

Recalling good memories

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Our chief want in life is somebody who will make us do what we can.

—Ralph Waldo Emerson

On 20 July 2013, the immunology community unexpectedly lost Leo Lefrançois. Leo was a pioneer in mucosal T-cell biology and immunological memory and very much in the prime of his research career. The field mourns his premature passing, the loss of the discoveries that he would have made, the ideas he would have inspired, and his straight-shooting but infectious personality.

Leo displayed an early aptitude for science. He obtained his PhD at Wake Forest University in only 2.5 years, while publishing many highly cited works characterizing mouse immune responses to vesicular stomatitis viruses. He provided additional evidence of his talent during postdoctoral training with Michael Bevan at Scripps. There, Leo published several papers, including one in *Nature*, while honing his scientific method, developing important collegial relationships, and cementing his lasting interest in CD8 T-cell memory. But it was only after taking an independent position, at the Upjohn Company in Kalamazoo, Michigan, that Leo developed his lifelong passion for mucosal immunology. During his brief tenure at Upjohn, Leo made a series of seminal discoveries. He reported that



Leo's "The Leo Project" hat watches over a former trainee and keeps him on point.

TCR $\gamma\delta^+$ T cells were highly enriched in the intestinal mucosal epithelium, that they were constitutively cytolytic, and that they can develop even in the absence of a thymus. This work launched a long career in the study of anatomically restricted T-cell populations and their phenotypic specialization within the intestinal mucosa.

Leo was always quick to adopt the latest technological innovations, and he pioneered the analysis of antigen-specific antiviral T-cell responses in the gut. In many ways, he was far ahead of his time. Leo reported that acute infections establish TCR $\alpha\beta^+$ T cells within the intestinal mucosa (and other nonlymphoid locations), where they adopt site-specific phenotypic signatures and functions. He was

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A lab get-together at Lynn Puddington and Leo Lefrançois' home, ca. 2000. Back row (left to right): Connie Pope, Kristina Williams, David Masopust, Vaiva Vezys, Sara Peterson, Warren D'Souza. Middle row (left to right): Kimberly Schluns, Amanda Marzo, Karen Laky, Barbara Fuller, Jim Huleatt. Front row (left to right): Sung-Kwon Kim, Leo Lefrançois, Lynn Puddington.

quite prescient in predicting very early that intestinal $\text{TCR}\alpha\beta^+$ memory CD8 T cells are resident. This idea, which proved to be true (Leo helped show this), launched the field of tissue-resident T-cell memory. These discoveries were coupled with insightful contributions to our understanding of the cytokine regulation of memory-T cell development and homeostasis: discoveries that have had important clinical ramifications.

When Leo died unexpectedly of a heart attack while hiking in northern Italy, he was at the peak of his scientific productivity. One of his most recent papers demonstrated that $\text{TCR}\gamma\delta^+$ T cells exhibit the cardinal features of immunological memory following resolution of an intestinal microbial infection. This startling observation thematically united his early scientific discoveries with his foundational work on mucosal adaptive immunity. It is gratifying that Leo was able to bridge these concepts in his lifetime. Of course, we will never know what other discoveries he might have made.

In addition to the many accolades for Leo's scientific achievements, we point out that he was a remarkable mentor and had a tremendous impact on the people he trained. We both entered the graduate program at the University of Connecticut Health Center largely because of the prospect of working with Leo. He had a cramped space at that time—we were shoehorned into a corner of the lab along with postdocs Kimberly Schluns and Amanda Marzo, a stereo that was often blaring, and the chromium waste. It was challenging to get time on the sole centrifuge, which was a washing machine-sized Beckman that was last inspected around 1970 (the inspection sticker was still there). Despite the lack of inspections, it never

broke. A poster of a shark on which Leo had scrawled "The competition never sleeps" hung prominently on the refrigerator.

Within the close confines of the Lefrançois lab, there was true intellectual ferment, cultivated by Leo's passion for science and unique personality. He set high standards. He loved making discoveries, and when that is one's true motivation, doing so with integrity is inherent. For Leo, being a scientist was a lifestyle. This life was meant to be enjoyed; measured not just by accomplishments but also by the relationships formed and lives impacted—legacies that persist long beyond one's self. Leo imparted these virtues to his trainees.

While he expected everyone to work hard, we were reminded to play hard as well. It was not uncommon to find oneself at Leo and Lynn's house at midnight on a Saturday night. Perhaps one was weary from the day's experiment (the lab hummed seven days a week, from early to late). Or eagerly awaiting the running of samples the next day to seek an answer. Over beers, the conversation would revolve around the science that we cared deeply about, along with plenty of good laughs.

This experience formed deep bonds between Leo and his people. It very much felt like one happy family. Like most families, it could be chaotic and mildly dysfunctional at times owing to the fervency. But like many great mentors, Leo allowed a healthy degree of intellectual freedom among his trainees. One was free to challenge concepts that Leo held dear. He would stay engaged and debate with you, and he could be a fairly vocal critic. But he did not stifle new ideas; he just liked to argue. And while he preferred to always be right, he never denied the data.

The last time we saw Leo was at the American Association of Immunologists annual meeting in Honolulu in May 2013. Leo had given a rousing talk on resident memory T cells, a field he helped pioneer. His current and former trainees all gathered for dinner that night. A group of former trainees sat with Leo, and they laughed and laughed; it was immediately like old times. We (Vaiva and Dave) were now married, and we consider those who were in our generation in Leo's lab to be dear friends. The thought that we would lose Leo so soon never crossed our minds.

As we reflect on what made Leo's lab so special, we feel it was his ability to stoke love and passion for science. It is said that one should lead by example. Leo's excitement about science was clear to see, and this was imprinted on us. By providing direction but allowing intellectual freedom, he empowered the people who worked with him. As a consequence, they learned to

become independent thinkers. It is remarkable how many of Leo's trainees have successful careers in industry or government or run university research labs. These days, being successful in science requires a total commitment; it is not a 9-to-5 job. Therefore, embracing it for the creative art that it is and learning to tolerate the constant critiques, competition, and stressed resources, while being consumed by the thrill of discovery and the humanity of cooperative research, are essential. These are the lessons we learned from Leo. It is easier said than done, but as we manage our own labs it is this spirit that we try to maintain and pass on.

Leo had many great friends in the field of immunology. We were among the very fortunate who got to train with him and to engage and grow and discover together on a daily basis. For that we are forever grateful. And the Leo Project will live on.

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