain and intestinal mucosa, there was almost no immigration of circulating memory T cells from the parabiont partner and no loss of the resident memory T cells. The concept of tissue-resident memory T cells was established.

Leo's passion to define the anatomy as well as the magnitude of an immune response led to further advances. With the ability to view antigen-specific cells in tetramer-stained thick tissue sections by single and multiphoton microscopy, the Lefrançois laboratory was able to monitor the anatomy of the endogenous T cell response to a bacterial infection for the first time. Antigen-specific, tetramer-stained cells became visible in the spleen sections about 3 days after immunization, initially as small clusters in the T cell areas. Their dramatic increase in number over the next few days, their migration out of the white pulp and their population contraction to memory cells was beautifully documented in this study. Having made many of the reagents used to analyze subsets of $\gamma\delta$ T cells while at Upjohn, Leo returned to this area of research recently, showing that a subset of $\gamma\delta$ T cells has a prominent protective role in recall responses to oral infection with *Listeria monocytogenes*.

In September 2007, as Leo walked into work at the University of Connecticut Health Center, he suffered a heart attack and collapsed. His life was saved by the quick action of a transportation aide trained in cardiopulmonary resuscitation. But that and subsequent health scares and stent operations did nothing to curtail Leo's drive or slow either his work ethic or his desire to live life to the fullest (he would later mention, offhandedly, that "I was dead for three minutes," never losing his infectious smile). His zest for adventure continued with many epic hikes with his wife Lynn Puddington and their close friends Suzie and Steve Hedrick. Together this group of friends had climbed Kilimanjaro (19,341 feet) and on another occasion hiked an Incan trail to Macchu Picchu. Leo was always ready for more and dismissed concerns about his health. It was on a trek in the Dolomites in Northern Italy that Leo passed away. He was taken away too soon. Everyone will miss his boisterous attitude, his joy in discovery and the future excitement he would undoubtedly have provided.

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